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Anesthesia and cancer: Friend or foe?

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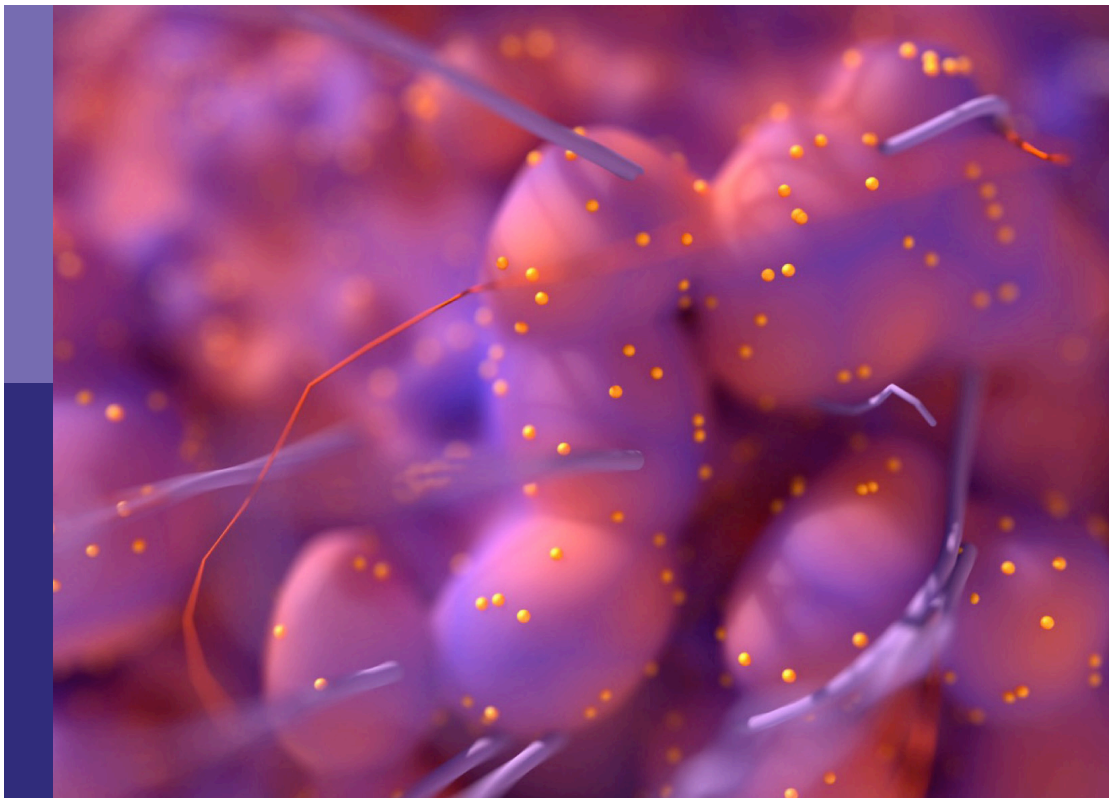

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Anesthesia and cancer: Friend or foe?

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Editorial: Anesthesia and cancer: Friend or foe?

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Editorial on the Research Topic
Anesthesia and cancer: Friend or foe?

Until now, the main objective of anesthesia has been efficient hypnosis and analgesia that are compatible with organismal homeostasis and the subsequent recovery of patients undergoing surgery. Over the past decade, some preclinical and observational clinical studies pointed towards the fact that certain anesthetic agents can impact therapeutic effects in cancer patients, for instance by modulating the rate of recurrence after oncological procedures (1–3). However, depending on the type of anesthetic and the clinical protocols employed, both pro- or antitumoral effects have been reported and therapeutic consequences have been debated (4). Thus, direct cytotoxic effects of local and systemic anesthetic agents such as lidocaine, ropivacaine, and propofol have been described suggesting anticancer effects (5, 6). However, morphine reportedly activates matrix metalloproteinases that then would promote the dissemination of tumors (7). Moreover, perioperative immunomodulatory factors such as undernutrition, anemia, neoadjuvant chemotherapy, as well as the concomitant use of mechanistically distinct anesthetic agents during oncosurgery, render the translation of partially promising preclinical results into clinical practice difficult. Altogether, results from preclinical studies stay conflicting, and clinical data are limited to retrospective studies that often are biased by confounding factors. Nevertheless, the potential impact on oncological patient care warrants further research for establishing guidelines on the use and regimens of anesthetic agents in oncosurgery.

The present Research Topic summarizes available data on potential anticancer effects of currently employed local, regional and general anesthesia that have been described in preclinical studies, as well as in prospective and retrospective clinical trials.

Several articles described the impact of anesthetic agents on the metabolism and survival of malignant cells, as well as on cancer immunity in various types of cancer cells. In their review, Chuang et al. summarize the direct cytotoxic effects and indirect immune-mediated

antitumor properties of local anesthetics used as standalone agents or combined with conventional antineoplastic therapies. Bezu et al. describe the epigenetic changes induced by local anesthetics, which can impact on tumor cell survival, proliferation and migration by an increase in the expression of tumor suppressor genes. In an original study, Shin et al. describe the effect of dexmedetomidine on the proliferation of SK-OV-3 ovarian cancer cells and on the Natural Killer cell activity in a tumor xenograft established in mice. Belltall et al. describe a potential association between the variation of opioid receptor gene expression and the incidence of neoplastic recurrence using a compendium of preclinical and clinical research methods. Fang et al. review the mechanisms of propofol and sevoflurane on cellular proliferation, migration, cell death and anticancer immunity in breast cancer. Finally, Huang et al. show *in vitro* anti-breast cancer effects induced by tramadol, an antalgic opioid currently used to minimize postoperative pain. Cell growth, invasion, migration and metabolism were monitored after exposure to tramadol alone, and synergistic effects were described for tramadol co-administered with doxorubicin.

Another set of articles explored the indirect effect of pain control and immunomodulation on cancer prognosis. Moorthy et al. furnish a systematic review addressing the question as to whether anesthesia techniques and analgesia management optimizing acute pain can control the risk of relapse and dissemination. In yet another review, Zhang et al. discuss the use of intra- and postoperative epidural anesthesia for reducing the consumption of potentially pro-tumoral opioids and volatiles. Moreover, they analyze the capacity of epidural anesthesia to indirectly control inflammatory responses.

Further articles reveal novel mechanisms induced by anesthetic agents that can control malignant progression. Thus, Zhu et al. propose an inhibitory effect of certain anesthetic agents that can counteract immunosuppressive effectors such as tumor-infiltrating myeloid-derived suppressor cells, which can promote the proliferation and the dissemination of residual cancer cells after surgery. Shi et al. focus on the implication of neurotransmitters and beta-adrenergic receptors in neoplastic progression.

Furthermore, the present thematic issue reflects efforts to design novel clinical predictors. Thus, Zheng et al. describe a prognostic model based on the differential expression of RNA binding proteins induced by anesthetics in cervical squamous cell carcinoma. The team of Andresciani et al. suggests the PERIDIAphragmatic surgery score (=PERIDIA-score), which is based on a combination of validated pre-existing scores for specific perioperative medical strategies to improve safety and patient care such as pre-habilitation or physiotherapy.

Two prospective clinical studies deal with the control of surgical stress. Based on results from a randomized controlled trial, Cho

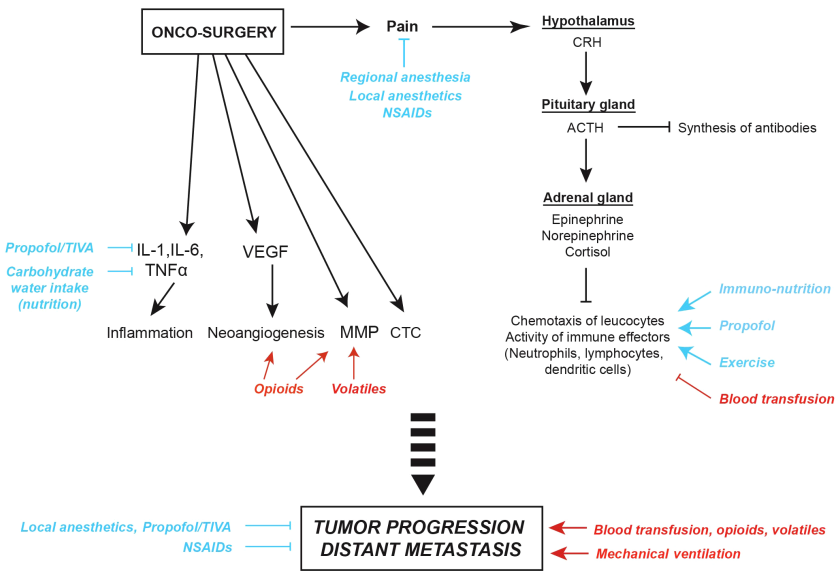

FIGURE 1
Surgical stress and potential anti- and pro-tumor effects of anesthesia, analgesia and peri-operative factors. Surgical pain can trigger corticotropic signaling, thus favoring the release of endocrine neurotransmitters such as epinephrine, norepinephrine and cortisol. Moreover, metabolic changes induced by surgical stress can impact on the chemotaxis of leucocytes and, as a consequence, induce leukopenia and suppress anticancer immune responses. Oncological procedures can also activate local and systemic inflammatory responses reflected by the release of interleukin-1 (IL-1), IL-6 and tumor necrosis factor alpha (TNFα), trigger the synthesis of vascular endothelial growth factor (VEGF) promoting neoangiogenesis, and increase the release of matrix metalloproteinases (MMP) facilitating the dissemination of circulating tumor cells (CTC). Thus, anesthetic agents and peri-operative factors may mediate either pro- (red) or anti-tumor effects (blue). ACTH, Adreno CorticoTropic Hormone; CRH, Corticotropin-Releasing Hormone; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; TIVA, Total IntraVenous Anesthesia.

et al. hypothesize that dexmedetomidine might sustain anticancer immunity, alleviate surgery-associated inflammatory responses and positively affect long-term therapeutic outcomes. Hu et al. report on pre-habilitation strategies in a single-center, double-blind prospective trial. The authors describe that, compared with both fasting and placebo, the intake of carbohydrates and water before the resection of prostate cancer attenuate the postoperative surge of inflammatory markers such as interleukin 6 (IL-6), IL-8 and tumor necrosis factor alpha (TNFα) in the serum of patients.

Finally, further reviews suggested a role of anesthetic regimens on cancer outcomes. The review of Liu and Wang provides a broad overview on the effects of local, regional or general anesthesia on tumor cells and immune effectors, the risk of recurrence according to the surgical stress and the immunomodulatory properties of various anesthetic agents. Based on preclinical data and retrospective evidence, Ramirez and Cata summarize the consequence of surgery, anesthetic agents (intravenous hypnotics, analgesics, inhalational agents), and the employment of regional *versus* general anesthesia on cancer progression with a particular focus on immune cells present in the tumor microenvironment. Based on preclinical and clinical readouts, Kim et al. also discuss the mechanisms through which surgical stress responses, opioids, and inhalation anesthesia may suppress T cell-mediated immunity and promote distant metastasis. The manuscript of Buddeberg and Seeberger completes this topic by discussing recent data on analgesics such as steroids, alpha-2 agonists or ketamine and by introducing the putative immunologic risks of blood transfusion. In a brief narrative, Montejano and Jevtovic-Todorovic efficiently summarize the potential benefit of intravenous or regional anesthesia contrasting with the risk of relapse increased by volatiles and opioids. Figure 1.

Conclusion

Onco-anesthesia is a hot topic and has become a research priority. The articles published in this Research Topic summarize recent findings in the field and underline the impact of anesthetic and analgesic procedures as well as that of perioperative care on cancer outcomes. The editors deeply thank all authors, reviewers and co-editors for their fruitful work and thoughtful implication.

Author contributions

All authors have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

OK is the scientific co-founder of Samsara Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: An updated meta-analysis. *Oncotarget* (2016) 7(12):15262–73. doi: 10.18632/oncotarget.7683

2. Desmedt C, Demicheli R, Fornili M, Bachir I, Duca M, Viglietti G, et al. Potential benefit of intra-operative administration of ketorolac on breast cancer recurrence according to the patient's body mass index. *J Natl Cancer Institute* (2018) 110(10):1115–22. doi: 10.1093/jnci/djy042

3. Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery: A retrospective analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/ALN.0000000000000936

4. Jing Y, Zhang Y, Pan R, Ding K, Chen R, Meng Q. Effect of inhalation anesthetics on tumor metastasis. *Technol Cancer Res Treat* (2022) 21:15330338221121092. doi: 10.1177/15330338221121092

5. Bezu L, Wu Chuang A, Sauvat A, Humeau J, Xie W, Cerrato G, et al. Local anesthetics elicit immune-dependent anticancer effects. *J Immunother Cancer* (2022) 10(4):1-17. doi: 10.1136/jitc-2021-004151

6. Zhou M, Dai J, Zhou Y, Wu J, Xu T, Zhou D, et al. Propofol improves the function of natural killer cells from the peripheral blood of patients with esophageal squamous cell carcinoma. *Exp Ther Med* (2018) 16(1):83–92. doi: 10.3892/etm.2018.6140

7. Khabbazi S, Hassanshahi M, Hassanshahi A, Peymanfar Y, YW Su, Xian CJ. Opioids and matrix metalloproteinases: Tthe influence of morphine on MMP-9 production and cancer progression. *Naunyn-Schmiedeberg's Arch Pharmacol* (2019) 392(2):123–33. doi: 10.1007/s00210-019-01613-6

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ORIGINAL RESEARCH
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Immunomodulatory Effects of Perioperative Dexmedetomidine in Ovarian Cancer: An *In Vitro* and Xenograft Mouse Model Study

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Background: The surgical stress response (SSR) causes immunosuppression which may cause residual tumor growth and micrometastasis after cancer surgery. We investigated whether dexmedetomidine affects cancer cell behavior and immune function in an ovarian cancer xenograft mouse model.

Methods: The effect of dexmedetomidine on cell viability and cell cycle was assessed using SK-OV-3 cells at drug concentrations of 0.5, 0.1, 5, and 10 μg mL^{-1}. BALB/c nude mice were used for the ovarian cancer model with the Dexmedetomidine group (n=6) undergoing surgery with dexmedetomidine infusion and the Control group (n=6) with saline infusion for 4 weeks. Natural killer (NK) cell activity, serum proinflammatory cytokines, and cortisol were measured at predetermined time points and tumor burden was assessed 4 weeks after surgery.

Results: Dexmedetomidine had no effect on cell viability or cell cycle. Following a sharp decrease on postoperative day (POD) 1, NK cell activity recovered faster in the Dexmedetomidine group with significant difference vs. the Control group on POD 3 (P=0.028). In the Dexmedetomidine group, cortisol levels were lower on POD 3 (P=0.004) and TNF-α levels were lower at 4 weeks after surgery (P<0.001) compared to the Control group. The Dexmedetomidine group showed lower tumor burden at 4 weeks vs. the Control group as observed by both tumor weight (P<0.001) and the *in vivo* imaging system (P=0.03).

Conclusions: Dexmedetomidine infusion may improve ovarian cancer surgery outcome by suppressing the SSR and stress mediator release. Further studies are needed to elucidate the mechanisms by which dexmedetomidine acts on cancer and immune cells.

Keywords: dexmedetomidine, immunomodulation, ovarian cancer, surgical stress response, sympathetic nervous system

INTRODUCTION

Although surgical excision remains the mainstay of treatment for solid tumors, perioperative immunosuppression may adversely promote residual tumor growth and micrometastasis after surgery (1, 2). Immunosuppression is a feature of the perioperative stress response which is associated with the hyperactivation of the sympathetic nervous system (SNS) and release of acute-phase proteins (3, 4). The deleterious effect of physiologic stress and SNS activation on cancer biology has been widely investigated (5). A key player in this process is the natural killer (NK) cell, which is critical for anti-tumor immunity, but becomes suppressed in proinflammatory and adrenergic stressor states (6).

As a potential method to alleviate the surgical stress response (SSR) and reduce immunosuppression, we focused on dexmedetomidine, a highly selective α2 adrenergic agonist well known for its analgesic properties and also the ability to suppress SNS activity (7). Moreover, NK cells express α2 adrenoreceptors (8, 9), and clonidine has been found to enhance NK cell cytotoxicity (9). Dexmedetomidine was reported to attenuate perioperative stress and inflammation induced by surgical trauma and to protect immune function of surgical patients in a recent systematic review (10). Interestingly, an *in vivo* study found dexmedetomidine to promote metastasis in breast, lung, and colon cancer in rodent models and found it to be dose-dependently deleterious (11). These conflicting results may be due to different cancer types expressing different adrenoreceptors or the use of varying doses of dexmedetomidine.

To further investigate the effect of dexmedetomidine on cancer cell behavior and immune function, we aimed to study 1) the effect of dexmedetomidine on ovarian cancer cell viability and its cell cycle *in vitro* 2) the effect of dexmedetomidine on NK cell cytotoxicity, cortisol and inflammatory cytokines levels in an ovarian cancer micrometastasis mouse model. Further, we investigated 3) whether the effect of dexmedetomidine would lead to a significant difference in tumor burden and metastasis *in vivo*.

MATERIALS AND METHODS

Cell Culture and Lentiviral Particles Transduction

The SK-OV-3 human ovarian cancer cell line (12) was purchased from the American Type Culture Collection (Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute (RPMI)-1640 medium (Hyclone, Logan, Utah, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Gibco), L-glutamine, 100 IU mL^{-1} penicillin, and 100 μg mL^{-1} streptomycin at 37°C in a humidified atmosphere of 5% CO_2. SK-OV-3 cells were seeded onto 24-well plates at a density of 2×10^4 cells per well in complete RPMI medium and incubated for 15-20 h. Redifect Red-Flu-Puromycin lentiviral particles (PerkinElimer, MA, USA) were thawed on ice. The culture medium for SK-OV-3 cells were replaced with 0.5 mL of fresh complete medium containing hexadimethrine bromide at a final concentration of 5 μg mL^{-1}. Thawed viral particles were added to the cells directly at a multiplicity of infection of 50. After 24 h, 500 μL of fresh pre-warmed complete culture medium was added and cells were incubated for 24 h. Transduced cells were selected with 2 μg mL^{-1} puromycin in fresh complete culture medium. Transduction efficiency was also determined by using the IVIS *In Vivo* Imaging System (Perkin Elmer, USA). SK-OV-3-Luc cells were assayed for luciferase expression.

Cell Viability and Cell Cycle Analysis

SK-OV-3 cells were plated onto 96-well plates at a density of 5×10^3 cells per well and divided into control and treatment groups. After 24h, dexmedetomidine (Hospira Inc., Rocky Mount, NC, USA) was added to the treatment group in four concentrations of 0.5, 0.1, 5 and 10 μg mL^{-1}, whereas phosphate buffered saline (PBS) was added to the Control group. Cell viability was assessed after 48 h using the EZ-Cytox Cell Viability Assay Kit (Dogen, Seoul, South Korea). Absorbance at 450 nm was measured in the experimental groups using a plate reader. Experiments were performed in six biological replicates and repeated three times.

For cell cycle analysis, SK-OV-3 cells were detached with 0.25% trypsin-EDTA (Gibco) and fixed in 70% ethanol for 30 min at 4°C. Cells were washed twice with cold PBS and treated with 0.25 mL RNase (10 mg mL^{-1}) in 50 mL of PBS for 20 min at 37°C; 5 mL of propidium iodide solution (ThermoFisher Scientific, Waltham, MA, USA) in 50 mL of PBS was then added and mixed well. Thereafter, cells were incubated for 30 min in the dark at room temperature. The labelled cells were analyzed using a BD FACScan flow cytometer (Becton Dickinson Biosciences, Franklin Lakes, NJ, USA).

Xenograft Models and Experimental Design

All animal procedures were approved by the Animal Care and Use Committee of Yonsei University Health System (IACUC 2017-0254). Seven-week-old female BALB/c nude mice weighing 18-20 g were experimented in accordance with the Guide for the Care and Use of Laboratory Animals (US National Institutes of Health).

For mouse ovarian cancer xenograft models, BALB/c nude mice were subcutaneously injected with SK-OV-3-Luc cells (5×10^6 cells in 0.1 mL PBS) in the dorsal skin. Tumors were allowed to grow into visible masses for 10 days and then excised in sizes of $2\times3\times2$ mm^3. Eighteen nude mice were randomly assigned to either the Sham group (n=6), the Control group (n=6), and the Dexmedetomidine group (n=6). The Sham group received only a skin incision. The mice of the remaining two groups underwent left ovariectomy and pre-grown tumor masses were sutured in place followed by dissemination of SK-OV-3-Luc cells in concentrations of 5×10^6 in 0.1 mL of PBS. Surgical procedures were performed under isoflurane anesthesia.

To evaluate the therapeutic response of the metastatic ovarian tumor xenografts to dexmedetomidine, a micro-osmotic pump system (ALZET model 1004, USA) was implanted subcutaneously in the left flank of the mice in the Control group and the

Dexmedetomidine group. The drug-loaded pump systems were assembled for infusion according to the manufacturer's instructions and implanted simultaneously with ovariectomy. The Dexmedetomidine group received an infusion of dexmedetomidine 12 μg kg^{-1} day^{-1} at a flow rate of 0.11 μL h^{-1} while the Control group received the same volume of normal saline. The infusion rate of dexmedetomidine was based on clinically recommended infusion rates in humans. Treatments were delivered continuously for 4 weeks with no signs of apparent sedation or procedural mortality. After 4 weeks, imaging was performed with an IVIS imaging system, and the mice were sacrificed. Tumor burden was assessed by weighing excised tumor masses.

Natural Killer Cell Activity

Whole blood samples were collected from the SK-OV-3-Luc xenograft mice right before surgery (day 0) and postoperative day (POD) 1, 3 and 5. NK cell activity was determined using the NK Vue Gold kit (ATGen, Seongnam-si, Korea) which measures the level of interferon-gamma (IFN-γ) released from activated NK cells using sandwich enzyme immunoassay.

Enzyme-Linked Immunosorbent Assay (ELISA)

Levels of serum tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) were analyzed at 4 weeks after surgery and cortisol levels were measured on POD 3 by using ELISA commercial kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions.

In Vivo Bioluminescence Imaging

Images were acquired using the IVIS Spectrum and analyzed using Living Image 4.5.5 software. To generate bioluminescence signals, D-luciferin (potassium salt, PerkinElmer Inc.) 150 mg kg^{-1} was intraperitoneally injected into mice prior to imaging. Animals were then anaesthetized with 2% isoflurane and placed in the imaging chamber. All fluorescence images were acquired with a 7 min exposure. For quantitative comparison, regions of interests (ROIs) were drawn over the tumor and the results were expressed as the mean ± standard deviation for a group of seven animals.

Statistical Analysis

All data from the *in vitro* and *in vivo* experiments are expressed as mean (standard deviation) and were analyzed using student's t-test, one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test or repeated measures ANOVA. $P<0.05$ was considered statistically significant.

RESULTS

Cell Viability and Cell Cycle *In Vitro*

As shown in **Figure 1A**, we were not able to see any effects on cell viability with dexmedetomidine. Compared to control, there were no changes in cell morphology and viability at four different concentrations of dexmedetomidine ranging from 0.5 μg mL^{-1} to 10 μg mL^{-1}. Similarly, there were no effects on cell cycle compared to control (**Figure 1B**) at the four different concentrations of dexmedetomidine. These results show that dexmedetomidine has no effect on ovarian cancer cell viability or cell cycle *in vitro*.

Natural Killer Cell Activity and Cortisol ELISA *In Vivo*

NK cell activity was measured on days 0, 1, 3, and 5 after surgery. NK cell activity decreased on POD 1 in both the control and dexmedetomidine treated mice. NK cell activity start increasing in both groups on POD 3, but a greater increase was seen in mice that received dexmedetomidine with a significant difference between the two groups (P=0.028). NK cell activity recovered to similar levels in both groups on POD 5 (**Figure 2A**). Serum

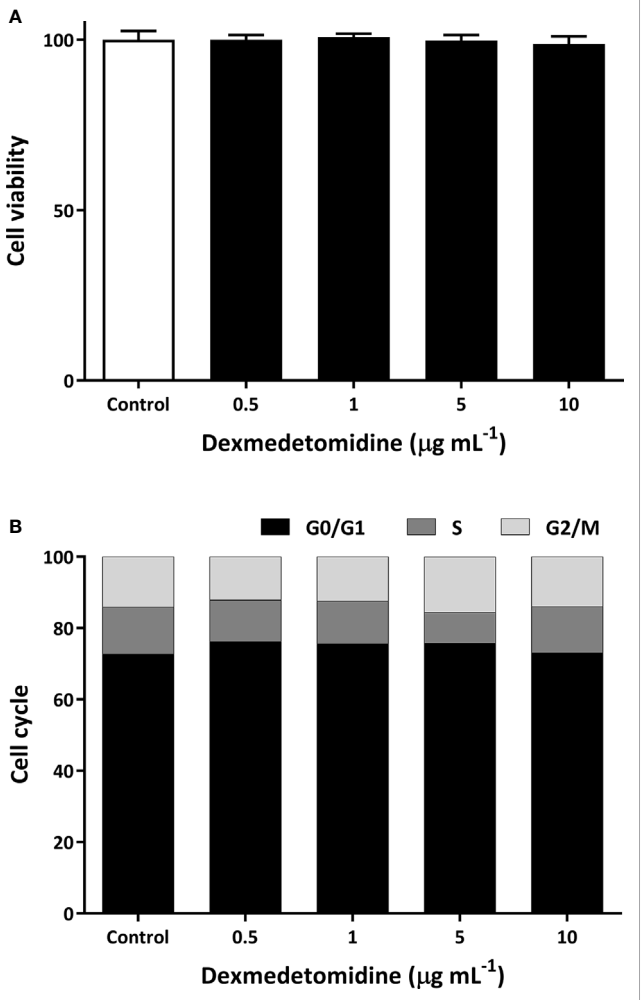

FIGURE 1 | Cell viability **(A)** and cell cycle **(B)** of SK-OV-3 human ovarian cancer cells with dexmedetomidine at 0.5, 1, 5, and 10 μg mL^{-1}. Error bars represent standard deviation.

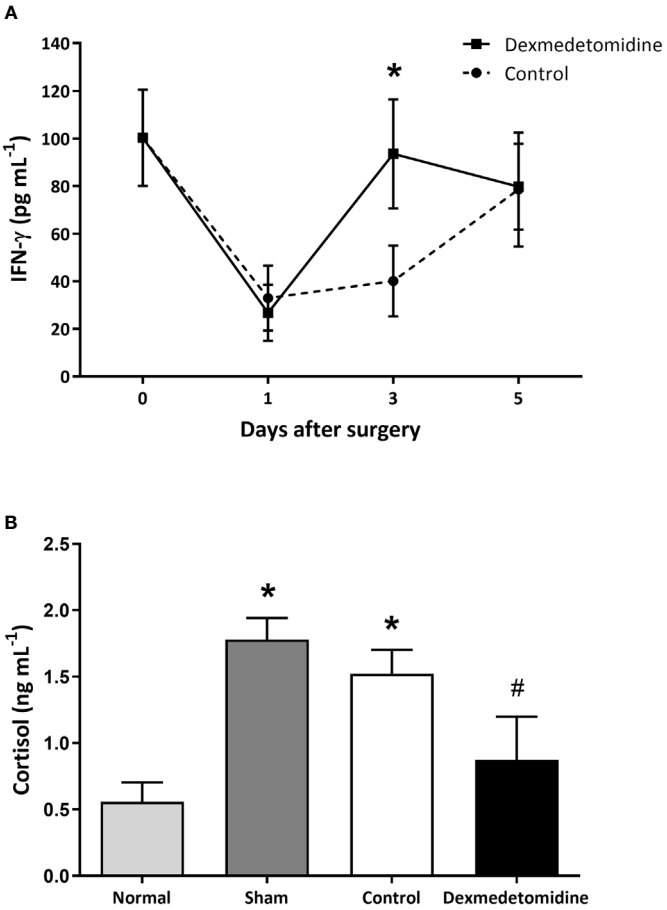

FIGURE 2 | **(A)** NK cell activity measured by IFN-γ released from activated NK cells in mice 1, 3, and 5 days after surgery. *$P < 0.05$ compared to Control. **(B)** Serum cortisol levels in mice 3 days after surgery. *$P < 0.05$ compared to Normal. #$P < 0.05$ compared to Sham and Control group. Error bars represent standard deviation.

cortisol levels measured on POD 3 showed cortisol levels to be significantly lower in the Dexmedetomidine group compared to the Control group (P=0.004). There was no difference between the Dexmedetomidine group and normal mice (**Figure 2B**).

Blood Cytokine Levels Measured With ELISA

Blood cytokine levels measured after sacrificing the mice 4 weeks after surgery showed TNF-α to be significantly lower in the Dexmedetomidine group compared to the Control group (P<0.001). However, IL-6 and IL-1β were similar between the Control and Dexmedetomidine groups, with both being significantly greater than the Sham group (**Figure 3**).

Tumor Growth and Burden

Tumor growth observed over 4 weeks showed slower growth and smaller tumor size with dexmedetomidine compared with control. Tumor weight was significantly smaller in mice treated with dexmedetomidine compared to control (P<0.001) (**Figure 4**).

Tumor Growth With *In Vivo* Imaging System

In the *in vivo* micrometastasis mice model, decreased cancer cell expression was observed in mice treated with dexmedetomidine at 4 weeks after surgery with IVIS. Quantified results were able to show a significantly lower expression of cancer cells in the Dexmedetomidine group compared to the Control group (P=0.03) (**Figure 5**).

DISCUSSION

It is ironic and worrisome that surgical excision of solid tumors may unintentionally accelerate cancer recurrence. The SSR leads to a phase of postoperative immunosuppression during the first three weeks, which has been described as the "immunological window of opportunity" (13). As a potential method to alleviate such immunosuppression after surgery, we studied the effects of dexmedetomidine in an ovarian cancer micrometastasis mouse

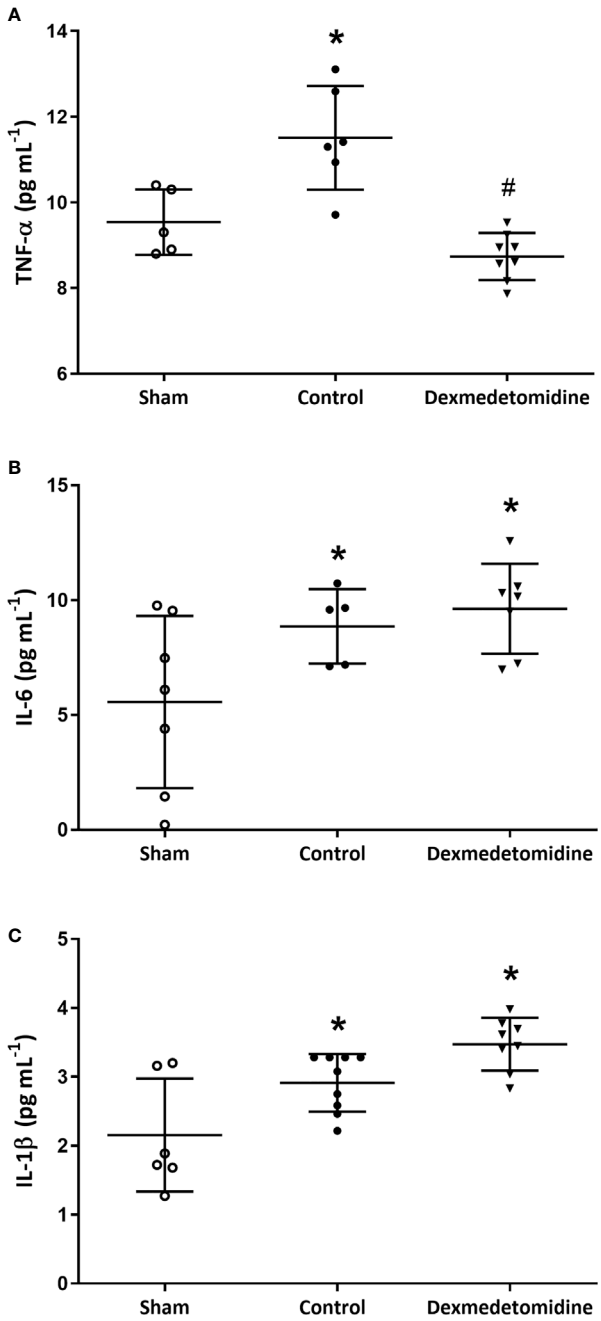

FIGURE 3 | **(A)** TNF-α levels at 4 weeks after surgery. *$P < 0.05$ compared to Sham. #$P < 0.05$ compared to Sham and Control group. **(B)** IL-6 levels at 4 weeks after surgery. *$P < 0.05$ compared to Sham. **(C)** IL-1β levels at 4 weeks after surgery. *$P < 0.05$ compared to Sham. Error bars represent standard deviation.

model, and found that while dexmedetomidine had no effect on cancer cell viability or cell cycle *in vitro*, it led to lower cortisol levels and faster recovery of NK cell activity *in vivo* postoperatively. Further, mice given dexmedetomidine showed significantly lower tumor burden and TNF-α levels compared to the Control group 4 weeks after surgery, suggesting a possible role for dexmedetomidine to abrogate the SSR and therefore alleviate immunosuppression during the perioperative window.

Dexmedetomidine and the Stress Response

Perioperative stress induces the secretion of stress-related mediators such as catecholamine and cortisol from SNS or hypothalamic-pituitary-adrenocortical (HPA) axis activation. Catecholaminergic signals are thought to be involved not only with tumor growth and progression, but also with metastasis and resistance to programmed cell death of tumor cells (14, 15). The role of neural regulation in tumor growth and metastasis has been established in different types of malignancies including ovarian cancer (16). Cortisol is known to act synergistically with adrenergic cellular mechanisms, potentiating adrenergically induced increases in cyclic AMP in tumor cells, therefore enhancing tumor growth (17, 18).

The adrenal medulla plays a central role in the secretion of systemic catecholamines where chromaffin cells release catecholamines into the bloodstream in response to acute and chronic stress. While this is mainly controlled by neural and humoral mechanisms, the secretory products themselves may also act in an autocrine or paracrine manner. A typical example are the α2 adrenoreceptors in chromaffin cells, which respond to catecholamines with negative feedback to self-limit further secretion (19). As a highly selective α2 agonist, dexmedetomidine exhibits a specificity of 1620:1 (α2:α1) which is almost 8 times greater than clonidine (20). Patients that received intraoperative dexmedetomidine showed lower levels of epinephrine, norepinephrine and cortisol during the perioperative period (10, 21, 22). In fact, intraoperative dexmedetomidine infusion was reported to be as effective as epidural anesthesia in reducing the SSR (23). Although we did not evaluate catecholamine levels in our study, the cortisol levels of mice treated with dexmedetomidine were not only significantly lower compared to the Control group, but also comparable to the cortisol levels in normal mice.

NK cells play a critical role in antitumor surveillance, which is unfortunately severely impaired during the perioperative period due to the release of stress mediators (24). While both groups experienced a dramatic decline in NK cell activity on POD 1 in our study, the Dexmedetomidine group showed NK cell activity to be restored to nearly baseline levels on POD 3 while the Control group showed almost no recovery. Based on these findings, a possible explanation for our results may be that dexmedetomidine was able to suppress the SSR and release of stress hormones, leading to a prompter restoration of NK cell activity to a degree that the growth of the ovarian cancer cells was ultimately reduced. However, it should be kept in mind that what we've observed in our study is the net result of a highly complex regulatory system that involves crosstalk between the autonomic nervous system and HPA axis in response to a stressor. Although the focus of this study is the mechanism by which dexmedetomidine may have affected the SNS and therefore cancer outcome in our animal model, we are not able to

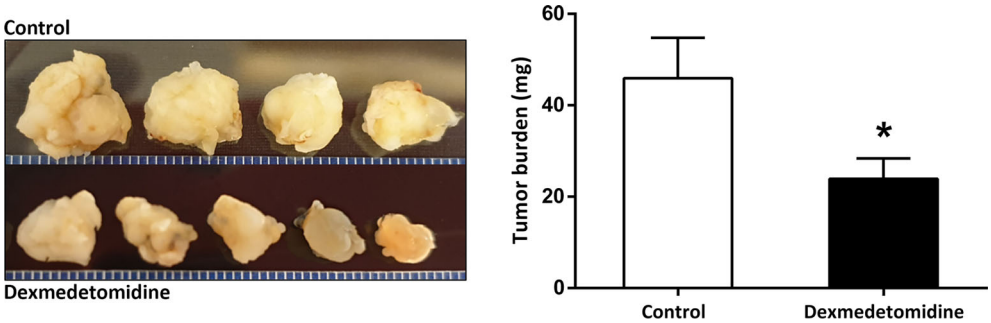

FIGURE 4 | Tumor size and weight at 4 weeks after surgery in the Control and Dexmedetomidine groups. *$P < 0.05$ compared to Control. Error bars represent standard deviation.

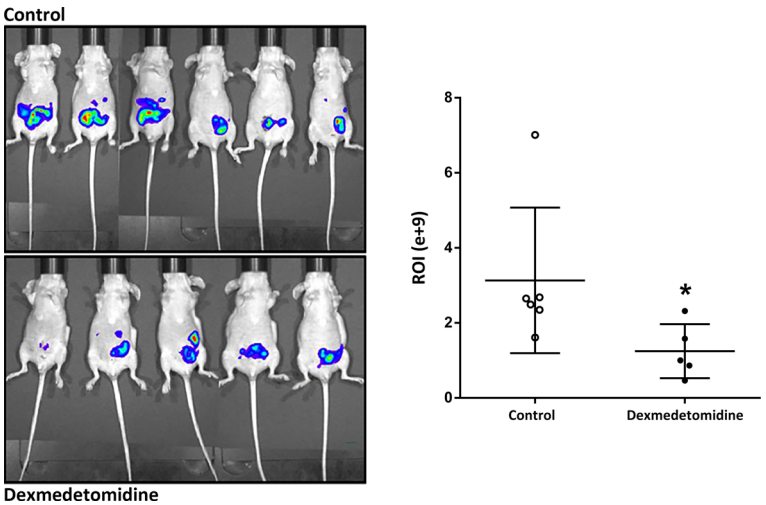

FIGURE 5 | Cancer cell expression observed with *in vivo* Imaging system at 4 weeks after surgery. *$P < 0.05$ compared to Control. Error bars represent standard deviation.

analyze the overall interaction and sequential feedback between the SNS, parasympathetic nervous system, and the HPA axis through our results.

Adrenoreceptors Expressed in Ovarian Cancer Cells

Another mechanism to consider is the possibility of dexmedetomidine acting directly on α2 adrenoreceptors expressed in cancer cells. In breast cancer, both human (25) and mouse mammary cell lines (26) have been found to express functional α2 adrenoceptors. In humans, α2 adrenoreceptors were found to be associated with an increase in cell proliferation (25). Similarly, a significant enhancement of mouse mammary tumor growth was observed with clonidine (26).

The main receptor identified in ovarian cancer cells is the β2 adrenergic receptor through which catecholaminergic signals are predominantly mediated (27). Surgical stress was shown to promote tumor growth through increased angiogenesis and vascular endothelial growth factor (VEGF) production *via* β adrenoreceptors on ovarian cancer cells. Moreover, remote surgical stress led to increased tumor growth in the ovary, and such effects were blocked by a nonspecific β blocker (28). As of now, however, whether α adrenoreceptors are expressed in ovarian cancer cells is not clear. If in fact ovarian cancer cells do express α2 adrenoreceptors, dexmedetomidine may have directly affected SK-OV-3 cells *in vitro*. Based on the fact that we were not able to observe any changes in ovarian cancer cell viability or cell cycle with dexmedetomidine, it seems unlikely that dexmedetomidine affected cell growth directly *via* α2 adrenoreceptors. Rather, the aforementioned ability of dexmedetomidine to alleviate the SSR may have acted indirectly on β adrenoreceptors of the ovarian cancer cells, resulting in reduced tumor burden *in vivo*.

α2 Adrenoreceptors Expressed in NK Cells

There is also the possibility of dexmedetomidine acting directly on α2 adrenoreceptors expressed on immune cells. As mentioned above, it has been shown in animal models and clinical studies that NK cell cytotoxicity is suppressed immediately after surgery (29, 30).

NK cells have been reported to express both α and β adrenoreceptors (8, 9) and in rats, activation of either α1- and α2- adrenoreceptors were found to augment NK cytotoxicity (9). This direct action of dexmedetomidine may have acted additively to its systemic suppression of the SSR, resulting in the faster recovery of NK cell activity in the Dexmedetomidine group.

Previously, dexmedetomidine was found to significantly suppress TNF- α and IL-6 levels in patients undergoing laparoscopic ovarian resection for cancer (31). Our results are in line with this previous study in that NK cell activity recovered faster after laparotomy while TNF-α levels were lower with significantly lower tumor burden in mice treated with dexmedetomidine.

The Current Evidence

The existing evidence on dexmedetomidine and cancer are conflicting, including opposing results between animal studies and human studies. One of the earlier animal studies reported that dexmedetomidine inhibited antitumor immunity due to a decreased Th1/Th2 ratio in thymoma cells, and stated that this result "was a surprise" (32). Of note, dexmedetomidine was not administered as a continuous infusion but as twice-daily bolus doses in mice for a week in this study. Similarly, dexmedetomidine was found to have deleterious effects on tumor metastasis in rodent models of breast, lung, and colon cancer (11). Here, the administration of yohimbine was found to prevent the metastasis promoting effects of dexmedetomidine, which also shows that these effects are mediated through α2 adrenoreceptors. However, the dose of dexmedetomidine used in this study far exceeded the clinically recommended infusion dose and was soon met with an opposing report where clonidine was not found to be associated with worse outcome in breast and lung cancer patients (33).

We are still at an early stage of investigating the effect of α-adrenoreceptors on cancers of various organs. At this point, even the effect of the relatively well-studied β adrenergic antagonists seem to be variable and tumor specific (34). α2 agonists such as dexmedetomidine require future studies that explore their effects in different types of malignancies at clinical doses and infusion periods.

Limitations

This study has several limitations. While the lower cortisol levels in the Dexmedetomidine group reflect lesser SNS activation, a serial measurement over the course of 5 days would have allowed more insight into the action of dexmedetomidine in cancer surgery. In the same vein, a serial measurement of blood cytokine levels would have offered relevant data to our study. One of the main mechanisms through which anesthetics may directly affect outcome after cancer surgery is the regulation of HIF levels (35). Increases in HIF-1α and HIF-2α have both been suggested to be associated with ovarian carcinoma progression (36). In the same respect, VEGF plays an important role in the pathogenesis of ovarian cancer by contributing to the development of peritoneal carcinomatosis, and its inhibition has been shown to suppress tumor growth and invasion (37). It would be interesting to see whether the use of dexmedetomidine in our animal model will affect HIF-1 expression and intraperitoneal concentrations of VEFG and whether this correlates with differences in tumor burden between groups. Most importantly, our study has the inherent limitation of being an animal study that cannot be directly translated into replications in a human trial. As mentioned above, we employed an infusion rate that is within the clinically recommended dose, which is significantly lower that the doses used in previous studies that reported problematic effects of dexmedetomidine on tumor growth and metastasis (11). Considering the fact that we maintained dexmedetomidine infusion for 4 weeks, our results suggest that dexmedetomidine is probably at least safe as a perioperative adjuvant drug in ovarian cancer when used within clinical recommendations, and has the potential to be an effective immunomodulatory drug during the perioperative period.

Conclusion

In conclusion, we found dexmedetomidine infusion to have a potentially positive effect on surgical outcome in a mouse model of ovarian cancer. This may be due to several reasons, as dexmedetomidine can be expected to act on different levels. Systemically on a neuroendocrine and paracrine level, dexmedetomidine is able to alleviate the SSR and therefore inhibit the release of stress mediators. This in turn may exert indirect effects on ovarian cancer cells and NK cells. There also lies the possibility of direct action on adrenoreceptors expressed in NK cells. Further studies are needed to elucidate potential mediating mechanisms and whether these effects are tumor-specific.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by The Animal Care and Use Committee of Yonsei University Health System.

AUTHOR CONTRIBUTIONS

SS: study design, data collection, data analysis, and writing the manuscript. KJK: study design and data analysis. HJH: data collection and data analysis. SN: data collection and data

analysis. JEO: study design, data collection, and data analysis. Y-CY: study design, data analysis, and writing the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The Effects of Surgery on Tumor Growth: A Century of Investigations. *Ann Oncol* (2008) 19 (11):1821–8. doi: 10.1093/annonc/mdn386
2. Ceelen W, Pattyn P, Mareel M. Surgery, Wound Healing, and Metastasis: Recent Insights and Clinical Implications. *Crit Rev Oncol Hematol* (2014) 89 (1):16–26. doi: 10.1016/j.critrevonc.2013.07.008
3. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative Events Influence Cancer Recurrence Risk After Surgery. *Nat Rev Clin Oncol* (2018) 15(4):205–18. doi: 10.1038/nrclinonc.2017.194
4. Hiller J, Brodner G, Gottschalk A. Understanding Clinical Strategies That May Impact Tumour Growth and Metastatic Spread at the Time of Cancer Surgery. *Best Pract Res Clin Anaesthesiol* (2013) 27(4):427–39. doi: 10.1016/j.bpa.2013.10.003
5. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. Sympathetic Nervous System Regulation of the Tumour Microenvironment. *Nat Rev Cancer* (2015) 15(9):563–72. doi: 10.1038/nrc3978
6. Goldfarb Y, Sorski L, Benish M, Levi B, Melamed R, Ben-Eliyahu S. Improving Postoperative Immune Status and Resistance to Cancer Metastasis: A Combined Perioperative Approach of Immunostimulation and Prevention of Excessive Surgical Stress Responses. *Ann Surg* (2011) 253(4):798–810. doi: 10.1097/SLA.0b013e318211d7b5
7. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet* (2017) 56(8):893–913. doi: 10.1007/s40262-017-0507-7
8. Jetschmann JU, Benschop RJ, Jacobs R, Kemper A, Oberbeck R, Schmidt RE, et al. Expression and *In-Vivo* Modulation of Alpha- and Beta-Adrenoceptors on Human Natural Killer (CD16+) Cells. *J Neuroimmunol* (1997) 74(1-2):159–64. doi: 10.1016/s0165-5728(96)00221-4
9. Xiao J, Huang HW, Peng YP, Bao JY, Huang Y, Qiu YH. Modulation of Natural Killer Cell Function by Alpha-Adrenoreceptor-Coupled Signalling. *Neuro Endocrinol Lett* (2010) 31(5):635–44.
10. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of Dexmedetomidine on Perioperative Stress, Inflammation, and Immune Function: Systematic Review and Meta-Analysis. *Br J Anaesth* (2019) 123 (6):777–94. doi: 10.1016/j.bja.2019.07.027
11. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120(1):188–96. doi: 10.1016/j.bja.2017.11.004
12. Fogh J, Fogh JM, Orfeo T. One Hundred and Twenty-Seven Cultured Human Tumor Cell Lines Producing Tumors in Nude Mice. *J Natl Cancer Inst* (1977) 59(1):221–6. doi: 10.1093/jnci/59.1.221
13. Coffey JC, Wang JH, Smith MJ, Bouchier-Hayes D, Cotter TG, Redmond HP. Excisional Surgery for Cancer Cure: Therapy at a Cost. *Lancet Oncol* (2003) 4 (12):760–8. doi: 10.1016/s1470-2045(03)01282-8
14. Sood AK, Armaiz-Pena GN, Halder J, Nick AM, Stone RL, Hu W, et al. Adrenergic Modulation of Focal Adhesion Kinase Protects Human Ovarian Cancer Cells From Anoikis. *J Clin Invest* (2010) 120(5):1515–23. doi: 10.1172/JCI40802
15. Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, et al. Behavioral Stress Accelerates Prostate Cancer Development in Mice. *J Clin Invest* (2013) 123(2):874–86. doi: 10.1172/JCI63324
16. Hanoun M, Maryanovich M, Arnal-Estape A, Frenette PS. Neural Regulation of Hematopoiesis, Inflammation, and Cancer. *Neuron* (2015) 86(2):360–73. doi: 10.1016/j.neuron.2015.01.026
17. Nakane T, Szentendrei T, Stern L, Virmani M, Seely J, Kunos G. Effects of IL-1 and Cortisol on Beta-Adrenergic Receptors, Cell Proliferation, and Differentiation in Cultured Human A549 Lung Tumor Cells. *J Immunol* (1990) 145(1):260–6.
18. Stern L, Kunos G. Synergistic Regulation of Pulmonary Beta-Adrenergic Receptors by Glucocorticoids and Interleukin-1. *J Biol Chem* (1988) 263 (31):15876–9. doi: 10.1016/S0021-9258(18)37531-8
19. Artalejo AR, Olivos-Ore LA. Alpha2-Adrenoceptors in Adrenomedullary Chromaffin Cells: Functional Role and Pathophysiological Implications. *Pflugers Arch* (2018) 470(1):61–6. doi: 10.1007/s00424-017-2059-y
20. Kamibayashi T, Maze M. Clinical Uses of Alpha2 -Adrenergic Agonists. *Anesthesiology* (2000) 93(5):1345–9. doi: 10.1097/00000542-200011000-00030
21. Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative Dexmedetomidine Attenuates Stress Responses in Patients Undergoing Major Spine Surgery. *Minerva Anestesiol* (2019) 85(5):468–77. doi: 10.23736/S0375-9393.18.12992-0
22. Kang R, Jeong JS, Ko JS, Lee SY, Lee JH, Choi SJ, et al. Intraoperative Dexmedetomidine Attenuates Norepinephrine Levels in Patients Undergoing Transsphenoidal Surgery: A Randomized, Placebo-Controlled Trial. *BMC Anesthesiol* (2020) 20(1):100. doi: 10.1186/s12871-020-01025-7
23. Li Y, Wang B, Zhang LL, He SF, Hu XW, Wong GT, et al. Dexmedetomidine Combined With General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared With a Combined General and Epidural Anesthetic Technique. *Anesth Analg* (2016) 122(4):1202–10. doi: 10.1213/ANE.0000000000001165
24. Brochner AC, ikkelsen S, Hegelund I, Hokland M, Mogensen O, Toft P. The Immune Response Is Affected for at Least Three Weeks After Extensive Surgery for Ovarian Cancer. *Dan Med J* (2016) 63(6):A5243.
25. Vazquez SM, Mladovan AG, Perez C, Bruzzone A, Baldi A, Luthy IA. Human Breast Cell Lines Exhibit Functional Alpha2-Adrenoceptors. *Cancer Chemother Pharmacol* (2006) 58(1):50–61. doi: 10.1007/s00280-005-0130-4
26. Bruzzone A, Pinero CP, Castillo LF, Sarappa MG, Rojas P, Lanari C, et al. Alpha2-Adrenoceptor Action on Cell Proliferation and Mammary Tumour Growth in Mice. *Br J Pharmacol* (2008) 155(4):494–504. doi: 10.1038/bjp.2008.278
27. Sood AK, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, et al. Stress Hormone-Mediated Invasion of Ovarian Cancer Cells. *Clin Cancer Res* (2006) 12(2):369–75. doi: 10.1158/1078-0432.CCR-05-1698
28. Lee JW, Shahzad MM, Lin YG, Armaiz-Pena G, Mangala LS, Han HD, et al. Surgical Stress Promotes Tumor Growth in Ovarian Carcinoma. *Clin Cancer Res* (2009) 15(8):2695–702. doi: 10.1158/1078-0432.CCR-08-2966
29. Da Costa ML, Redmond HP, Finnegan N, Flynn M, Bouchier-Hayes D. Laparotomy and Laparoscopy Differentially Accelerate Experimental Flank Tumour Growth. *Br J Surg* (1998) 85(10):1439–42. doi: 10.1046/j.1365-2168.1998.00853.x
30. Da Costa ML, Redmond P, Bouchier-Hayes DJ. The Effect of Laparotomy and Laparoscopy on the Establishment of Spontaneous Tumor Metastases. *Surgery* (1998) 124(3):516–25. doi: 10.1067/msy.1998.89410
31. Liu M, Yi Y, Zhao M. Effect of Dexmedetomidine Anesthesia on Perioperative Levels of TNF-Alpha and IL-6 in Patients With Ovarian Cancer. *Oncol Lett* (2019) 17(6):5517–22. doi: 10.3892/ol.2019.10247
32. Inada T, Shirane A, Hamano N, Yamada M, Kambara T, Shingu K. Effect of Subhypnotic Doses of Dexmedetomidine on Antitumor Immunity in Mice. *Immunopharmacol Immunotoxicol* (2005) 27(3):357–69. doi: 10.1080/08923970500240883
33. Forget P, Berliere M, Poncelet A, De Kock M. Effect of Clonidine on Oncological Outcomes After Breast and Lung Cancer Surgery. *Br J Anaesth* (2018) 121(1):103–4. doi: 10.1016/j.bja.2018.04.020
34. Yap A, Lopez-Olivo MA, Dubowitz J, Pratt G, Hiller J, Gottumukkala V, et al. Effect of Beta-Blockers on Cancer Recurrence and Survival: A Meta-Analysis of Epidemiological and Perioperative Studies. *Br J Anaesth* (2018) 121(1):45–57. doi: 10.1016/j.bja.2018.03.024
35. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer Recurrence After Surgery: Direct and Indirect Effects of Anesthetic Agents. *Int J Cancer* (2012) 130(6):1237–50. doi: 10.1002/ijc.26448
36. Osada R, Horiuchi A, Kikuchi N, Yoshida J, Hayashi A, Ota M, et al. Expression of Hypoxia-Inducible Factor 1alpha, Hypoxia-Inducible Factor 2alpha, and Von

Hippel-Lindau Protein in Epithelial Ovarian Neoplasms and Allelic Loss of Von Hippel-Lindau Gene: Nuclear Expression of Hypoxia-Inducible Factor 1alpha Is an Independent Prognostic Factor in Ovarian Carcinoma. *Hum Pathol* (2007) 38(9):1310–20. doi: 10.1016/j.humpath.2007.02.010

37. Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of Vascular Endothelial Growth Factor in Growth and Peritoneal Dissemination of Ovarian Cancer. *Cancer Metastasis Rev* (2012) 31(1-2):143–62. doi: 10.1007/s10555-011-9337-5

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A New Score to Assess the Perioperative Period of the Cancer Patient Undergoing Non-Palliative Elective Surgery: A Retrospective Evaluation of a Case Report by PERIDIA Score

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The complexity of cancer patients and the use of advanced and demolitive surgical techniques frequently need post-operatory ICU hospitalization. To increase safety and to select the best medical strategies for the patient, a multidisciplinary team has performed a new peri-operatory assessment, arising from evidence-based literature data. Verifying that most of the cancer patients, admitted to the intensive care unit, undergo major surgery with localizations in the supramesocolic thoraco-abdominal area, the team focused the attention on supramesocolic peridiaphragmatic cancer surgery. Some scores already in use in clinical practice were selected for the peri-operatory evaluation process. None of them evaluate parameters relating to the entire peri-operative period. In detail, only a few study models were found that concern the assessment of the intra-operative period. Therefore, we wanted to see if using a mix of validated scores, it was possible to build a single evaluation score (named PERIDIAphragmatic surgery score or PERIDIA-score) for the entire peri-operative period that could be obtained at the end of the patient's hospitalization period in post-operative ICU. The main property sought with the creation of the PERIDIA-score is the proportionality between the score and the incidence of injuries, deaths, and the length of stay in the ward. This property could organize a tailor-made therapeutic path for the patient based on pre-rehabilitation, physiotherapy, activation of social assistance services, targeted counseling, collaborations with the continuity of care network. Furthermore, if the pre-operative score is particularly high, it

could suggest different or less invasive therapeutic options, and if the intra-operative score is particularly high, it could suggest a prolongation of hospitalization in ICU. The retrospective prospective study conducted on 83 patients is still ongoing. The first data would seem to prove an increase of clinical complications in patients who were assigned a one-third score with respect to the maximum (16/48) of PERIDIA-score. Moreover, patients with a 10/16 score within each phase of the evaluation (pre, peri, and post) more frequently develop injuries. In the light of these evidence, the 29-point score assigned to our patient can be considered as predictive for the subsequent critical and fatal complications the patient faced up.

Keywords: perioperative score, peridiaphragmatic surgery, anesthesiology, ICU, cancer patients

INTRODUCTION

The perioperative evaluation concerns the analysis of the characteristics of the cancer patient related to the possibility of undergoing surgery, the monitoring of vital functions in relation to surgical and anesthetic procedures during surgery, the primary and secondary prevention of complications related to surgery in post-operative intensive care unit.

The standardization of peri-operatory assessments in cancer patients undergoing peridiaphragmatic thoraco-abdominal surgery (such as esophagectomy, lobectomy and pneumonectomy, hepatic metastasectomy, pancreatectomy, gastrectomy, and splenectomy) is a very complex challenge, particularly in the case of multiorgan localization. This aim is worldwide pursued for each patient through the application of international evaluation scores in the pre-operatory step (fragility, nutritional structure, comorbidities, previous thoraco-abdominal problems) and/or the prediction of the post-operatory onset of complications.

To our knowledge, only a few experiences are reported in literature in terms of peri-operatory evaluation; in particular, the intra-operatory phase lacks shared and validated references as regards clinical scores in critical patients, passing through the three steps, pre-, intra-, and post-surgery.

The clinical data concerning 83 patients hospitalized in 2018 in post-operative ICU of the Cancer Institute Giovanni Paolo II of Bari were retrospectively analyzed. The following case report aims at demonstrating how a peri-operative evaluation is necessary to predict complications related to surgical treatment *versus* non-multidisciplinary and unstructured assessments. Our first results will be confirmed by an ongoing retrospective study on a large number of patients and by future prospective studies.

MATERIALS AND METHODS

A multidisciplinary group, consisting of anesthesiologists, abdominal cancer surgeons and thoracic cancer surgeons, pharmacists, psychologists, statisticians, and nurses, has elaborated the PERIDIA Score (**Figures 1A, B**), starting from the analysis of the literature reference scores.

In the first step of our study, some scores already in use in clinical practice were selected for the peri-operatory evaluation process. Edmonton Frail Scale, Mini Nutritional Assessment Short Form, Charlson Age Morbidity Index, Assess Respiratory Risk in Surgical Patients in Catalogna (ARISCAT Index), Lee's Revised Cardiac Risk Index, Preoperative Esophagectomy Risk, Clavien Dindo Classification, Child Pugh Score, Model for End Stage Liver Disease, Simple Risk Score for Pancreatectomy Surgical Outcomes Analysis and Research, Hacor Score, and World Society of Emergency Surgery Sepsis Score were deeply analyzed and synthetized by the team to extract the most significant items to build our new score, named PERIDIAphragmatic surgery score or PERIDIA score (1–20).

The PERIDIA score has been subsequently divided into three scores, each of which expressing a score from 0 to 16 for a maximum of 48 points. The first score concerns the pre-operatory period and supports the anesthetic and surgical evaluations of pre-hospitalization. It consists in four scores, to each of which a score from 0 to 4 points can be assigned. With regard to the Modified Edmonton Frail Scale, a point is assigned to the verification of each of the following conditions: ≥2 hospitalizations in the last year; need for help with daily activities; sadness, depression, psychosis, or neurodegenerative disease in treatment; absence of family members or caregivers. Regarding the Modified Mini Nutritional Assessment Short Form, a point is assigned to the verification of each of the following conditions: weight loss in the last 3 months ≥4 kg; sedentarism (transition from bed to chair); previous major surgery (thoracic, abdominal); BMI ≤21 or ≥30. About the Modified Charlson Age Morbidity Index, ARISCAT Index, and Lee's Revised cardiac Risk Index, 1 point is assigned for each of the following conditions: age ≥70 years; SpO2 ≤90% in air environment or need for oxygen therapy or non-invasive ventilation; hemoglobinemia ≤6.21 mmol/L; AMI or heart failure or lung infections or diabetes with organ damage or liver injury or metastatic solid tumor in the last year. Finally, the ASA score is taken from the anesthetic assessment pre-hospitalization and in any case is assigned on the basis of the following criteria: 1 point for no organic, biochemical, or psychiatric alteration; 2 points for mild systemic disease related or not to the reason for the surgery; 3 points for severe but not disabling systemic pathology related or not to the reason for the surgery; 4 points for severe systemic disease with a severe prognosis that affects survival regardless of surgery.

A

Pre operatory Score

Frailty: Modified Edmonton Frail Scale

0 1 2 3 4

- ≥2 hospitalizations in the last year
- Need for help with daily activities
- Sadness, depression, psychosis, neurodegenerative disease under treatment
- No family members or care giver

Nutritional Status: Modified MNA-SF

0 1 2 3 4

- Weight loss in the last 3 months ≥4 kg
- Sedentarism (transition from bed to chair)
- Previous major surgery (thoracic, abdominal)
- BMI ≤21 or ≥30

Comorbidity: Modified CACI – ARISCAT - RCRI

0 1 2 3 4

- Age ≥70
- SpO2 ≤90 in air or need for oxygen therapy or NIV
- Hb ≤6.21 mmol/L
- AMI / Heart failure / lung infections / Diabetes with organ damage / Liver damage / Metastatic cancer in the last year

Anaesthesiology Rescue: ASA score

0 1 2 3 4

- 0 pt for normal healthy patient (ASA I)
- 1 pt for patient with mild systemic disease (ASA II)
- 2 pts for patient with severe systemic disease (ASA III)
- 3 pts for patient with severe systemic disease that is a constant threat to life (ASA IV)
- 4 pts for moribund patient who is not expected to survive without the operation (ASA V)

Intra operatory Score

HR Intraoperatory Score

0 1 2 3 4

1 point is counted for each change ≥10 b / min compared to the baseline value (minimum value detected in the pre-operating room after premedication)

MAP Intraoperatory Score

0 1 2 3 4

1 point is counted for each change ≥20 mmHg compared to the baseline value (minimum value detected in the pre-operating room after premedication)

SpO2 Intraoperatory Score

0 1 2 3 4

1 point is counted for each variation ≥5% compared to the baseline value (minimum value detected in the pre-operating room after premedication)

EtCO2 Intraoperatory Score

0 1 2 3 4

1 point is counted for each change ≥5 mmHg compared to the baseline value (minimum value detected in the operating room after induction and optimization of mechanical ventilation)

Post operatory Score

Morbidity: Modified Clavien Dindo Classification

0 1 2 3 4

- Intensive medical therapy (transfusions, parenteral nutrition, dialysis, NIV, ...)
- New surgery under general anesthesia
- New hospitalization in post-operative ICU
- Multiorgan dysfunction

Breathing: Modified Hacor Score

0 1 2 3 4

- HR ≥120/min or RR ≥35/min
- Ph ≤7.3
- GCS ≤10
- PaO2/FiO2 ≤150

Hepato-renal status: Modified Child-Pugh Score & MELD

0 1 2 3 4

- Total Bilirubin ≥ 51.3 umol/L
- Albumin ≤ 28 g/L
- INR ≥2
- Creatinine ≥ 0.18 mmol/L

Sepsis: Modified WSES Sepsis Score

0 1 2 3 4

- Severe sepsis with acute organ dysfunction
- Septic shock with drug support
- Hospital infection
- Immunosuppression: Glucocorticoids, immunosuppressive agents, chemotherapy, leukemia, lymphomas, viral diseases)

B

PERIDIA score calculator

Insert 0=false 1=true

Pre operative assessment		Tot	Intra operative assessment		Tot	Post operative assessment		Tot
Frailty assessment			**HR assessment**			**Morbidity assessment**		
A) ≥2 hospitalizations in the last year			A) a change ≥10 b / min compared to baseline value			A) Intensive medical therapy		
B) Need for help with daily activities			B) a change ≥10 b / min compared to baseline value			B) New surgery under general anesthesia		
C) Sadness, depression, psychosis, neurodegen. dis.			C) a change ≥10 b / min compared to baseline value			C) New hospitalization in post-operative ICU		
D) No family members or care giver			D) a change ≥10 b / min compared to baseline value			D) Multiorgan dysfunction		
Frailty value (A+B+C+D)		0	**HR value** (A+B+C+D)			**Morbidity value** (A+B+C+D)		0
Nutritional Status assessment			**MAP assessment**			**Breathing assessment**		
A) Weight loss in the last 3 months ≥4 kg			A) a change ≥20 mmHg compared to baseline value			A) HR ≥120/min or RR ≥35/min		
B) Sedentarism (transition from bed to chair)			B) a change ≥20 mmHg compared to baseline value			B) Ph ≤7.3		
C) Previous major surgery (thoracic, abdominal)			C) a change ≥20 mmHg compared to baseline value			C) GCS ≤10		
D) BMI ≤21 or ≥30			D) a change ≥20 mmHg compared to baseline value			D) PaO2/FiO2 ≤150		
Nutritional Status value (A+B+C+D)		0	**MAP value** (A+B+C+D)		0	**Breathing value** (A+B+C+D)		0
Comorbidity assessment			**SpO_2 assessment**			**Hepato-Renal Status assessment**		
A) Age ≥70			A) a change ≥5% compared to baseline value			A) Total Bilirubin ≥51.3 umol/L		
B) SpO2 ≤90 in air or need for oxygen therapy or NIV			B) a change ≥5% compared to baseline value			B) Albumin ≤ 28 g/L		
C) Hb ≤6.21 mmol/L			C) a change ≥5% compared to baseline value			C) INR ≥2		
D) AMI/Heart fail/Lung inf/DM org dam/Liver dam/M			D) a change ≥5% compared to baseline value			D) Creatinine ≥ 0.18 mmol/L		
Comorbidity value (A+B+C+D)		0	**SpO_2 value** (A+B+C+D)		0	**Hepato-Renal Status value** (A+B+C+D)		0
Anaesthesiology Rescue assessment			**$EtCO_2$ assessment**			**Sepsis assessment**		
1 point for ASA II			A) a change ≥5 mmHg compared to baseline value			A) Severe sepsis with acute organ dysfunction		
2 point for ASA III			B) a change ≥5 mmHg compared to baseline value			B) Septic shock with drug support		
3 point for ASA IV			C) a change ≥5 mmHg compared to baseline value			C) Hospital infection		
4 point for ASA V			D) a change ≥5 mmHg compared to baseline value			D) Immunosuppression		
Anaesthesiology Rescue value (insert value 1-4)			**$EtCO_2$ value** (A+B+C+D)		0	**Sepsis value** (A+B+C+D)		0
Pre operative value (Frailty + Nutritional St. + Comorbidity + Anaesth. Resc.)		0	**Intra operative value** (HR + MAP + SpO_2 + $EtCO_2$)		0	**Post operative value** (Morbidity + Breathing + Hepato-Renal St. + Sepsis)		0

TOT 0

PERIDIA TOT = {Pre operatory value + Intra operatory value + Post operatory value}

$$PERIDIA\ TOT = \{[\sum Frailty_{A\to D} + \sum Nutritional\ St._{A\to D} + \sum Comorbidity_{A\to D} + Anaesth.Resc. + \sum HR_{A\to D} + \sum MAP_{A\to D} + \sum SpO_{2A\to D} + \sum EtCO_{2A\to D} + \sum Morbidity_{A\to D} + \sum Breathing_{A\to D} + \sum Hepato\text{-}Renal\ St._{A\to D} + \sum Sepsis_{A\to D}]\}$$

FIGURE 1 | Continued

FIGURE 1 | **(A)** PERIDIA SCORE, **(B)** PERIDIA Calculator. The PERIDIA score is divided into three scores (pre-operatory score, intra-operative score, post-operative score), each of which expressing a score from 0 to 16 for a maximum of 48 points. Pre-operatory score concerns the pre-operatory period and supports the anesthetic and surgical evaluations of pre-hospitalization. It consists of four scores, to each of which a result from 0 to 4 points can be assigned. Pre-operatory score estimates Frailty with the Modified Edmonton Frail Scale, Nutritional Status with the Modified Mini Nutritional Assessment Short Form, Comorbidity with the Modified Charlson Age Morbidity Index, ARISCAT Index, and Lee's Revised cardiac Risk Index, Anaesthesiology Rescue with the ASA score. With regard to the Modified Edmonton Frail Scale, a point is assigned to the verification of each of the following conditions: ≥2 hospitalizations in the last year; need for help with daily activities; sadness, depression, psychosis, or neurodegenerative disease in treatment; absence of family members or caregivers. Regarding the Modified Mini Nutritional Assessment Short Form, a point is assigned to the verification of each of the following conditions: weight loss in the last 3 months ≥4 kg; sedentarism (transition from bed to chair); previous major surgery (thoracic, abdominal); BMI ≤21 or ≥30. About the Modified Charlson Age Morbidity Index, ARISCAT Index, and Lee's Revised cardiac Risk Index, one point is assigned for each of the following conditions: age ≥70 years; SpO2 ≤90% in air environment or need for oxygen therapy or non-invasive ventilation; hemoglobinemia ≤6.21 mmol/L; AMI or heart failure or lung infections or diabetes with organ damage or liver injury or metastatic solid tumor in the last year. Finally, the ASA score is taken from the anesthetic assessment pre-hospitalization and in any case is assigned on the basis of the following criteria: 1 point for no organic, biochemical, or psychiatric alteration; 2 points for mild systemic disease related or not to the reason for the surgery; 3 points for severe but not disabling systemic pathology related or not to the reason for the surgery; 4 points for severe systemic disease with a severe prognosis that affects survival regardless of surgery. Intra-operative score assesses the variation of four vital parameters commonly used during the monitoring of general anesthesia (heart rate or HR, mean arterial pressure or MAP, saturation or SpO2, capnometry or EtCO2). So 1 point was assigned in the HR Intra-operatory Score for each change (±) ≥10 b/min with respect to the baseline value (minimum value detected after premedication); 1 point was assigned in the MAP Intra-operatory Score for each change (±) ≥20 mmHg with respect to the baseline value (minimum value detected after premedication); 1 point was assigned in the SpO2 Intra-operatory Score for each change ≥5% from the baseline value (minimum value detected after premedication), and 1 point was assigned in the EtCO2 Intra-operatory Score for each variation (±) ≥5 mmHg compared to the baseline value (minimum value detected after induction and optimization of mechanical ventilation). Post-operative score concerns the period of hospitalization in the ICU. It consists of four scores, to each of which a result from 0 to 4 points can be assigned. Post-operatory score estimates Morbidity with the Modified Clavien Dindo Classification, Breathing with the Modified Hacor Score, Hepato-Renal status with the Modified Child-Pugh Score & MELD, Sepsis with the Modified WSES Sepsis Score. Regarding the Modified Clavien Dindo Classification, a point was assigned to the occurrence of each of the following conditions: intensive medical therapy (transfusions, parenteral nutrition, dialysis, NIV, …); new surgical evaluation under general anesthesia; further hospitalization in post-operatory ICU; multiorgan dysfunction. About the Modified Hacor Score, a point was assigned to the occurrence of each of the following conditions: HR ≥120/min or RR ≥35/min; pH ≤7.3; GCS ≤10; PaO2/FiO2 ≤150. Regarding the Modified Child-Pugh Score & MELD, a point was assigned to the occurrence of each of the following conditions: Bilirubin tot ≥51.3 umol/L; Albumin ≤28 g/L; INR ≥2; Creatinine ≥0.18 mmol/L. With reference to the Modified WSES Sepsis Score, a point was assigned to the occurrence of each of the following conditions: severe sepsis with acute organ dysfunction; septic shock with vasopressors; nosocomial infection; immune suppression: glucocorticoids, immunosuppressive agents, chemotherapy, leukemia, lymphomas, viral diseases. ARISCAT Index, Assess Respiratory Risk in Surgical Patients in Catalogna; ASA score, American Society of Anesthesiologists score; BMI, Body Mass Index; EtCO2, End Tidal Carbon dioxide; GCS, Glasgow Coma Scale; HR, Heart Rate; INR, International Normalized Ratio; MAP, Mean Arterial Pressure; MELD, Model for End-Stage Liver Disease; NIV, Non-Invasive Ventilation; PERIDIA score, a new score used to the standardization of peri-operatory assessments in cancer patients undergoing peridiaphragmatic thoraco-abdominal surgery, particularly in the case of multiorgan localization; SPO2, Percentage Saturation of hemoglobin with Oxygen; WSES score, World Society of Emergency Surgery Sepsis score.

For the intra-operative period, the multidisciplinary technical team aimed at matching the main phases of the surgery (T0: pre-treatment after pre-dressing; T1: post-induction; T2: post-cutting; T3: post-retractor or pneumo; T4: post-surgery; T5: post-anesthesia) with the variation of four vital parameters commonly used during the monitoring of general anesthesia (heart rate or HR, mean arterial pressure or MAP, saturation or SpO2, capnometry or EtCO2).

However, due to the lack of punctual clinical parameters in intra-operatory period, in the present case report, we had to adapt these evaluations, regardless of the surgical phase. Therefore, 1 point was assigned in the HR Intra-operatory Score for each change (±) ≥10 b/min with respect to the baseline value (minimum value detected after premedication); 1 point was assigned in the MAP Intra-operatory Score for each change (±) ≥20 mmHg with respect to the baseline value (minimum value detected after premedication); 1 point was assigned in the SpO2 Intra-operatory Score for each change ≥5% from the baseline value (minimum value detected after premedication), and 1 point was assigned in the EtCO2 Intra-operatory Score for each variation (±) ≥5 mmHg compared to the baseline value (minimum value detected after induction and optimization of mechanical ventilation).

The post-operative score is also based on four scores, each of which being assigned a score from 0 to 4 points. Regarding the Modified Clavien Dindo Classification, a point was assigned to the occurrence of each of the following conditions: intensive medical therapy (transfusions, parenteral nutrition, dialysis, NIV, …); new surgical evaluation under general anesthesia; further hospitalization in post-operatory ICU; multiorgan dysfunction. About the Modified Hacor Score, a point was assigned to the occurrence of each of the following conditions: HR ≥120/min or RR ≥35/min; pH ≤7.3; GCS ≤10; PaO2/FiO2 ≤150. Regarding the Modified Child-Pugh Score & MELD, a point was assigned to the occurrence of each of the following conditions: Bilirubin tot ≥51.3 umol/L; Albumin ≤28 g/L; INR ≥2; Creatinine ≥0.18 mmol/L. With reference to the Modified WSES Sepsis Score, a point was assigned to the occurrence of each of the following conditions: severe sepsis with acute organ dysfunction; septic shock with vasopressors; nosocomial infection; immune suppression: glucocorticoids, immunosuppressive agents, chemotherapy, leukemia, lymphomas, viral diseases.

RESULTS

The PERIDIA score was applied to the patient (**Figures 2**, **3A, B**). In the pre-operatory period, the score assigned 12 points to the patient due to two hospitalizations in the last year, sadness and depression, sedentary lifestyle without caregivers, weight loss in the last 3 months of 8 kg, previous major abdominal surgery, BMI

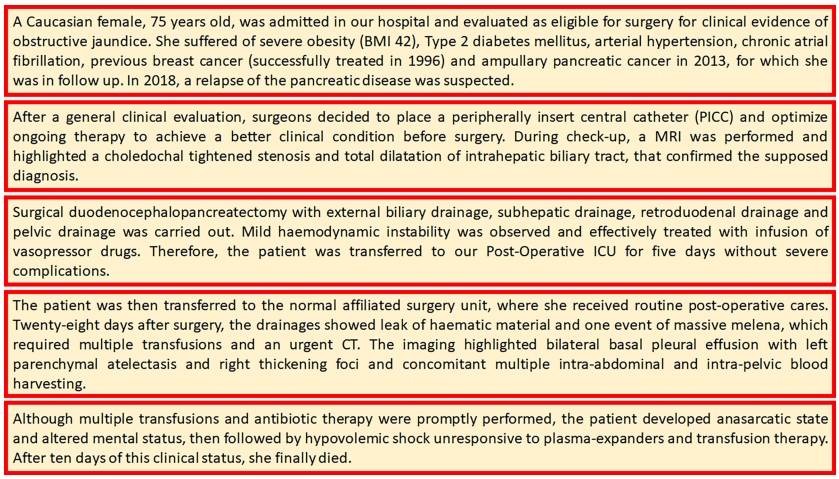

FIGURE 2 | Case Presentation.

42, age 75 years, hemoglobinemia 5.28 mmol/L, diabetes mellitus with left lower limb neuropathy and local cancer recurrence, anesthetic evaluation of ASA IV.

In the intra-operatory period, the score assigned 10 points to the patient, due to four variations of HR ≥10 b/min, four variations of MAP ≥20 mmHg, one variation of SpO2 ≥5%, one variation of EtCO2 ≥5 mmHg with respect to the baseline value, respectively.

In the post-operatory period, the score assigned 7 points to the patient due to the several transfusions and the necessity of parenteral nutrition, HR 128/min, pH 7.25, total Bilirubin 239.4 umol/L, Albumin 21 g/L, INR 2.5, previous chemotherapy.

The total PERIDIA score was 30 points. Due to the numerous adhesions related to the previous surgical procedure, the last surgery lasted 8 h; in post-operative ICU the patient stayed 5 days, while the whole hospitalization was 61 days.

DISCUSSION

After a previous cancer, the patient was affected by a relapse of a pancreatic tumor, with a poor prognosis, with local recurrence in a context of comorbidities (arrhythmia, jaundice, metabolic syndrome) that was presumably not adequately assessed for the possibility/need for surgery.

In these clinical cases, a peri-operative evaluation score able to trace the right route of treatment could provide alerts both in the pre-operative period (for example, the possibility to start a tailored prehabilitation path or a surgical procedure rather than a path of palliative care) and in the intra-operative (need to use invasive monitoring of cardiac output by catecholamines in continuous infusion) and in the post-operative, for instance for a prolonged hospitalization, the destination of a semi-intensive post-operative room, where the patient can receive a continuous monitoring of vital functions.

The multidisciplinary team assigned a 29/48 score to the patient. This value is far beyond the upper threshold we are defining as a minimum score to identify possible predictable risks, according to our first results in the ongoing retrospective PERIDIA01 study. This study is demonstrating an increase of clinical complications in patients who were assigned a one-third score with respect to the maximum (16/48). Moreover, patients with a 10/16 score within each phase of the evaluation (pre, peri, and post) more frequently develop clinical complications.

In the light of these evidence, the 29-point score assigned to our patient can be considered as predictive for the subsequent critical and fatal complications the woman faced up.

The use of a peri-operative score elaborated by a multidisciplinary team even if in retrospective evaluation also allows to formulate other considerations on the clinical course of the patient, in particular from a pharmacological point of view. The patient administered before and during hospitalization Diltiazem Hydrochloride 60 mg (1/2 tablet twice a day), Digoxin 0.125 mg (one tablet a day), Warfarin (one tablet a day), Irbersartan + Hydrochlorothiazide 150 mg +12.5 mg (one tablet a day). At the hospitalization, she showed significant extension of the INR and electrolyte alteration.

This clinical condition could derive also from pharmacological interactions. In fact, Hydrochlorothiazide can produce hypokalemia and hypomagnesemia, which increase the inhibition of Na/K ATPasi mediated by Digoxin. Furthermore, Diltiazem may cause increases in digoxin plasma levels, probably by decreasing digoxin clearance. Hypokalemia and hypomagnesemia induced by diuretics may predispose patients on digitalis treatment to arrhythmias.

During the 2 months of hospitalization, the patient received Furosemide 20 mg (twice a day). The combination with a thiazide loop diuretic drug (Hydrochlorothiazide) may produce additive or synergistic effects on diuresis and

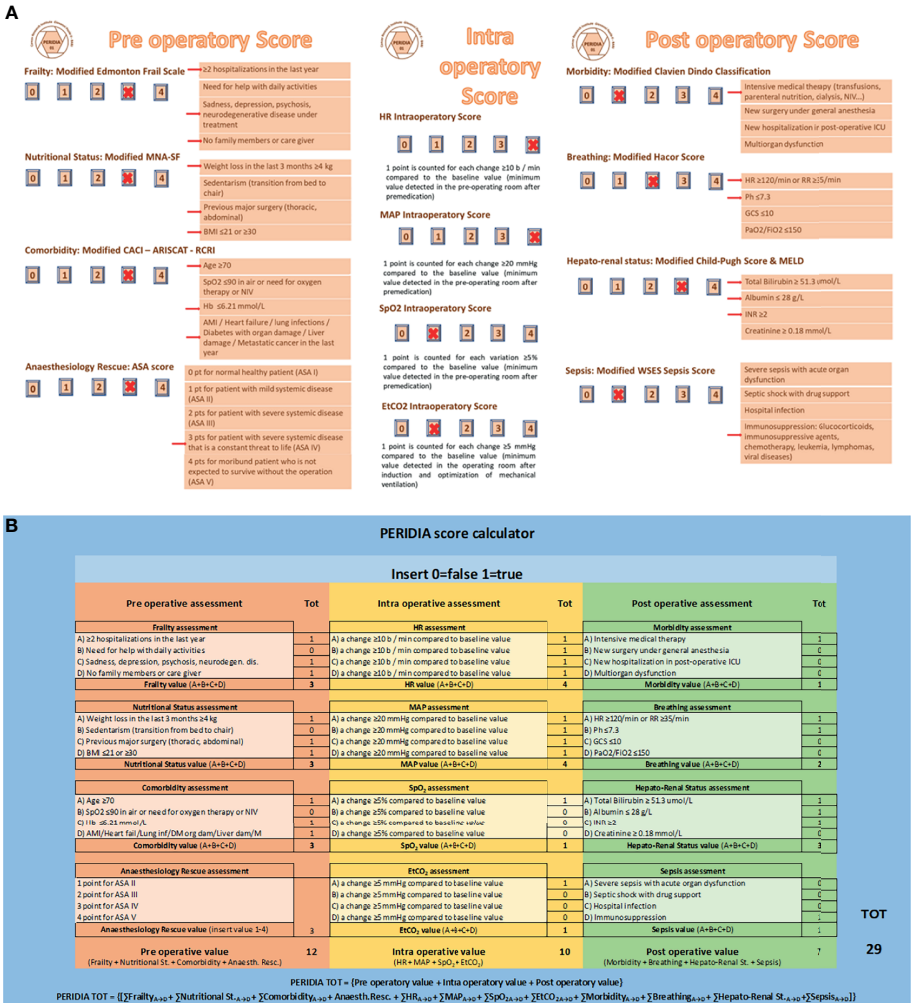

FIGURE 3 | **(A)** PERIDIA SCORE applied to the patient, **(B)** PERIDIA Calculator applied to the patient. The score assigns 12/16 points in pre-operatory phase: 3 points for Frailty (1 point due to two hospitalizations in the last year, 1 point due to sadness and depression, 1 point due to sedentary lifestyle without caregivers), 3 points for Nutritional Status (1 point due to weight loss in the last 3 months of 8 kg, 1 point due to previous major abdominal surgery, 1 point due to BMI 42), 3 points for Comorbidity (1 point due to age 75 years, 1 point due to hemoglobinemia 5.28 mmol/L, 1 point due to diabetes mellitus with left lower limb neuropathy and local cancer recurrence), 3 points for Anesthesiology Rescue (anesthetic evaluation of ASA IV). In the intra-operatory period, the score assigned 10/16 points to the patient, due to four variations of HR ≥10 b/min, four variations of MAP≥20 mmHg, one variation of SpO2 ≥5%, one variation of EtCO2 ≥5 mmHg with respect to the baseline value, respectively. In the post-operatory period (ICU phase), the score assigned 7/16 points to the patient: 1 point for Morbidity (1 point due to the several transfusions and the necessity of parenteral nutrition), 2 points for Breathing (1 point due to HR 128/min, 1 point due to pH 7.25), 3 points for Hepato-Renal Status (1 point due to total Bilirubin 239.4 umol/L, 1 point due to Albumin 21 g/L, 1 point due to INR 2.5), 1 point for Sepsis (1 point due to previous chemotherapy). The X marks indicate the score awarded. The arrows indicate the parameter whose change caused the scoring. The total of score is 29/48 point. ARISCAT Index, Assess Respiratory Risk in Surgical Patients in Catalogna; ASA score, American Society of Anesthesiologists score; BMI, Body Mass Index; EtCO2, End Tidal Carbon dioxide; GCS, Glasgow Coma Scale; HR, Heart Rate; INR, International Normalized Ratio; MAP, Mean Arterial Pressure; MELD, Model for End-Stage Liver Disease; NIV, Non-Invasive Ventilation; PERIDIA score, a new score used to the standardization of peri operatory assessments in cancer patients undergoing peridiaphragmatic thoraco-abdominal surgery, particularly in the case of multiorgan localization; SPO2, Percentage Saturation of hemoglobin with Oxygen; WSES score, World Society of Emergency Surgery Sepsis score.

excretion of electrolytes including sodium, potassium, magnesium, and chloride. This condition could explain the electrolytic alteration. Furthermore, the patient was treated with proton pump inhibitor Pantoprazole 40 mg per day, which is reported to induce hypomagnesemia in chronic use, and the risk may be further increased when combined with other medications such as furosemide. Although diuretics and digitalis glycosides are frequently and appropriately used together, diuretic-induced hypokalemia and hypomagnesemia may predispose these patients on digitalis treatment to arrhythmias. In fact, during hospitalization, cardiologists reported arrhythmic tones.

In the light of the results obtained from the application of the PERIDIA score in some patients, our multidisciplinary team

intends to continue the application of this new evaluation system retrospectively to a larger cohort of patients to provide a further scaling up in the assessment process of the peri-operative score in oncologic patients, with a particular reference also to the pharmacologic treatment to choose in each step of the care pathway (22–27).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico–IRCCS Istituto Tumori "Giovanni Paolo II"–Bari, Italy. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.733621/full#supplementary-material

REFERENCES

1. Perna S, D'Arcy FM, Bologna C, Moncaglieri F, Riva A, Morazzoni P, et al. Performance of Edmonton Frail Scale on Frailty Assessment: Its Association With Multi-Dimensional Geriatric Conditions Assessed With Specific Screening Tools. *BMC Geriatr* (2016) 17:2. doi: 10.1186/s12877-016-0382-3
2. Tegels JJW, De Maat MFG, Hulsewé KWE, Hoofwijk AGM, Stoot JHMB. Improving the Outcomes in Gastric Cancer Surgery. *World J Gastroenterol* (2014) 20(38):13692–704. doi: 10.3748/wjg.v20.i38.13692
3. Amrock LG, B S, Deiner S, M D, M S. The Implication of Frailty on Preoperative Risk Assessment. *Curr Opin Anaesthesiol* (2014) 27(3):330–5. doi: 10.1097/ACO.0000000000000065
4. Steenhagen E, van Vulpen JK, van Hillegersberg R, May AM, Siersema PD. Nutrition in Peri-Operative Esophageal Cancer Management. *Expert Rev Gastroenterol Hepatol* (2017) 11:663–72. doi: 10.1080/17474124.2017.1325320
5. Yang C-C, Fong Y, Lina L-C, Que J, Ting W-C, Change C-L, et al. Theage-Adjusted Charlson Comorbidity Index is a Better Predictor of Survival in Operated Lung Cancer Patients Than the Charlson and Elixhauser Comorbidity Indices. *Eur J Cardio Thoracic Surg* (2018) 53:235–40. doi: 10.1093/ejcts/ezx215
6. Asano T, Yamada S, Fujii T, Yabusaki N, Nakayama G, Sugimoto H, et al. The Charlson Age Comorbidity Index Predicts Prognosis in Patients With Resected Pancreatic Cancer. *Int J Surg* (2017) 169–75. doi: 10.1016/j.ijsu.2017.01.115
7. Perilli V, Aceto P, Ancona P, De Cicco R, Papanice D, Magalini S, et al. Role of Surgical Setting and Patients-Related Factors in Predicting the Occurrence of Postoperative Pulmonary Complications After Abdominal Surgery. *Eur Rev Med Pharmacol Sci* (2018) 22:547–50.
8. iPROVE Network investigators, Belda J, Ferrando C, Garutti I. The Effects of an Open-Lung Approach During One-Lung Ventilation on Postoperative Pulmonary Complications and Driving Pressure: A Descriptive, Multicenter National Study. *J Cardiothoracic Vasc Anesthesia* (2018) 32(6):P2665–72. doi: 10.1053/j.jvca.2018.03.028
9. de la Gala F, Pineiro P, Reyes A, Vara E, Olmedilla L, Cruz P, et al. Postoperative Pulmonary Complications, Pulmonary and Systemic Inflammatory Responses After Lung Resection Surgery With Prolonged One-Lung Ventilation. Randomized Controlled Trial Comparing Intravenous and Inhalational Anaesthesia. *Br J Anaesthesia* (2017) 119(4):P655–63. doi: 10.1093/bja/aex230
10. Boersma E, Kertai AMD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW, et al. Perioperative Cardiovascular Mortality in Noncardiac Surgery: Validation of the Lee Cardiac Risk Index. *Am J Med* (2005) 118(10):1134–41. doi: 10.1016/j.amjmed.2005.01.064
11. pReeh M, Metze J, Uzunoglu FG, Nentwich M, Ghadban T, Wellner U, et al. The PER (Preoperative Esophagectomy Risk) Score: A Simple Risk Score to Predict Short-Term and Long-Term Outcome in Patients With Surgically Treated Esophageal Cancer. *Medicine* (2016) 95(7):e2724. doi: 10.1097/MD.0000000000002724
12. Huang C-M, Tu R-H, Lin J-X, Zheng C-H, Li P, Xie J-W, et al. A Scoring System to Predict the Risk of Postoperative Mcomplications After Laparoscopic Gastrectomy for Gastric Cancer Based on a Large-Scale Retrospective Study. *Medicine* (2014) 94(17):e812. doi: 10.1097/MD.0000000000000812
13. Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, et al. Extended Clavien-Dindo Classification of Surgical Complications: Japan Clinical Oncology Group Postoperative Complications Criteria. *Surg Today* (2016) 46:668–85. doi: 10.1007/s00595-015-1236-x
14. Li Z, Bai B, Ji G, Li J, Zhao Q. Relationship Between Clavien–Dindo Classification and Long-Term Survival Outcomes After Curative Resection for Gastric Cancer: A Propensity Score-Matched Analysis. *Int J Surg* (2018) 60:67–73. doi: 10.1016/j.ijsu.2018.10.044
15. Wang W-G, Babu SR, Wang Li, Chen Y, Tian B-L, He H-B. Use of Clavien-Dindo Classification in Evaluating Complications Following Pancreaticoduodenectomy in 1,056 Cases: A Retrospective Analysis From One Single Institution. *Oncol Lett* (2018) 16:2023–9. doi: 10.3892/ol.2018.8798
16. Peng Y, Qi X, Guo X. Child–Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis A Systematic Review and Meta-Analysis of Observational Studies. *Medicine* (2018) 95(8):2016. doi: 10.1097/MD.0000000000002877
17. Al Abbas AI, Borrebach JD, Bellon J, Zureikat AH. Does Preoperative MELD Score Predict Adverse Outcomes Following Pancreatic Resection: An ACS NSQIP Analysis. *J Gastrointest Surg* (2019) 24:2259–68. doi: 10.1007/s11605-019-04380-0
18. Ragulin-Coyne E, PH M, Carroll JE, Smith JK, Witkowski ER, Ng SC, et al. Perioperative Mortality After Pancreatectomy: A Risk Score to Aid Decision-Making. *Surgery* (2012) 152(3):S120–7. doi: 10.1016/j.surg.2012.05.018

19. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of Heart Rate, Acidosis, Consciousness, Oxygenation, and Respiratory Rate to Predict Noninvasive Ventilation Failure in Hypoxemic Patients. *Intensive Care Med* (2017) 43 (2):192–9. doi: 10.1007/s00134-016-4601-3
20. Duan J, Wang S, Liu P, Han X, Tian Y, Gao F, et al. Early Prediction of Noninvasive Ventilation Failure in COPD Patients: Derivation, Internal Validation, and External Validation of a Simple Risk Score. *Ann Intensive Care* (2019) 9:108. doi: 10.1186/s13613-019-0614-8
21. Sartelli M, Abu-Zidan FM, Catena F, Griffiths EA, Di Saverio S, Coimbra R, et al. Global Validation of the WSES Sepsis Severity Score for Patients With Complicated Intra-Abdominal Infections: A Prospective Multicentre Study (WISS Study). *World J Emergency Surg* (2015) 10:61. doi: 10.1186/s13017-015-0055-0
22. Rodin SM, Johnson BF. Pharmacokinetic Interactions With Digoxin. *Clin Pharmacokinet* (1988) 15:227–44. doi: 10.2165/00003088-198815040-00003
23. Bloedow DC, Piepho RW, Nies AS, Gal J. Serum Binding of Diltiazem in Humans. *J ClinPharmacol* (1982) 22:201–5. doi: 10.1002/j.1552-4604.1982.tb02163.x
24. Kazierad DJ, Lalonde RL, Hoon TJ, Mirvis DM, Bottorff MB. The Effect of Diltiazem on the Disposition of Encainide and Its Active Metabolites. *Clin Pharmacol Ther* (1989) 46:668–73. doi: 10.1038/clpt.1989.203
25. Semple P, Tilstone WJ, Lawson DH. Furosemide and Urinary Digoxin Clearance. *N Engl J Med* (1975) 293:612–3. doi: 10.1056/NEJM197509182931220
26. Tilstone WJ, Semple PF, Lawson DH, Boyle JA. Effects of Furosemide on Glomerular Filtration Rate and Clearance of Practolol, Digoxin, Cephaloridine, and Gentamicin. *Clin Pharmacol Ther* (1977) 22:389–94. doi: 10.1002/cpt1977224389
27. Cohen L, Kitzes R. Magnesium Sulfate and Digitalis-Toxic Arrhythmias. *JAMA* (1983) 249:2808–10. doi: 10.1001/jama.1983.03330440046030

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Effects of Perioperative Dexmedetomidine on Immunomodulation in Uterine Cancer Surgery: A Randomized, Controlled Trial

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Objective: Dexmedetomidine has sympatholytic, anti-inflammatory, and analgesic effects and may exert anti-tumor effect by acting on α2A adrenoreceptor. We investigated whether perioperative dexmedetomidine preserves immune function in patients undergoing uterine cancer surgery.

Methods: One hundred patients were randomly assigned to the control or dexmedetomidine groups (50 patients each). Dexmedetomidine was infused at rates of 0.4 μg/kg/h intraoperatively and 0.15 μg/kg/h during the first 24 h postoperatively. The primary outcome was natural killer (NK) cell activity, which was measured preoperatively and 1, 3, and 5 days postoperatively. The inflammatory response was measured by interleukin-6, interferon-γ, and neutrophil/lymphocyte ratio, and pain scores and opioid consumption were assessed. Cancer recurrence or metastasis and death were evaluated 2 years postoperatively.

Results: NK cell activity decreased postoperatively in both groups and changes over time were not different between groups (P=0.496). Interferon-γ increased postoperatively in the dexmedetomidine group, whereas it maintained at the baseline value in the control group. Change in interferon-γ differed significantly between groups (P=0.003). Changes in interleukin-6 and neutrophil-lymphocyte ratio were comparable between groups. Both pain score with activity during the first 1 h and opioid consumption during the first 1–24 h postoperatively were lower in the dexmedetomidine group. Rates of cancer recurrence/metastasis (16.3% vs. 8.7%, P=0.227) and death within 2 years postoperatively (6.7% vs. 2.2%, P=0.318) were not different between groups.

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Conclusions: Perioperative dexmedetomidine had no favorable impacts on NK cell activity, inflammatory responses, or prognosis, whereas it increased interferon-γ and reduced early postoperative pain severity and opioid consumption in uterine cancer surgery patients.

Keywords: dexmedetomidine, immunity, interferon-γ, natural killer cell, uterine cancer

INTRODUCTION

Although surgical resection is the main and curative treatment for solid tumors, the spread of tumor cells in the blood and lymphatic system might occur by surgical manipulation (1). Surgical trauma-induced systemic stress and inflammatory responses and the use of anesthetics and opioid analgesics impair immune function (2). This perioperative immunosuppression may predispose already immunocompromised cancer patients further vulnerable to tumor growth and spread. Whether residual tumor cells adversely affect patient's outcome depends on the balance between the host's immune defenses against tumor and factors promoting tumor cell survival and growth.

Dexmedetomidine is a highly selective α2 adrenoreceptor agonist and has broad pharmacologic effects including anesthesia, analgesia, sedation, and anxiolysis (3). Perioperative dexmedetomidine attenuates stress responses and reduces pain and opioid requirement in the perioperative periods (4–6). In addition, dexmedetomidine has sympatholytic and anti-inflammatory effects (5, 7). Perioperative immunosuppression is characterized by suppressed cell-mediated immunity and excessive pro-inflammatory responses (8). Dexmedetomidine has been demonstrated to preserve natural killer (NK) cell function, which is a critical part of innate immunity, and reduce pro-inflammatory cytokines in both experimental and clinical settings (4, 7). Despite possible beneficial effects of dexmedetomidine on immunity, its immunomodulatory role in cancer surgery has not been established.

Gynecologic cancer contributes significantly to the morbidity and mortality of females worldwide (9), and cervical and endometrial cancers are the most frequent gynecologic malignancies (10). In this randomized, controlled trial, we investigated the effect of dexmedetomidine on immunomodulation in women undergoing uterine cancer surgery. Based on the immunomodulatory effects of dexmedetomidine, we hypothesized that dexmedetomidine would attenuate the immunosuppression during the critical perioperative period.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital, Yonsei University Health System, Seoul, Korea (#4-2015-0453) and registered at ClinicalTrials.gov (NCT02896413). Inclusion criteria were women 20–65 years old, who had American Society of Anesthesiologists (ASA) physical status classification of I–III and underwent elective surgery for uterine cancer. Exclusion criteria were renal or hepatic impairment, immunosuppressive therapy, immune system disorders, or cancer metastasis. Informed consent was obtained from all patients before participating in this study.

Investigation

In total, 100 patients were enrolled and randomly assigned into one of the study groups (50 patients each) using a computer-generated random numbers table. In the dexmedetomidine group (DEX group), dexmedetomidine was infused at 0.4 μg/kg/h from anesthetic induction to the end of surgery and continued at 0.15 μg/kg/h for the first 24 h postoperatively. The dose of dexmedetomidine was determined based on that of previous studies showing no hemodynamic instability or deep sedation (4, 11). In the Control group, saline was infused at the same rates. One researcher prepared dexmedetomidine (Precedex; Hospira Inc, Lake Forest, IL, USA) or saline in identical 50-mL syringes labelled as "study drug" for double-blind purposes. Patients, surgeons, and anesthesiologists were blinded to the group assignment, which was revealed after participants were discharged from the hospital.

Anesthetic Management

After monitors including electrocardiography, pulse oximetry and blood pressure monitor were applied, anesthesia was induced with propofol 1–2 m/kg and remifentanil 1–2 μg/kg. Rocuronium 0.6 mg/kg was administered to facilitate endotracheal intubation. Anesthesia was maintained with 4%–7% desflurane and remifentanil 0.05–0.1 μg/kg/min to maintain the mean arterial pressure within 20% of the preoperative value and the bispectral index between 40 and 60. Body temperature was maintained at 36.5 ± 0.5°C throughout surgery. At 15 min before the end of surgery, all patients received fentanyl 50 μg and ramosetron 0.3 mg for prevention of postoperative pain and nausea/vomiting. At the end of surgery, patients received neostigmine 1 mg and glycopyrrolate 0.2 mg for reversal of residual neuromuscular blockade. For postoperative analgesia, all patients received intravenous patient-controlled analgesia (IV-PCA) consisting of fentanyl 15 μg/kg and ramosetron 0.3 mg (total volume of 100 mL, basal rate of 2 mL/h, bolus of 0.5 mL, and lockout time of 15 min). Intravenous ketorolac 30 mg was administered three times per day on the day of surgery. Additional analgesics were available for patients having an 11-point numeric pain rating scale score ≥4 or requesting supplemental analgesics: intravenous fentanyl 50 μg or pethidine 25 mg in the post-anesthesia care unit and pethidine 25 mg or tramadol 50 mg in the postoperative ward. Drugs possessing anti-inflammatory effects (e.g., lidocaine, dexamethasone) were not administered during the first 48 h postoperatively. An investigator unaware of the group assignment evaluated possible dexmedetomidine-related adverse effects (e.g., deep sedation, hypotension, bradycardia).

Outcome Measures

The primary outcome measure was NK cell activity, which was measured preoperatively and on postoperative days (PODs) 1, 3, and 5. NK cell activity was analysed using the NK Vue kit (ATGen, Sungnam, Korea). One mL of whole blood was drawn into a NK Vue tube containing Promoca (a cytokine that stimulates NK cell activity) and RPMI 1640 media and then incubated at 37°C for 24 h. This selected stimulatory cytokine and incubation period allows NK cells to secrete interferon-γ (IFN-γ) preferentially over other immune cells, and the supernatant IFN-γ level measured by NK Vue ELISA may be an indicator of NK cell activity. We calculated the mean IFN-γ value from duplicate readings.

Other outcome measures included inflammatory responses assessed by interleukin-6 (IL-6), IFN-γ, and neutrophil-lymphocyte-ratio (NLR), which were measured preoperatively and on POD 1, 3, and 5. Pain severity and opioid requirement were assessed 1, 24, and 48 h postoperatively. Pain severity was evaluated using an 11-point numerical scale (0 = no pain, 10 = worst symptom). The opioid requirement was assessed by IV-PCA fentanyl dose and additional opioid consumption (morphine equivalent dose). Rates of cancer recurrence or metastasis and death were assessed 2 years after surgery.

Statistical Analysis

The sample size was calculated based on a previous study showing a reduction of NK cell activity on POD 1 (compared with baseline) of 83.1 ± 25.2% (12). Forty-eight patients in each group would be required to detect a 20% relative decrease in NK cell activity reduction with 90% probability (ß=0.1) at a significance level (α) of 0.05. Assuming a 5% dropout rate, the final sample size was 50 patients per group.

Continuous variables were analysed using the independent *t*-test or Mann-Whitney U test after testing for normality of distribution using the Kolmogorov-Smirnov test and expressed as mean ± SD or median (interquartile range). Categorical variables were analysed using χ^2 or Fisher exact tests and expressed as absolute number (percentage). Variables measured repeatedly, such as NK cell activity, INF-γ, IL-6, and NLR, were analysed using a linear mixed model, with patient indicator as the random effect and group, time, and group-by-time as the fixed effects, after log-transformed for normality of distribution. *Post-hoc* analyses with Bonferroni correction were performed when variables measured repeatedly showed significant differences between groups. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 25.0, IBM Corp., Armonk, NY, USA).

RESULTS

Of 100 patients enrolled, 9 patients were eliminated. One patient in the Control group withdrew consent for participation and 4 patients did not meet the study protocol (they were anesthetized with propofol or sevoflurane instead of desflurane). The remaining 91 patients completed the study without any complications (**Figure 1** and **Table 1**).

Natural Killer Cell Activity

NK cell activity before surgery was comparable between groups (*P*=0.113) and it decreased significantly below baseline after surgery in both groups. Linear mixed model analysis showed that the perioperative change of NK cell activity over time was not different between groups (*P*=0.697) (**Figure 2**).

Inflammatory Responses Measured by IFN-γ, IL-6, and NLR

IFN-γ level before surgery was comparable between groups (*P*=0.777). Compared to the baseline, IFN-γ level increased after surgery and was higher on PODs 3 and 5 in the DEX group, whereas it was maintained in the Control group. The change of IFN-γ over time was statistically significant between groups (*P*=0.010). IFN-γ level on POD 3 was higher in the DEX group compared to the Control group.

IL-6 level before surgery was lower in the DEX group than in the Control group (*P*=0.002). In both groups, IL-6 increased after surgery, peaking on POD 1. Compared to the baseline, IL-6 level was higher on PODs 1, 3, and 5 in the DEX group and on POD 1 in the Control group. The change of IL-6 over time was not significant between groups (*P*=0.117).

NLR before surgery was similar between groups. It increased after surgery and was higher than baseline on PODs 1 and 3 in both groups. The change of NLR was not different between groups (*P*=0.494) (**Figure 3**).

Pain Score and Opioid Consumption

Pain score during activity (sitting up) 1 h postoperatively was lower in the DEX group than in the Control group (3 [3–3] vs. 3 [3–5], *P*=0.016). At other times, pain scores were not different between groups. Fentanyl IV-PCA dosage during the first 48 h postoperatively was comparable between groups. Additional opioid consumption 1–24 h postoperatively was lower in the DEX group than in the Control group (3.3 [3.3–5.5] mg vs. 8.3 [5.0–10.8] mg, *P*=0.031). At other times, additional opioid consumption (converted to morphine equivalent) was similar between groups (**Table 2**).

Prognosis

Four patients (8.7%) in DEX group and 7 patients (16.3%) in the Control group had cancer recurrence and/or metastasis during the 2-year follow-up period (*P*=0.277). Death occurred in 1 patient (2.2%) in the DEX group (due to cancer recurrence with lung metastasis) and 3 patients (6.7%) in the Control group (due to cancer recurrence in 1 patient and cancer recurrence with lung metastasis in 2 patients) (**Table 3**).

DISCUSSION

Main Finding

Dexmedetomidine administration in patients undergoing uterine cancer surgery did not demonstrate a favorable impact on immunity in terms of perioperative changes of NK cell activity, IL-6, and NLR. However, dexmedetomidine was associated with higher IFN-γ postoperatively and reduced both pain severity and

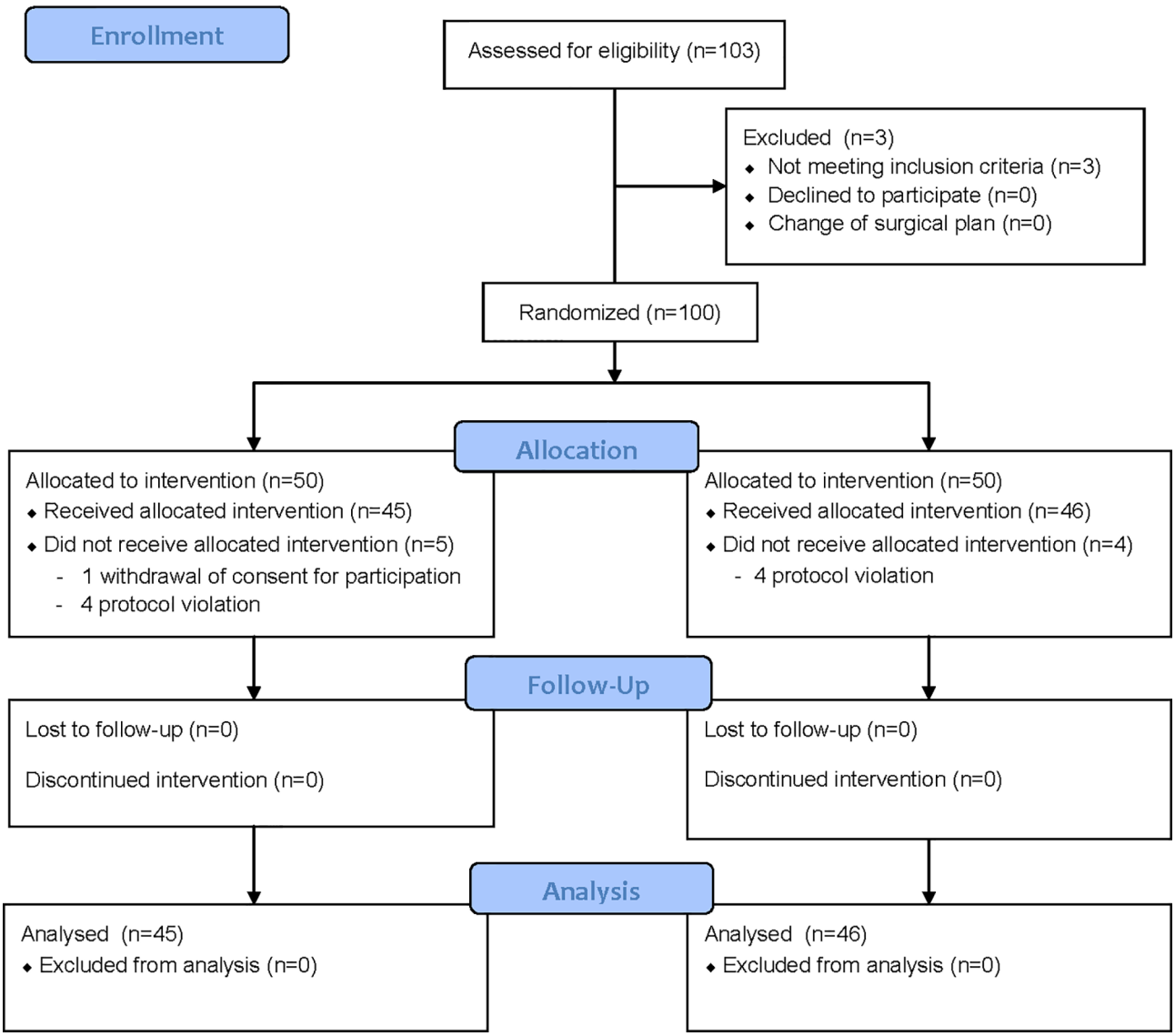

FIGURE 1 | Consort diagram.

opioid requirement early postoperatively. Although statistically insignificant, rates of cancer recurrence/metastasis (8.7 vs. 16.3%) and death (2.2 vs. 6.7%) within 2 years after surgery were much lower in the dexmedetomidine group.

Immunomodulation Effects of Dexmedetomidine

Major oncologic surgeries with extensive resection impair immunity, by causing sympathetic hyperactivation and excessive inflammation (13). It is important to carefully select anesthetics and analgesics not to aggravate perioperative immunosuppression. Theoretically, dexmedetomidine has beneficial effects on immunomodulation. Dexmedetomidine reduces surgical stress and inflammatory responses and attenuates the releases of catecholamines, cortisol, and pro-inflammatory cytokines (3). It also has analgesic and opioid-sparing effects and reduced postoperative pain and opioid consumption in major surgery, including cancer surgery (6, 14). A recent meta-analysis concluded

TABLE 1 | Patient characteristics and operation details.

Variables	Control group (n = 45)	DEX group (n = 46)	*P* value
age (years)	52.2 (8.2)	51.4 (9.6)	0.641
body mass index (kg/m)	25.2 (3.9)	23.8 (3.4)	0.067
diabetes mellitus	8 (17.8%)	7 (15.2%)	0.742
ASA class I/II/III	21/13/11	24/17/4	0.135
cancer type			
cervix	9 (20.0%)	16 (34.8%)	0.201
endometrium	33 (73.3%)	29 (63.0%)	
myosarcoma	3 (6.7%)	1 (2.2%)	
operation			
total hysterectomy	14 (31.1%)	8 (17.4%)	
total hysterectomy with salpingo-oophorectomy	19 (42.2%)	20 (43.5%)	0.240
radical hysterectomy	12 (26.7%)	18 (39.1%)	
lymph node sampling	7 (15.6%)	5 (10.9%)	0.509
Cancer (FIGO) stage I/II/III/IV;	35/1/6/3	41/3/2/0	0.091
Preoperative neoadjuvant therapy	0	0	
Postoperative chemotherapy	16 (35.6%)	9 (19.6%)	0.088
Postoperative radiotherapy	15 (33.3%)	12 (26.1%)	0.449
Postoperative hormone therapy	0	0	
duration of operation (min)	194.3 (82.0)	175.2 (60.8)	0.211
duration of anesthesia (min)	230.1 (85.0)	209.0 (62.0)	0.180
propofol (mg/kg)	1.4 (0.3)	1.4 (0.2)	0.477
remifentanil (μg/kg/min)	0.06 (0.02)	0.05 (0.02)	0.004
bleeding (ml)	50 (20–100)	50 (30–100)	0.913
patients receiving erythrocyte transfusion	3 (6.7%)	2 (4.3%)	0.628

Values are mean (standard deviation), number (percent), or median (interquartile range). ASA class, American Society of Anesthesiologists physical status classification; FIGO staging, International Federation of Gynecology and Obstetrics staging.

that dexmedetomidine preserves immune function of surgical patients, decreases postoperative complications, and improves clinical outcomes (15). In addition, recent evidence indicates that α2A adrenoreceptors are involved in the progression of several malignancies, including breast, hepatocellular, and cervical cancers (16–18). α2A adrenoreceptor expression was significantly downregulated, which was associated with poor prognosis in cervical cancer patients (18). α2A adrenoreceptors suppressed cell proliferation, migration, and invasion and promote cell senescence and apoptosis, suggesting that this receptor might be a tumor-suppressor protein in cervical cancer (18). Thus, as a highly selective and potent α2A adrenoreceptor agonist, dexmedetomidine may be expected to exert beneficial immune effects in cervical cancer patients.

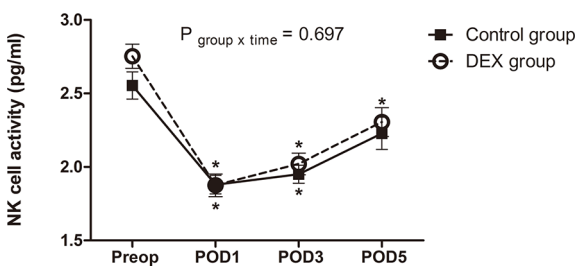

FIGURE 2 | The change of natural killer cell activity. The perioperative change in natural killer cell activity was similar between groups ($P = 0.697$). Data was analyzed using a linear mixed model after log-transformation for normality of distribution. NK cell, natural killer cell; Preop, preoperatively; POD, postoperative day; DEX group, dexmedetomidine group; *$P < 0.05$ compared to preoperatively.

Natural Killer Cell Effects

Perioperative immune dysfunction includes profound suppression of cell-mediated immunity, expressed as a decrease in the number and activity of immunocompetent cells such as NK and T cells (8). NK cells are a critical component of innate immunity and the main defence against cancer cell spread (19). A decrease in NK cell activity was associated with increased risk of mortality in patients undergoing cancer surgery (1). Adrenaline receptors are present in immune cells, and adrenergic mechanisms play an important role in regulating innate immunity (20). Cell-intrinsic adrenergic signalling is required for NK cells to exhibit optimal adaptive features during their responses against pathogens (21). Dexmedetomidine may affect NK cell activity by reducing the stress responses through sympatholytic action (3) and affecting α2 adrenoreceptors expressed in NK cells themselves. Few studies have examined the effects of dexmedetomidine on NK cells in cancer surgery patients. Dexmedetomidine attenuated the decrease in number of NK cells in patients undergoing radical mastectomy or brain neoplasm surgery (22, 23). Whereas previous studies measured NK cell number, we measured NK cell activity as an activity rather than a number should be a more reliable indicator of NK cell function. In the present study, dexmedetomidine did not attenuate postoperative suppression of NK cell activity in patients undergoing uterine cancer surgery. Further studies are necessary to clarify the effects of dexmedetomidine on NK cell function by measuring both number and activity.

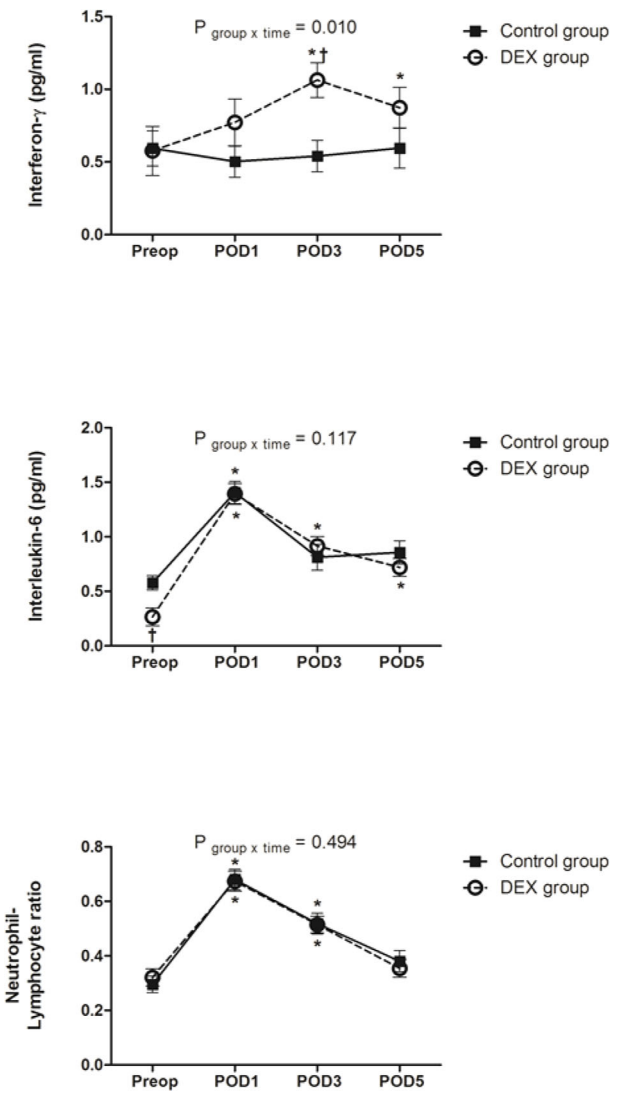

FIGURE 3 | The change of interferon-γ, interleukin-6, and neutrophil/lymphocyte ratio. Change in interferon-γ over time was significantly different between groups ($P = 0.010$), whereas changes in interleukin-6 and neutrophil/lymphocyte ratio were similar between two groups. Data was analyzed using a linear mixed model after log-transformation for normality of distribution. Preop, preoperatively; POD, postoperative day; DEX group, dexmedetomidine group; $^{*}P < 0.05$ compared to preoperatively; $^{\dagger}P < 0.05$ compared to the Control group.

Inflammation Effects

Exaggerated inflammatory responses with excessive production of proinflammatory cytokines induced by surgical trauma also contribute to immune dysfunction (8). Dexmedetomidine modulates cytokine production by macrophages and monocytes and activates cholinergic anti-inflammatory pathways by stimulating α2 adrenoreceptors. Dexmedetomidine has been well demonstrated to exert anti-inflammatory properties and reduce the release of proinflammatory cytokines, such as IL-6, tumor necrosis factor-α, and C-reactive protein, in major surgery (4, 14). Contrary to the findings that dexmedetomidine attenuated the early postoperative increase in IL-6 after radical gastric or colon cancer surgery (5, 14), there was no difference in the changes of IL-6 between our study groups. These discrepant results may be attributed to the time points of IL-6 measurement, which were measured later in our study (PODs 1, 3, and 5) than in previous studies (at the end of surgery and 24 h postoperatively). In patients undergoing gastric cancer surgery, IL-6 at 48 h after surgery did not differ between control and dexmedetomidine groups (14).

Interestingly, dexmedetomidine was associated with a higher IFN-γ level postoperatively. IFN-γ is produced by activated T cells and NK cells in response to immune stimuli and enhances cellular immune immunity (24). It exerts both anti- and pro-tumorigenic effects. IFN-γ signalling inhibits tumor growth by inducing tumor cell apoptosis and necrosis, producing tumor ischemia, and activating antigen-presenting and effector cells, while inhibiting suppressive immune cells (25, 26). On the other hand, IFN-γ exerts feedback inhibitory effects by suppressing over-activation of the immune system, which is related to immune escape from the tumor microenvironment and contributes to tumor growth (25). IFN-γ-producing capability was impaired in patients with invasive cervical cancer (27). IFN-γ genetic polymorphisms increased the risk of cervical cancer (28), and low levels of intra-tumoral IFN-γ mRNA was associated with poor prognosis (29). IFN-γ inhibits the proliferation of endometrial carcinoma cells (30). In the present study, dexmedetomidine significantly increased IFN-γ levels, which was not accompanied by a favorable impact on NK cell activity. Our finding is in line with a previous study reporting no clear association between IFN-γ gene expression and NK cell infiltration in invasive cervical carcinoma (29). Although tumor-infiltrating NK cells and T cells are the main sources of IFN-γ, several factors also regulate IFN-γ expression, including lactic acidosis, epigenetic modifications, and microRNA-155 (25). Further investigations are required to determine whether dexmedetomidine-induced increases in IFN-γ have beneficial effects on clinical outcomes in cancer surgery.

Pain Effects

Pain suppresses NK cell activity directly and indirectly by activating the sympathetic nervous system and increasing the secretion of catecholamine (31, 32). Although opioid is essential for analgesia after cancer surgery, it suppresses immunity by acting on the μ-opioid receptor expressed in immune cells and indirectly *via* the hypothalamic-pituitary-adrenal axis (33, 34). Based on these theoretical basis, dexmedetomidine may help preserve immune function by reducing pain and opioid requirement and suppressing sympathetic activation (3). In the present study, dexmedetomidine reduced both postoperative pain and opioid consumption in the early postoperative period. Pain severity with activity during the first 1 h and additional opioid consumption during the first 1–24 h after surgery were lower in the DEX group.

Limitations

This study has several limitations. First, different types of uterine cancer were included, which might have influenced the immune

TABLE 2 | Pain scores and additional analgesic requirements.

Variable/ Time points	Control group (n = 45)	DEX group (n = 46)	*P* value
Pain score (resting/ activity)			
at 1 h after surgery	3 (3–3)/ 3 (3–5)	3 (2–3)/ 3 (3–3)	0.339/ 0.016
at 24 h after surgery	2 (0–3)/ 4 (2–5)	2 (0–4)/ 3 (2–5)	0.888/ 0.629
at 48 h after surgery	2 (1–3)/ 3 (2–5)	2 (0–3)/ 3 (2–5)	0.493/ 0.553
Fentanyl administered via intravenous patient-controlled analgesia (μg)			
0–24 h after surgery	462.8 (157.8)	402.2 (148.8)	0.064
24–48 h after surgery	296.6 (188.7)	303.9 (202.2)	0.860
Additional opioid analgesics requirement (morphine equivalent dose, mg)			
0–1 h after surgery	4.0 (3.2–5.0) (13)*	4.0 (3.0–4.0) (7)*	0.304 (0.102)
1–24 h after surgery	8.3 (5.0–10.8) (13)*	3.3 (3.3–5.4) (18)*	0.031 (0.303)
24–48 h after surgery	5.0 (3.3–10.0) (12)*	5.0 (5.0–8.3) (20)*	0.744 (0.093)

*Values are median (interquartile range), mean (standard deviation), or number. Pain score, a numerical pain intensity scale (0 = no pain, 10 = the worst pain); *, number of patients receiving additional opioids.*

TABLE 3 | Prognosis.

Time points	Control group (n = 45)	Dex group (n = 46)	*P* value
Recurrence and/or Metastasis			
6 months after surgery	1 (2.2%)	0	0.309
1 year after surgery	6 (13.3%)	3 (6.5%)	0.276
2 years after surgery	7 (16.3%)	4 (8.7%)	0.277
Death			
6 months after surgery	0	0	
1 year after surgery	0	0	
2 years after surgery	3 (6.7%)	1 (2.2%)	0.318

Values are number (percent).

and inflammatory responses and prognosis, although the cancer types were comparable between the groups. Second, intraoperative remifentanil concentration was higher in the Control group, and thus its potential effects on immunity cannot be excluded. However, remifentanil in clinically relevant doses did not impair NK cell function (35). Third, rates of cancer recurrence/metastasis (16.3% vs. 8.7%) and death within 2 years after surgery (6.7% vs. 2.2%) were 2 times higher in the Control group than in the DEX group, but there was no statistical difference. As the sample size might have been insufficient to detect differences in these secondary outcomes, the association between dexmedetomidine and recurrence/ metastasis cannot be concluded from our results. To clarify the effect of dexmedetomidine on cancer prognosis, further study with this as a primary outcome is needed.

CONCLUSION

Perioperative administration of dexmedetomidine did not preserve NK cell activity in patients undergoing uterine cancer surgery. It did not affect the inflammatory responses, cancer recurrence/metastasis rate, and mortality. However, dexmedetomidine had favourable effects of increasing IFN-γ and reducing early postoperative pain and opioid consumption.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital, Yonsei University Health System, Seoul, Korea (#4-2015-0453) and registered at ClinicalTrials.gov (NCT02896413). The patients/ participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC: Conceptualization, Funding acquisition, Investigation, Data curation, Formal analysis, Writing- original draft. KS: Investigation, Data curation, Formal analysis. M-YK: Investigation, Data curation, Formal analysis. SK and YY: Conceptualization, Supervision, Writing - review & editing. JC, MK, SK, and YY: Agreement to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.749003/full#supplementary-material

REFERENCES

1. Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative Immunosuppression in Cancer Patients. *J Environ Pathol Toxicol Oncol* (2003) 22:139–46. doi: 10.1615/JEnvPathToxOncol.v22.i2.70
2. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of Perioperative Anaesthetic and Analgesic Interventions on Oncological Outcomes: A Narrative Review. *Br J Anaesth* (2019) 123:135–50. doi: 10.1016/j.bja.2019.04.062
3. Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care* (2001) 7:221–6. doi: 10.1097/00075198-200108000-00002
4. Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative Dexmedetomidine Attenuates Stress Responses in Patients Undergoing Major Spine Surgery. *Minerva Anestesiol* (2019) 85:468–77. doi: 10.23736/S0375-9393.18.12992-0
5. Wang K, Li C. Effects of Dexmedetomidine on Inflammatory Factors, T Lymphocyte Subsets and Expression of NF-kappaB in Peripheral Blood Mononuclear Cells in Patients Receiving Radical Surgery of Colon Carcinoma. *Oncol Lett* (2018) 15:7153–7. doi: 10.3892/ol.2018.8205
6. Naik BI, Nemergut EC, Kazemi A, Fernández L, Cederholm SK, McMurry TL, et al. The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery. *Anesth Analg* (2016) 122:1646–53. doi: 10.1213/ANE.0000000000001226
7. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and Time-Related Effects of Dexmedetomidine on Mortality and Inflammatory Responses to Endotoxin-Induced Shock in Rats. *J Anesth* (2008) 22:221–8. doi: 10.1007/s00540-008-0611-9
8. Ni Choileain N, Redmond HP. Cell Response to Surgery. *Arch Surg* (2006) 141:1132–40. doi: 10.1001/archsurg.141.11.1132
9. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. *JAMA Oncol* (2015) 1:505–27. doi: 10.1001/jamaoncol.2015.0735
10. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68:394–424. doi: 10.3322/caac.21492
11. Kweon DE, Koo Y, Lee S, Chung K, Ahn S, Park C. Postoperative infusion of a low dose of dexmedetomidine reduces intravenous consumption of sufentanil in patient-controlled analgesia. *Korean J Anesthesiol* (2018) 71:226–31. doi: 10.4097/kja.d.18.27056
12. Angka L, Martel AB, Kilgour M, Jeong A, Sadiq M, Souza CTD, et al. Natural Killer Cell IFNgamma Secretion is Profoundly Suppressed Following Colorectal Cancer Surgery. *Ann Surg Oncol* (2018) 25:3747–54. doi: 10.1245/s10434-018-6691-3
13. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. *J Transl Med* (2018) 16:8. doi: 10.1186/s12967-018-1389-7
14. Wang Y, Xu X, Liu H, Ji F. Effects of Dexmedetomidine on Patients Undergoing Radical Gastrectomy. *J Surg Res* (2015) 194:147–53. doi: 10.1016/j.jss.2014.10.008
15. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of Dexmedetomidine on Perioperative Stress, Inflammation, and Immune Function: Systematic Review and Meta-Analysis. *Br J Anaesth* (2019) 123:777–94. doi: 10.1016/j.bja.2019.07.027
16. Kaabi B, Belaaloui G, Benbrahim W, Hamizi K, Sadelaoud M, Toumi W, et al. ADRA2A Germline Gene Polymorphism is Associated to the Severity, But Not to the Risk, of Breast Cancer. *Pathol Oncol Res* (2016) 22:357–65. doi: 10.1007/s12253-015-0010-0
17. Jia Y, French B, Tillman B, French S. Different Roles of FAT10, FOXO1, and ADRA2A in Hepatocellular Carcinoma Tumorigenesis in Patients With Alcoholic Steatohepatitis (ASH) vs non-Alcoholic Steatohepatitis (NASH). *Exp Mol Pathol* (2018) 105:144–9. doi: 10.1016/j.yexmp.2018.07.005
18. Wang W, Guo X, Dan H. Alpha2a-Adrenergic Receptor Inhibits the Progression of Cervical Cancer Through Blocking PI3K/AKT/mTOR Pathway. *Onco Targets Ther* (2020) 13:10535–46. doi: 10.2147/OTT.S264409
19. Brittenden J, Heys SD, Ross J, Eremin O. Natural Killer Cells and Cancer. *Cancer* (1996) 77:1226–43. doi: 10.1002/(SICI)1097-0142(19960401)77:7<1226::AID-CNCR2>3.0.CO;2-G
20. Scanzano A, Cosentino M. Adrenergic Regulation of Innate Immunity: A Review. *Front Pharmacol* (2015) 6:171. doi: 10.3389/fphar.2015.00171
21. Diaz-Salazar C, Bou-Puerto R, Mujal AM, Lau CM, Hoesslin MV, Zehn D, et al. Cell-Intrinsic Adrenergic Signaling Controls the Adaptive NK Cell Response to Viral Infection. *J Exp Med* (2020) 217:e20190549. doi: 10.1084/jem.20190549
22. Yang XH, Bai Q, Lv MM, Fu HG, Dong TL, Zhou Z. Effect of Dexmedetomidine on Immune Function of Patients Undergoing Radical Mastectomy: A Double Blind and Placebo Control Study. *Eur Rev Med Pharmacol Sci* (2017) 21:1112–6.
23. Wu L, Lv H, Luo W, Jin S, Hang Y. Effects of Dexmedetomidine on Cellular Immunity of Perioperative Period in Children With Brain Neoplasms. *Int J Clin Exp Med* (2015) 8:2748–53.
24. Burke JD, Young HA. IFN-Gamma: A Cytokine at the Right Time, is in the Right Place. *Semin Immunol* (2019) 43:101280. doi: 10.1016/j.smim.2019.05.002
25. Ni L, Lu J. Interferon Gamma in Cancer Immunotherapy. *Cancer Med* (2018) 7:4509–16. doi: 10.1002/cam4.1700
26. Zaidi MR. The Interferon-Gamma Paradox in Cancer. *J Interferon Cytokine Res* (2019) 39:30–8. doi: 10.1089/jir.2018.0087
27. Mori H, Hanabayashi T, Yamada Y, Tamaya T. Decrease in Interferon-Gamma Production by Peripheral Blood Mononuclear Cells in Patients With Uterine Cervical Cancer. *J Clin Immunol* (1990) 10:45–51. doi: 10.1007/BF00917497
28. Liu N, Song Y, Shi W. IFN-Gamma +874 T/A Polymorphisms Contributes to Cervical Cancer Susceptibility: A Meta-Analysis. *Int J Clin Exp Med* (2015) 8:4008–15.
29. Tartour E, Gey A, Sastre-Garau X, Lombard Surin I, Mosseri V, Fridman WH. Prognostic Value of Intratumoral Interferon Gamma Messenger RNA Expression in Invasive Cervical Carcinomas. *J Natl Cancer Inst* (1998) 90:287–94. doi: 10.1093/jnci/90.4.287
30. Tabibzadeh SS, Satyaswaroop PG, Rao PN. Antiproliferative Effect of Interferon-Gamma in Human Endometrial Epithelial Cells *In Vitro*: Potential Local Growth Modulatory Role in Endometrium. *J Clin Endocrinol Metab* (1988) 67:131–8. doi: 10.1210/jcem-67-1-131
31. Page GG, Blakely WP, Ben-Eliyahu S. Evidence That Postoperative Pain is a Mediator of the Tumor-Promoting Effects of Surgery in Rats. *Pain* (2001) 90:191–9. doi: 10.1016/S0304-3959(00)00403-6
32. Shavit Y, Martin FC, Yirmiya R, Ben-Eliyahu S, Ben-Eliyahu GW, Weiner H, et al. Effects of a Single Administration of Morphine or Footshock Stress on Natural Killer Cell Cytotoxicity. *Brain Behav Immun* (1987) 1:318–28. doi: 10.1016/0889-1591(87)90034-1

33. Ninkovic J, Roy S. Role of the Mu-Opioid Receptor in Opioid Modulation of Immune Function. *Amino Acids* (2013) 45:9–24. doi: 10.1007/s00726-011-1163-0
34. Liang X, Liu R, Chen C, Ji F, Li T. Opioid System Modulates the Immune Function: A Review. *Transl Perioper Pain Med* (2016) 1:5–13.
35. Cronin AJ, Aucutt-Walter NM, Budinetz T, Bonafide CP, DiVittore NA, Gordin V, et al. Low-Dose Remifentanil Infusion Does Not Impair Natural Killer Cell Function in Healthy Volunteers. *Br J Anaesth* (2003) 91:805–9. doi: 10.1093/bja/aeg273

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Effects of Preoperative Carbohydrate Intake on Inflammatory Markers and Clinical Outcomes in Elderly Patients Undergoing Radical Prostatectomy: A Single-Centre, Double-Blind Randomised Controlled Trial

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Background: This study aimed to analyse the effects of carbohydrate (CHO) intake on inflammatory markers, comfort, and clinical outcomes in elderly patients undergoing open radical prostatectomy.

Methods: Patients aged ≥65 years who underwent open radical prostatectomy were randomly divided into CHO, drinking water, and fasting groups. A total of 90 patients were enrolled in this study (CHO group, $n = 28$; placebo group, $n = 30$ and fasting group, $n = 32$). Patients in the CHO group were given 800 and 400 ml of carbohydrates 8 and 2–3 h before surgery, respectively. Patients in the placebo group were given 800 and 400 ml of water 8 and 2–3 h before surgery, respectively. Patients in the fasting group did not consume any liquids. The main result is levels of inflammation markers. Secondary results included cellular immunity, comfort, body weight, grip index, and clinical results.

Results: Compared with the fasting group, the CHO group exhibited a decrease in interleukin 6 (IL-6) levels on days 1 and 7 (75.47 and 7.06 pg/mL, respectively), IL-8 levels on day 1 (274.61 pg/mL) and tumour necrosis factor (TNF) levels on days 1, 3, and 7 (11.16, 9.55, and 9.67 pg/mL, respectively). The placebo group exhibited a decrease in IL-8 (390.26 pg/mL) and TNF levels (13.99 pg/mL) on day 1. Compared with the placebo group, the CHO group exhibited a decrease in IL-6 levels on day 1 and TNF levels on day 3. In the CHO and placebo groups, the thirst and hunger scores decreased on the morning of surgery.

Conclusion: Preoperative CHO and drinking water are associated with decreased levels of IL-6, IL-8, and TNF. CHO and water can also reduce thirst and hunger scores. Therefore, we recommend that patients without contraindications should be given 200–400 ml of fluid 2–3 h before surgery, preferably CHO.

Clinical Trial Registration: http://www.chictr.org.cn/edit.aspx?pid=21783&htm=4; ChiCTR-INR-17012867.

Keywords: carbohydrate, inflammatory markers, enhanced recovery after surgery (ERAS), clinical outcomes, radical prostatectomy

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INTRODUCTION

Patients who undergo radical prostatectomy are generally at an advanced age with multiple comorbidities. Surgical trauma generally leads to a longer recovery time; therefore, accelerated rehabilitation is required. Owing to the popularity of enhanced recovery after surgery (ERAS) (1, 2), administering preoperative oral carbohydrate (CHO) has become a common clinical practise (3, 4). Preoperative administration of CHO can reduce insulin resistance, protein loss, hunger, and anxiety in patients without affecting gastric emptying (5). CHO can promote early recovery of the intestinal function and shorten the hospitalisation period (6). Currently, the most common studies include assessment of the effects of CHO on insulin resistance (7) and comfort (8) and the effects of minimally invasive surgery (9) and unconventional fasting (10) on postoperative immune function. A few studies have been concerned with the improvement of postoperative immune function by CHO.

Major open abdominal or pelvic surgery has a higher incidence of postoperative adverse events such as cardiopulmonary insufficiency, pain, thromboembolic complications, and infection. The main reason for such complications is the stress response caused by surgical trauma, followed by a relatively high-level demand for a patient's immunity and energy reserve. The relatively high-level demand for a patient's organ function is considered to be mediated by endocrine and metabolic changes caused by trauma.

The levels of C-reactive protein (CRP) and cytokines are closely related to immune reaction, inflammatory response and the extent of the inflamed tissue. Interleukin (IL-6) levels are associated with the incidence of postoperative complications and are one of the predictors of the incidence of adverse events postoperatively.

We hypothesise that drinking fluids before surgery can improve the immune function of patients after surgery, and the level of certain important inflammatory factors has increased. The level of inflammatory factors has a certain warning effect on the outcome of patients (such as infection, etc.). Therefore, this study hypothesises that drinking liquids before surgery can improve the outcome of patients by regulating inflammatory factors.

METHODS

Patients who underwent open radical resection of prostate cancer in the Shanghai Tenth People's Hospital were selected for this study. The inclusion criteria were as follows: elective radical resection of prostate cancer; age ranging from 65 to 85 years; body mass index (BMI) ranging from 17.0 to 32.0 kg/m^2; the American Society of Anesthesiologists (ASA) physical status I-III and normal heart, lung, liver, kidney, and blood coagulation function. Oral anticoagulants were discontinued 5–7 days before the operation. The exclusion criteria were as follows: age <65 years, inability to drink transparent liquid or allergy, gastrointestinal emptying disorder or obstruction, diabetes, liver cirrhosis, severe cardiac and renal insufficiency, corticosteroid administration at a dose more than 5 mg/day, and ASA physical status IV. The trial was approved by the Ethics Committee of the Shanghai Tenth People's Hospital, and all patients signed a written informed consent form before participating in the study.

All patients were randomly divided into the following three groups: CHO, water (placebo group) and routine water abstinence groups (fasting group). The patients were divided as

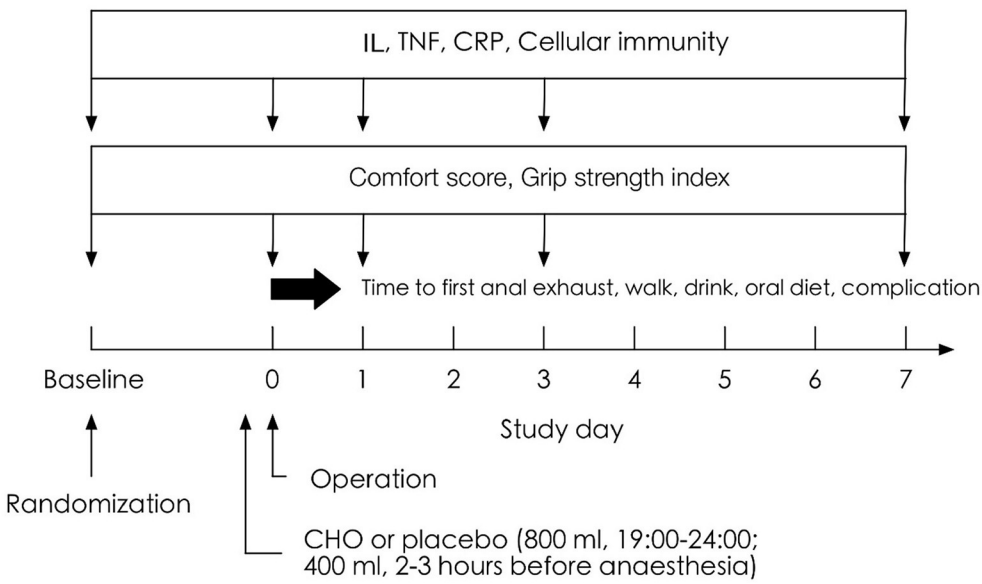

FIGURE 1 | Illustration of the experimental design.

follows: According to the required sample size of 120 patients, 120 two-digit random number series were generated using a random number table. The order of the remainder obtained by dividing the two-digit random number series by 3 was the order in which the patients were randomly divided into three groups. Eventually, the grouping scheme was kept in a sealed envelope. The patients were assigned to the three respective groups based on the grouping scheme. Both patients and researchers were unaware of fluid distribution in patients. Fluid was given to patients by a person who knew the distribution of CHO and placebo water and was not involved in the study.

Patients who met the criteria were selected and randomly assigned to the CHO, water (placebo group), and routine water abstinence (fasting group) groups according to the envelope clue. CHO (Su Qian, commonly known as maltodextrin fructose drink) and placebo products were produced by Jiangsu Zhengda Fenghai Pharmaceutical Co., Ltd., and both products had the same outer packaging. After completing data entry and database locking, the company revealed the product code to the researchers. The study design is demonstrated in **Figure 1**, and a flow chart is demonstrated in **Figure 2**.

All three groups were banned from solid food at least 6 h before surgery. From 07:00 PM to 12:00 AM on the evening before surgery, patients in the CHO group were given 800 mL of a CHO drink (Su Qian contains 12.6% CHO, 50 kcal/100 mL, 290 mOsm/kg, pH 5.0, and 200 mL per bottle). On the day of surgery, patients in the CHO group consumed ∼400 mL of Su Qian 2–3 h before the scheduled induction of anaesthesia, with an interval of more than 20 min. Patients in the placebo group were given the same amount of seasoning water at the same time points (sucralose, 0 kcal/100 mL; citric acid, 0 kcal/100 mL, 107 mOsm/kg, pH 5.0), which had the same taste and appearance as the CHO drink. In the fasting group, no fluid was given to patients preoperatively. To ensure smooth implementation of the experiment, the patients were scheduled for the first operation on the day of surgery. All operations were performed by the same group of experienced urological surgeons.

All patients received the same general anaesthesia regimen, with sufentanil at a dose of 0.25–0.5 μg/kg, propofol at a dose of 1.5–2 mg/kg and cisatracurium benzenesulfonate at a dose of 0.2 mg/kg. After endotracheal intubation, sevoflurane inhalation was used to maintain anaesthesia with end-expiratory sevoflurane

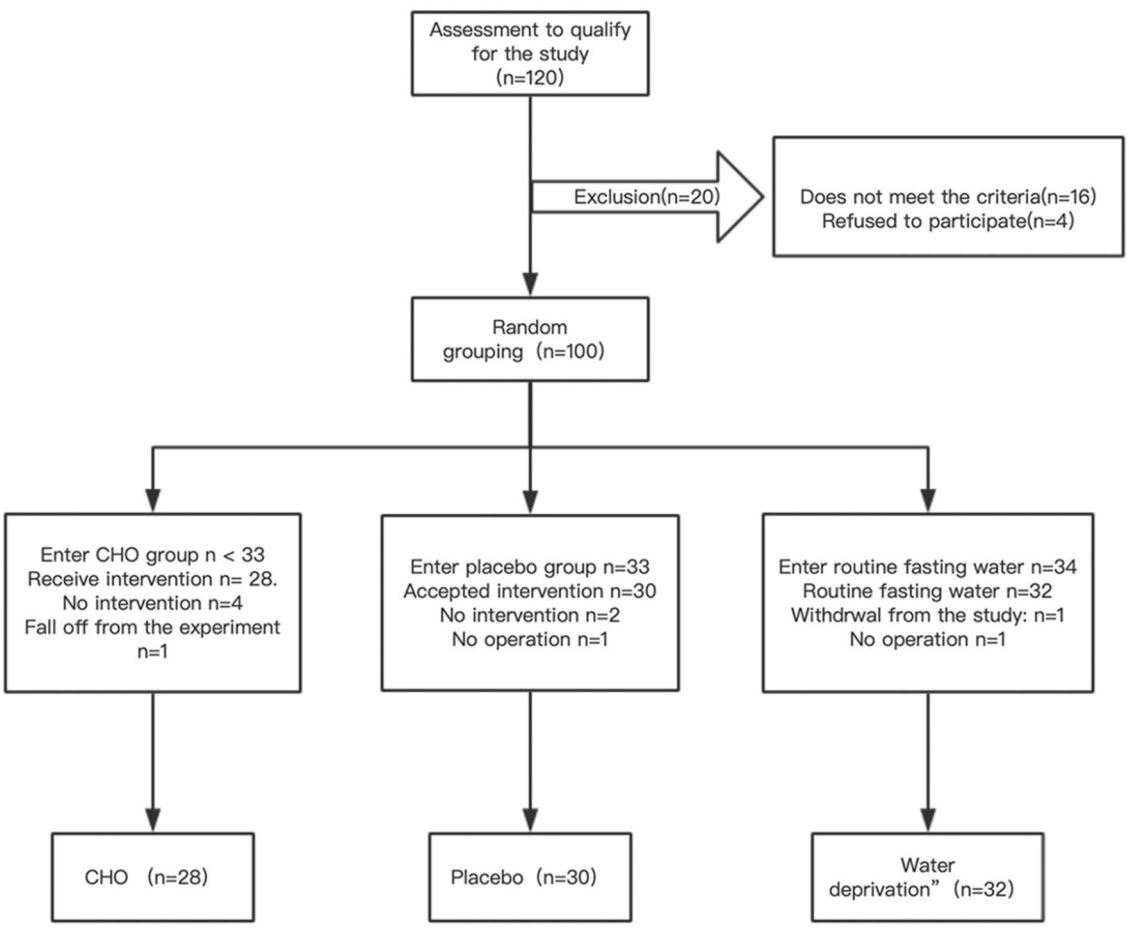

FIGURE 2 | Experimental flow chart.

TABLE 1 | Patient demographics and surgical characteristics.

Characteristics[a]	CHO ($n = 28$)	Placebo ($n = 30$)	Fasted ($n = 32$)	Standardised differences[b]
Age at surgery (years)	71.7 (68.5–74.5)	70.5(68.5–75.0)	70.4 (66.5–71.9)	0.421
BMI (kg/m^2)	23.54 (22.1–26.3)	23.86 (21.4–26.28)	23.97 (23.03–25.06)	0.09
OR time (min)	152.5 (135–205)	162.5 (140–195)	154.27 (120–165)	0.387
Blood loss (mL)	200 (100–200)	200 (125–225)	200 (100–225)	0.798
Intraoperative fluid (mL) mean (min–max)	2,250 (2,000–2,250)	2,000 (1,750–2,250)	1,925 (1,750–2,000)	0.246
ASA grade (*n* [%])				0.059
I	5 (18)	6 (20)	6 (19)	
II	17 (61)	18 (60)	19 (59)	
III	6 (21)	6 (20)	7 (22)	

CHO, Carbohydrate; BMI, body mass index; ASA, American Society of Anesthesiologists; OR, Operative.
[a]*Values are expressed as median (interquartile range) for skewed distribution data or as n (%) for categorical data.*
[b]*Standardised difference was calculated using the R software.*

volume fraction of 0.9–1.2 minimum alveolar concentration, remifentanil at a dose of 2–5 μg/kg/h was used to induce analgesia, and cis-atracurium besylate at a dose of 4–10 mg/h was used to maintain muscle relaxation. During surgery, fluid infusion was guided based on blood pressure, heart rate, bleeding, and urine volume. Ringer's lactate solution and hydroxyethyl starch were used as supplements, crystal fluid: Colloidal fluid = 3/1 and appropriate adjuvant vasoactive drugs were also used.

After surgery, the patients were encouraged to sit by the bedside or get out of the bed as soon as their health conditions permitted. If there was no nausea and vomiting, the patients were asked to drink water and eat as soon as possible. Infection is defined as the presence of sepsis, which can be diagnosed as follows: body temperature >38°C or <36°C, heart rate >90 beats/min, systolic blood pressure ≤100 mmHg, respiratory rate >22 beats min or partial pressure of carbon dioxide ($PaCO_2$) <32 mmHg (<4.3 kPa), white blood cell count >12 × 10 ^9/L or <4 × 10 ^9/L or immature cell count >10% and changes in the consciousness level.

At ∼7 AM before surgery, venous blood was collected from the patients to measure the levels of IL, tumour necrosis factor (TNF), and CRP and cellular immunity. Venous blood samples were collected at the same time point on days 1, 3, and 7 postoperatively. In addition, comfort and grip strength of the patients were measured at the same time point preoperatively and on days 1, 3, and 7 postoperatively. Comfort was measured using a 100-mm visual analogue scale (VAS) (5) based on the following parameters: anxiety, hunger, thirst, nausea, and fatigue. Grip strength was measured using a grip force device, and all measurements were performed on the same dominant hand. The first exhaust time, independent standing time after surgery, time to the intake of water and time to the intake of oral diet were recorded, and the results related to postoperative infection were assessed.

Outcome indicators included the following:

1. Main outcome indicators: levels of inflammatory markers (IL-6, IL-8, IL-10, TNF, and CRP);
2. Secondary outcomes indicators: cellular immunity level (CD3, CD4, CD8, CD4/CD8, CD19, and CD16/CD56), comfort (anxiety, hunger, thirst, nausea, and fatigue), the index of grip strength of body mass (grip strength [kg]/body weight [kg] × 100%) and clinical outcomes (first exhaust time, independent standing time after surgery, time to intake of water, time to intake of oral diet and the incidence of postoperative infection).

Statistical Analysis

Measurement data conforming to normal distribution were represented by mean (standard deviation); non-normal distribution was represented by median (lower and upper quartiles, i.e., the interquartile range), and count data were represented by the rate of adoption (%) or composition ratio (%). Standardised differences were used to evaluate the chief demographic and clinical characteristics among different groups, and the maximum value of standardised differences between two groups compared in pairs was used as the evaluation index. The measurement data were used for repeated measures analysis of variance with adjusted covariates including Age, BMI, AT, Fluid, Blood Loss, and ASA. If the difference between the treatment groups and interaction between the repetitive (time) and treatment factors were statistically significant, multiple comparisons of the treatment factors were performed according to the measurement time points (Bonferroni method). $P \leq 0.05$ indicated that the difference was statistically significant. IBMSPSS 20.0 was used for statistical analysis, and the statistical graphs were plotted using GraphPad Prism version 8.3.0.

RESULTS

Table 1 demonstrates that the three groups were well-matched in terms of age, BMI, ASA physical status classification, operative time, blood loss, and fluid rehydration. A patient in the placebo group had intraoperative bleeding of 900 mL and was infused with 1unit red blood cell suspension.

Table 2, **Figure 3** demonstrate the pairwise comparison of inflammatory factors at each time point in the three groups. Compared with the fasting group, the CHO group was associated with a decrease in IL-6 levels on days 1 and 7, IL-8 levels

TABLE 2 | Comparison among the levels of inflammatory factors of the three groups.

	CHO mean (SEM)	Placebo mean (SEM)	Fasted mean (SEM)	*P*-value	CHO vs. placebo mean difference (95% CI); *P*-value	CHO vs. fasted mean difference (95% CI); *P*-value	Placebo vs. fasted mean difference (95% CI); *P*-value
IL-6 (pg/mL)				0.001			
Day 0	9.3 (4.5)	11.0 (4.3)	15.8 (4.0)		−1.7 (−17.7 to 14.2); 1.000	−6.5 (−21.1 to 8.1); 0.834	−4.8 (−19.1 to 9.6); 1.000
Day 1	75.5 (15.7)	123.0 (15.1)	134 (13.9)		−65.5 (−121.654 to −9.4); **0.017**	−76.5 (−127.9 to −25.1); **0.001**	−11.0 (−61.6 to 39.5); 1.000
Day 3	27.9 (8.8)	33.0 (8.5)	34.1 (7.8)		−5.1 (−36.8 to 26.5); 1.000	−6.3 (−35.2 to 22.7); 1.000	−1.1 (−29.7 to 27.4); 1.000
Day 7	7.1 (4.3)	20.5 (4.1)	26.11 (3.8)		−13.4 (−28.8 to 1.9); 0.106	−19.1 (−33.1 to −5.0); **0.004**	−5.6 (−19.5 to 8.2); 0.973
IL−8 (pg/mL)				0.011			
Day 0	170 (56)	192 (54)	188 (50)		−23 (−223 to 177); 1.000	−18.2 (−201.3 to 164.8); 1.000	4.4 (−175.6 to 184.5); 1.000
Day 1	275 (141)	390 (136)	852 (125)		−116 (−620 to 389); 1.000	−576.9 (−1038.4 to −115.4); **0.009**	−461.3 (−915.2 to −7.3); **0.045**
Day 3	341 (133)	473 (129)	417 (118)		−132 (−608 to 345); 1.000	−75.9 (−512.3 to 360.6); 1.000	55.8 (−373.5 to 485.1); 1.000
Day 7	309 (137)	305 (132)	620 (121)		4.2 (−487 to 495); 1.000	−310.8 (−760.0 to 138.4); 0.284	−315.0 (−756.8 to 126.9); 0.256
TNF (pg/mL)				0.001			
Day 0	13.9 (3.3)	14.5 (1.2)	20.3 (2.9)		−0.5 (−12.3 to 11.2); 1.000	−6.4 (−17.1 to 4.4); 0.451	−5.8 (−16.4 to 4.7); 0.541
Day 1	11.2 (2.4)	14.0 (2.4)	23.9 (2.2)		−2.8 (−11.6 to 5.9); 1.000	−12.7 (−20.7 to −4.7); **0.001**	−9.9 (−17.8 to −2.0); **0.009**
Day 3	9.6 (2.8)	20.7 (2.7)	20.5 (2.5)		−11.2 (−21.1 to −1.2); **0.023**	−11.0 (−20.1 to −1.8); **0.013**	1.2 (−8.8 to 9.2); 1.000
Day 7	9.7 (1.9)	13.9 (1.9)	18.9 (1.7)		−4.2 (−1.2 to 2.8); 0.428	−9.2 (−15.6 to −2.8); **0.002**	−5.0 (−11.3 to 1.3); 0.170

CHO, Carbohydrate; IL−6, Interleukin 6; IL-8, Interleukin 8; SEM, Standard error of the mean; TNF, Ttumor necrosis factor; Day 0, Before the operation; Day 1, The first postoperative day; Day 3, The third postoperative day; Day 7, The seventh postoperative day. P < 0.05 is displayed in bold.

on day 1 and TNF levels on days 1, 3, and 7. Patients in the placebo group exhibited a decrease in IL-8 and TNF levels on day 1. Compared with the placebo group, the CHO group was associated with a decrease in IL-6 levels on day 1 and TNF levels on day 3. No significant difference was observed in the levels of IL-10 and CRP among the three groups. No statistical difference was observed in the cellular immune indexes among the three groups.

The results of repeated measures analysis of variance revealed no interaction between IL-10 levels and measurement time points ($F = 0.746$, $P = 0.471$) among the groups. Statistical differences were observed in IL-10 levels at different time points preoperatively and postoperatively ($F = 8.112$, $P = 0.001$). No statistically significant differences were observed in IL-10 levels among the three groups ($F = 1.148$, $P = 0.322$).

Table 3 demonstrates that compared with the fasting group, the thirst (0.68 and 1.26, respectively) and hunger (0.24 and 0.47, respectively) scores of the CHO and placebo groups on the morning of surgery were significantly reduced (both $P < 0.01$). No difference was observed in the weight grip index among the three groups.

Table 4 demonstrates no differences in independent standing time, the first exhaust time, the first water intake time, the first mealtime and the incidence of postoperative infection among the three groups.

DISCUSSION

Indicators for the clinical evaluation of immune function include inflammatory markers (IL-2, IL-6, IL-8, IL-10, TNF, and CRP) (11) and cellular immunity (T cells, T helper cells, natural killer [NK] cells, and human leukocyte antigens DR [HLA-DR]). Of these inflammatory factors, IL-6, IL-8, TNF, and CRP are all pro-inflammatory factors, and some studies have reported that IL-10 is an anti-inflammatory factor. A decrease in the levels of inflammatory markers and an increase in cellular immunity indicate that an individual's immune function is better (12, 13). To reduce the occurrence of postoperative complications, studies have suggested that accelerated rehabilitation surgery, especially minimally invasive surgery (14), and unconventional fasting before surgery can improve postoperative immune function, reduce inflammation levels, and increase cell-mediated specificity. In 2006, the Gerdien et al. (15) investigated the effect of preoperative liquid CHO intake on postoperative immune function. Compared with the routine preoperative water

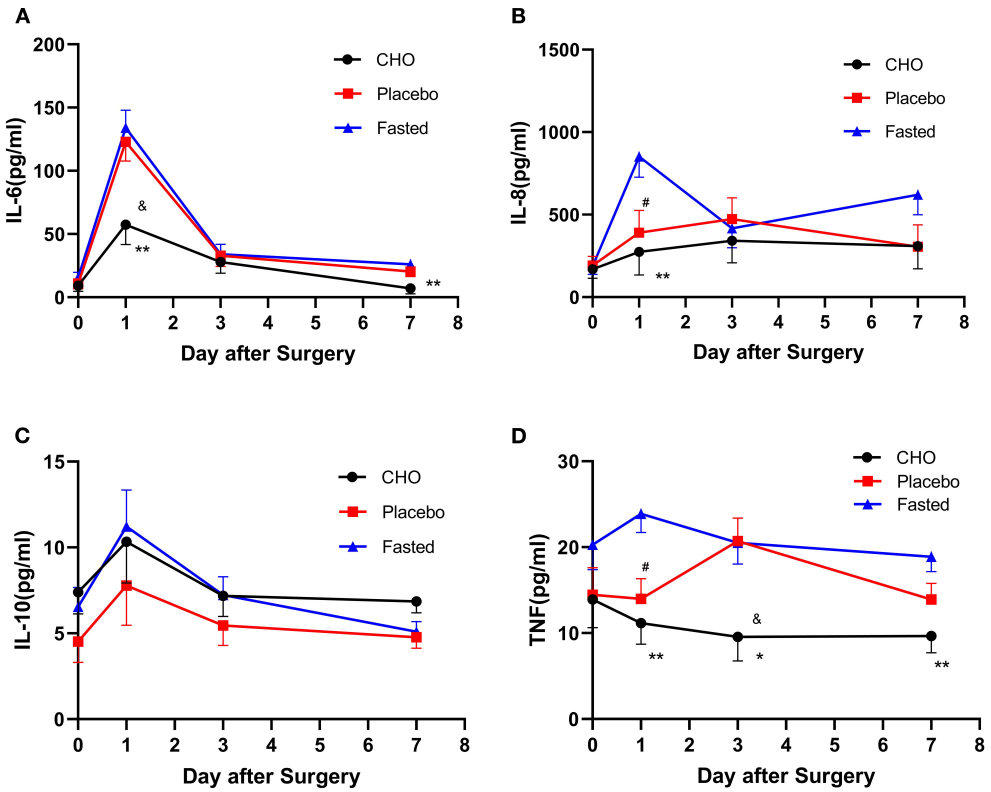

FIGURE 3 | Changes in the levels of postoperative inflammatory markers including IL-6 **(A)**, IL-8 **(B)**, IL-10 **(C)**, and TNF **(D)** in different groups. CHO vs. 0.01; Placebo vs. Fasted, $^{\#}P \leq 0.05$, Placebo vs. Fasted, $^{\&}P \leq 0.05$, $^{*}P \leq 0.05$, $^{**}P \leq 0.01$.

deprivation group, the HLA-DR levels of the oral CHO group did not decrease and body fluid balance was not disturbed, indicating that preoperative oral administration of CHO can avoid subsequent immune reactions and reduce the incidence of complications such as infection. However, another study by Mathur et al. demonstrated that CRP and IL-6 levels exert no effect on systemic inflammation in patients undergoing major abdominal surgery (16). Therefore, the authors believed that there is no evidence that CHO load is essential to reduce surgical pressure. Tran et al. (17) found that the levels of IL-6 and CRP were not affected by the use of CHO before coronary artery bypass grafting and spinal surgery.

This study revealed that the levels of inflammatory markers in the placebo and CHO groups were lower than those of the fasting group; the levels were especially lower in the CHO group. Compared with the fasting group, the CHO group exhibited a decrease in TNF levels on days 1, 3, and 7 postoperatively, IL-6 levels on days 1 and 7 postoperatively and IL-8 levels on day 1 postoperatively. Compared with the fasting group, the placebo group exhibited a decrease in IL-8 and TNF levels on the first postoperative day. The levels of three major inflammatory factors (IL-6, IL-8, and TNF) were significantly reduced on the first postoperative day, indicating that CHO was closely associated with decreased levels of inflammatory markers. The levels of two inflammatory factors (IL-8 and TNF) in the placebo group were also significantly reduced on the first postoperative day, indicating that drinking water was also associated with the reduction of inflammatory factors. Compared with the placebo group, the CHO group only exhibited a decrease in IL-6 levels on the first postoperative day and TNF levels on the third postoperative day, indicating that CHO did not offer many advantages to reduce the levels of inflammatory factors. Therefore, preoperative consumption of a certain amount of liquid, whether CHO, sweet water, or other clear liquids, exerts similar effects on postoperative inflammation indicators. Su Qian is an energy-rich CHO beverage, whereas water is a transparent liquid without energy-rich nutrients; the difference between Sugan and water is that their sugar and energy contents are 1 and 0, respectively. Sugar and energy may not play an important role in regulating the level of inflammatory markers, and a certain amount of fluid intake preoperatively may exert significant effects on postoperative results. Compared with water deprivation, preoperative intake of a certain amount of fluid can significantly reduce the levels of inflammatory markers in the body.

Anti-inflammatory cytokines are immunoregulatory molecules that control the pro-inflammatory cytokine response. They interact with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiological role in inflammation and pathological role in systemic inflammatory states are increasingly being

TABLE 3 | Comparison among subjective comfort in the three groups.

	CHO	Placebo	Fasted	*P*-value (CHO vs. fasted)	*P*-value (placebo vs. fasted)
Anxiety					
Day 0	1.2 (0–8)	1.8 (0–5)	1.6 (0–4)	0.141	0.338
Day of surgery	1.0 (0–4)	1.7 (0–5)	1.2 (0–8)	0.838	0.119
Day 1	0.9 (0–7)	0.6 (0–5)	0.7 (0–4)	0.603	0.999
Day 3	0.3 (0–2)	0.2 (0–2)	0.5 (0–5)	0.339	0.365
Thirst					
Day 0	1.7 (0–6.5)	1.4 (0–5)	2.4 (0–5)	0.451	0.52
Day of surgery	0.7 (0–4)	1.3 (0–4)	3.0 (1–8.5)	0.002	0.001
Day 1	2.2 (0–8)	1.8 (0–8)	2.2 (0–7)	0.7	0.335
Day 3	1.2 (0–7)	0.4 (0–2)	0.8 (0–5)	0.692	0.306
Hunger					
Day 0	0.9 (0–3)	0.4 (0–4.5)	1.0 (0–4)	0.934	0.78
Day of surgery	0.2 (0–3)	0.5 (0–3)	1.4 (0–7)	0.008	0.01
Day 1	1.9 (0–8)	1.2 (0–5)	1.5 (0–6)	0.474	0.886
Day 3	0.8 (0–5.5)	0.4 (0–5)	0.9 (0–5)	0.889	0.439
Nausea					
Day 0	0 (0–0)	0.2 (0–3)	0 (0–0)	0.999	0.07
Day of surgery	1.2 (0–3)	1.5 (0–6)	2 (0–6)	0.666	0.916
Day 1	0.5 (0–5)	1.8 (0–6)	1.3 (0–3)	0.828	0.758
Day 3	0.6 (0–5)	0.1 (0–1)	0.1 (0–3)	0.138	0.585
Fatigue					
Day 0	1.1 (1–2)	1.0 (1–2)	1 (0–2)	0.125	0.563
Day of surgery	2.2 (0–6)	2.5 (1–6)	2.4 (0–6)	0.553	0.979
Day 1	1.6 (0–7.5)	0.9 (0–3)	1.0 (0–4)	0.128	0.786
Day 3	0.9 (0–5)	0.4 (0–3)	0.7 (0–2)	0.791	0.172
Grip strength index (%)					
Day 0	44.7 (29.0–67.7)	46.9 (33.4–67.7)	44.1 (30.7–62.3)	0.211	0.588
Day of surgery	38.4 (26.2–68.1)	41.5 (32.8–57.5)	41.3 (25.9–57.9)	0.57	0.475
Day 1	39.2 (27.6–66.0)	42.1 (24.8–63.2)	43.0 (30.9–61.2)	0.968	0.567
Day 3	42.4 (29.7–66.1)	44.1 (25.1–63.1)	44.1 (28.8–64.9)	0.496	0.691

CHO, Carbohydrate; Day 0, Before the operation; Day 1, The first postoperative day; Day 3, The third postoperative day; Day 7, The seventh postoperative day.

TABLE 4 | Comparison among the postoperative rehabilitation indices of the three groups.

	CHO mean (min–max)	Placebo mean (min–max)	Fasted mean (min–max)	CHO vs. placebo mean difference (95% CI); *P*–value	CHO vs. fasted mean difference (95% CI); *P*-value	Placebo vs. fasted mean difference (95% CI); *P*-value
Time to first anal exhaust (h)	24.7 (5.5–101)	26.5 (7.5–64)	25.0 (1.5–93)	−1.8 (−11.2 to 7.7); 1.000	−0.32 (−9.30 to 8.65); 1.000	1.44 (−7.91 to 10.79); 1.000
Time to first walk (h)	28.6 (10–100)	28.7 (12–70)	39.2 (15–93)	−1.4 (−10.2 to 9.9); 1.000	−10.64 (−20.03 to −1.25); 0.081	−10.50 (−20.29 to −0.712); 0.108
Time to first drink (h)	24.7 (5.5–101)	26.5 (7.5–64)	25.0 (1.5–93)	−3.9 (−4.6 to 3.8); 1.000	−1.97 (−5.87 to 1.92); 0.948	−1.58 (−5.69 to 2.53); 1.000
Time to start oral diet (h)	27.9 (12–73)	34.8 (8–72)	34.6 (2.5–80)	−6.9 (−16.5 to 2.7); 0.474	−6.65 (−15.72 to 2.40); 0.441	0.22 (−9.68 to 9.24); 1.000
Infection (*n*)						
Day 1	4	4	3	1.000	1.000	1.000
Day 3	2	2	3	1.000	1.000	1.000
Day 7	0	0	0	1.000	1.000	1.000

CHO, Carbohydrate; Day 0, Before the operation; Day 1, The first postoperative day; Day 3, The third postoperative day; Day 7, The seventh postoperative day.
CHO vs. fasted.

recognised. Major anti-inflammatory cytokines include IL-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13. Of all anti-inflammatory cytokines, IL-10 exhibits potent anti-inflammatory properties, repressing the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-1 by activated macrophages. In addition, IL-10 can upregulate endogenous anti-cytokines and downregulate pro-inflammatory cytokine receptors. Therefore, it can counter-regulate the production and function of pro-inflammatory cytokines at multiple levels (18).

In this study, no statistical difference was observed in IL-10 levels among the three groups, indicating that the effect of preoperative liquid intake was weaker on anti-inflammatory factors such as IL-10 than that on pro-inflammatory factors such as IL-6, IL-8, and TNF.

Although significant differences were observed in the levels of IL-6, IL-8, and TNF among the three groups, no difference was observed in the levels of cellular immunity indicators and the incidence of postoperative infection among the three groups; therefore, the clinical significance of CHO administration could not be determined. Because several factors affect the incidence of postoperative infection, preoperative fluid intake may not be a key factor in reducing the incidence of postoperative infections.

Several studies (19) have demonstrated that preoperative administration of CHO can significantly reduce preoperative hunger and anxiety and does not affect gastric volume. The present study found that preoperative administration of fluid, either CHO or clear liquid, can significantly improve thirst and hunger scores in the early morning (usually 90–120 min after the intake of liquid in the morning) as compared with water deprivation. A similar effect was observed on the comfort parameters on the day of surgery. Furthermore, drinking a liquid beverage, not necessarily CHO, may significantly provide improved comfort to patients.

Clinical outcomes among the three groups were not significantly different. Preoperative liquid intake did not play an important role because several factors affect the clinical outcome of patients. For example, the time to get out of bed is affected by factors such as medical staff education, medical cognition update, fear of getting out of bed, postoperative pain, and weakness. Some studies (20) have reported that preoperative CHO load is only related to a small reduction in the length of hospital stay and exerts no effect on the incidence of complications. In China, the length of hospital stay is affected by various factors; therefore, the clinical results of this study do not include postoperative hospital stay. Compared with a study conducted by Veenhof et al. (14), this study included a group of placebo controls. Compared with a study conducted by Mathur et al. (16), this study included a set of blank controls. This study demonstrated that CHO and placebo almost offer the same advantages in reducing the levels of inflammatory markers; however, no significant difference was observed in the incidence of postoperative infection among the three groups.

This quality study has some limitations. The sample size was small, and the level of inflammatory markers was not necessarily associated with the incidence of infection. Therefore, it is necessary to further investigate the influence of CHO or clear liquid on the inflammatory markers and clinical outcomes of elderly patients undergoing major surgery.

CONCLUSIONS

Preoperative CHO and drinking water are associated with decreased levels of IL-6, IL-8, and TNF. CHO and water can also reduce thirst and hunger scores. Therefore, we recommend that patients without contraindications should be given 200–400 ml of fluid 2–3 h before surgery, preferably CHO.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical standards of Shanghai Tenth People's Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZH planned and implemented the experiment and wrote the article. JL retouched, revised, and contributed to the article. FW supervised the experiment and supported it with financial support. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Bilku DK, Dennison AR, Hall TC, Metcalfe MS, Garcea G. Role of preoperative carbohydrate loading: a systematic review. *Ann R Coll Surg Engl.* (2014) 96:15–22. doi: 10.1308/003588414X13824511650614
2. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. *Lin Nutr.* (2006) 25:224–44. doi: 10.1016/j.clnu.2006.01.015
3. Feldheiser A, Aziz O, Baldini G, Cox BPBW, Fearon KCH, Feldman LS, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand.* (2016) 60:289–334. doi: 10.1111/aas.12651
4. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg.* (2002) 183:630–41. doi: 10.1016/S0002-9610(02)00866-8
5. Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg.* (2001) 93:1344–50. doi: 10.1097/00000539-200111000-00063
6. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis.* (2006) 8:563–9. doi: 10.1111/j.1463-1318.2006.00965.x
7. Dilmen OK, Yentur E, Tunali Y, Balci H, Bahar M. Does preoperative oral carbohydrate treatment reduce the postoperative surgical stress response in lumbar disc surgery? *Clin Neurol Neurosurg.* (2017) 153:82–6. doi: 10.1016/j.clineuro.2016.12.016
8. Zhang Y, Min J. Preoperative carbohydrate loading in gynecological patients undergoing combined spinal and epidural anesthesia. *J Invest Surg.* (2019) 33:587–95. doi: 10.1080/08941939.2018.1546352
9. Porcaro AB, de Luyk N, Corsi P, Sebben M, Tafuri A, Inverardi D, et al. Robotic assisted radical prostatectomy accelerates postoperative stress recovery: final results of a contemporary prospective study assessing pathophysiology of cortisol peri-operative kinetics in prostate cancer surgery. *Asian J Urol.* (2016) 3:88–95. doi: 10.1016/j.ajur.2016.03.002
10. Pedziwiatr M, Pisarska M, Matłok M, Major P, Kisielewski M, Wierdak M, et al. Randomized clinical trial to compare the effects of preoperative oral carbohydrate loading versus placebo on insulin resistance and cortisol level after laparoscopic cholecystectomy. *Pol Przegl Chir.* (2015) 87:402–8. doi: 10.1515/pjs-2015-0079
11. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, TNF-α: receptors. functions, and roles in diseases. *J Allergy Clin Immunol.* (2016) 138:984–1010. doi: 10.1016/j.jaci.2016.06.033
12. Wu FPK, Sietses C, von Blomberg BME, van Leeuwen PAM, Meijer S, Cuesta MA. Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. *Dis Colon Rectum.* (2003) 46:147–55. doi: 10.1007/s10350-004-6516-2
13. Schwenk W, Jacobi C, Mansmann U, Böhm B, Müller JM. Inflammatory response after laparoscopic and conventional colorectal resections-results of a prospective randomized trial. *Langenbecks Arch Surg.* (2000) 385:2–9. doi: 10.1007/s004230050002
14. Veenhof AAFA, Vlug MS, van der Pas MHGM, Sietses C, van der Peet DL, de Lange-de Klerk ESM, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg.* (2012) 255:216–21. doi: 10.1097/SLA.0b013e31824336e2
15. Melis GC, van Leeuwen PA, von Blomberg-van der Flier BM, Goedhart-Hiddinga AC, Uitdehaag BM, Strack van Schijndel RJ, et al. A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression:a randomized, controlled,clinical trial. *JPEN J Parenter Enteral Nutr.* (2006) 30:21–6. doi: 10.1177/014860710603000121
16. Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK, et al. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. *Br J Surg.* (2010) 97:485–94. doi: 10.1002/bjs.7026
17. Tran S, Wolever TM, Errett LE, Ahn H, Mazer CD, Keith M. Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery. *Anesth Analg.* (2013) 117:305–13. doi: 10.1213/ANE.0b013e318295e8d1
18. Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin Spring.* (2007) 45:27–37. doi: 10.1097/AIA.0b013e318034194e
19. Çakar E, Yilmaz E, Çakar E, Baydur H. The effect of preoperative oral carbohydrate solution intake on patient comfort: a randomized controlled study. *J Perianesth Nurs.* (2017) 32:589–99. doi: 10.1016/j.jopan.2016.03.008
20. Watt DG, McSorley ST, Horgan PG, McMillan DC. Enhanced recovery after surgery: which components, if any, impact on the systemic inflammatory response following colorectal surgery?: A systematic review. *Medicine.* (2015) 94:e1286. doi: 10.1097/MD.0000000000001286

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REVIEW
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Anesthesia Techniques and Long-Term Oncological Outcomes

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Despite advances in cancer treatments, surgery remains one of the most important therapies for solid tumors. Unfortunately, surgery promotes angiogenesis, shedding of cancer cells into the circulation and suppresses anti-tumor immunity. Together this increases the risk of tumor metastasis, accelerated growth of pre-existing micro-metastasis and cancer recurrence. It was theorized that regional anesthesia could influence long-term outcomes after cancer surgery, however new clinical evidence demonstrates that the anesthesia technique has little influence in oncologic outcomes. Several randomized controlled trials are in progress and may provide a better understanding on how volatile and intravenous hypnotics impact cancer progression. The purpose of this review is to summarize the effect of the anesthesia techniques on the immune system and tumor microenvironment (TME) as well as to summarize the clinical evidence of anesthesia techniques on cancer outcomes.

Keywords: anesthesia, analgesia, cancer recurrence, metastasis, general anesthesia (GA), regional anesthesia - palliative care - cancer pain, opioids, total intravenous anaesthesia (TIVA)

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INTRODUCTION

Cancer is a major global health concern since it is the second cause of death after cardiovascular disease (1). According to the World Health Organization, an estimated 19.3 million new cancer cases were recorded in 2020 with almost 10 million cancer deaths worldwide (2). In addition, given the unprecedented effects of the COVID-19 pandemic on the health care system, many patients received a delayed diagnosis and treatment (including surgery) which will significantly impact their cancer prognosis. The American Cancer Society estimates an additional 25.7 million new cancer cases worldwide and 16.3 million cancer deaths by 2040 (3). This upward trend may be secondary to earlier cancer diagnosis and improvement in prevention and treatments.

Cancer treatment may involve a combination of chemotherapy, radiotherapy, immunotherapy and surgery. The latter is also used to provide diagnosis and palliative therapy for solid tumors. While surgical excision continues to be the gold standard treatment for cancer, accumulative evidence (mostly from preclinical studies) has suggested that surgery itself and multiple perioperative events (i.e., blood transfusion, analgesics and anesthetics) might accelerate the progression of minimal residual disease, formation of new metastatic foci and cancer recurrence (4). In this review, we will focus on key mechanisms that allow surgery to provide suitable conditions for shedding, implantation and subsequently proliferation or circulating tumor cells (CTCs). Additionally, we will provide a comprehensive review of the pre-clinical data on the effect of anesthesia technique (total intravenous anesthesia [TIVA] versus volatile anesthesia) and

analgesia (regional versus opioid based techniques) on cancer cells, the TME and immunosurveillance. Lastly, we will summarize the clinical data regarding the effects of the anesthesia techniques on cancer outcomes including survival.

THE ROLE OF SURGERY IN CANCER PROGRESSION

Surgery Triggers Inflammation Followed by Immunosuppression

Cancer metastasis is the major cause of morbidity and mortality, and in fact it accounts for 90% of deaths in cancer patients (5). In order to successfully colonize a distant site CTCs must complete a sequence of events before they become clinically detectable metastasis. The development of metastasis therefore requires; 1) escape of tumor cells from primary tumor, 2) intravasation, 3) circulation in the blood stream, 4) extravasation through endothelial cells into the surrounding tissue, and 5) survival and proliferation in the TME by induction of angiogenesis and immune escape (**Figure 1**) (6). Also, an essential step on the metastatic process is the epithelial-mesenchymal transition (EMT). EMT allows the transformation of epithelial cancer cells into mesenchymal cancer cells (7). This phenotypic transformation enables mesenchymal cells to migrate, invade and resist apoptosis as they colonize distant sites. Cumulative evidence indicates that surgery increases the shedding of tumor cells into the circulation (8) and activates the sympathetic nervous response which ultimately triggers inflammation followed by immunosuppression (**Figure 2**) (9).

The initial acute inflammatory stress response is mediated by neutrophils, macrophages and monocytes at the site of injury. These immune cells release a massive production of pro-inflammatory cytokine including interleukin -1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and neutrophils extracellular traps (NETs). All these cytokines shift CD4+ helper cells to a th1 profile (10). The Th1 profile, generally accepted as anti-tumoral, is characterized by the secretion of interferon gamma (INF)-γ and IL-2 with regulation of the cell mediated immunity (11). It is important to point out that the inflammatory response is directly proportional to the degree of surgical trauma. Human studies assessing the effect of minimally invasive versus open surgery have shown significant differences between the two interventions when reporting the function of immune cells and cytokine profile(12); "Inflammatory Response After Laparoscopic Versus Open Resection of Colorectal Liver Metastases Data From the Oslo-CoMet Trial: Erratum," (13). For instance, laparotomy triggers higher concentrations of IL-6 than laparoscopic cancer surgery("Inflammatory Response After Laparoscopic Versus Open Resection of Colorectal Liver Metastases Data From the Oslo-CoMet Trial: Erratum," (13).

The surgical inflammatory response is followed by a compensatory anti-inflammatory response; however it can also lead to dysregulation of the cell mediated immunity with subsequent immunosuppression (14). IL-6 induces the release of prostaglandin E_2 (PGE_2) from macrophages (15). PGE2 is a lipid mediator that exerts its activity *via* PGE_2 receptors (EP1-4). EP2 and EP4 are both G_s-couple receptors that signal through the adenylate cyclase-dependent cAMP/PKA/CREB pathways (16). The effects of PGE_2 includes the inhibition of neutrophil, natural killer (NK) and T-cell mitogenesis (17). Furthermore, protanglandin regulates lymphatic vessles dilatation and therefore could enables cancer mestatasis (18). Additionally, PGE_2 inhibits the production of IL-1β, IL-6 and TNF-α and stimulates the release of IL-10, IL-1Ra (19). This cytokine imbalance results in a shift toward th2 profile (pro-tumoral), which favors tumor growth by inhibiting cell-mediated immunity (20).

The stress response to surgery is also characterized by the secretion of cortisol and catecholamines (21). Cortisol can diffuse the cellular membrane to bind the glucocorticoid receptor intracellularly. This complex, then translocates into the nucleus where it interacts with glucocorticoid-responsive elements (DNA sequence) and different transcription factors such as NF-kB to inhibit or promote the production of inflammatory cytokines

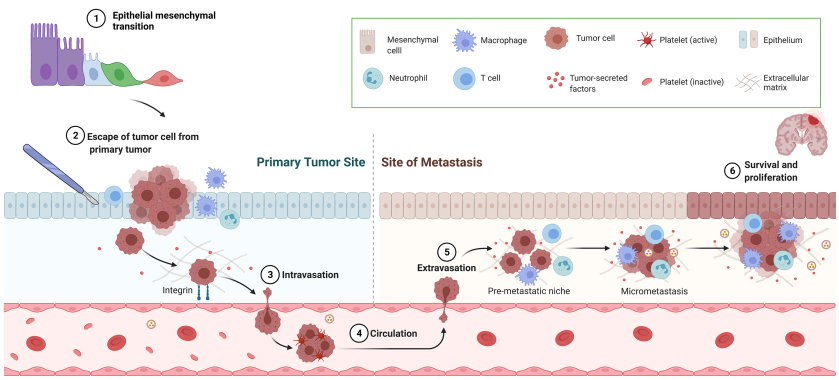

FIGURE 1 | Overview of metastatic cascade. This figure represents the necessary steps for successful metastasis including epithelial-mesenchymal transition, escape of tumor cell from primary tumor, intravasation, circulation, extravasation and survival and proliferation.

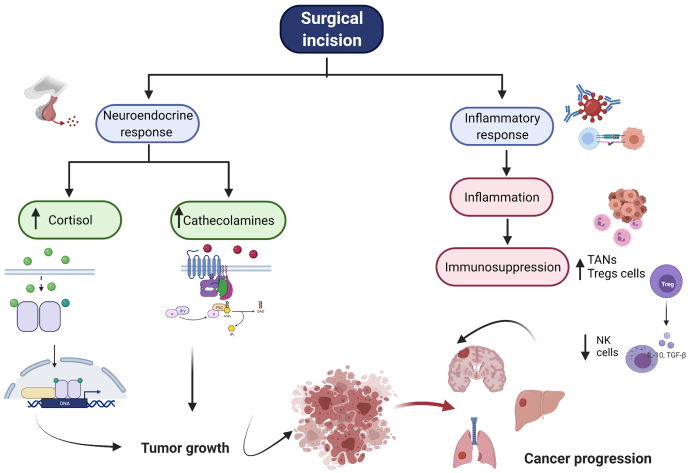

FIGURE 2 | Overview of Surgical Stress Response. The figure represents the neuroendorine and the inflammatory response associated with surgery. After surgical incision, there is an increase of cortisol and cathecholamines. Additionally, there is a profound inflammatory response folllowed by immunosupression. All these together enables cancer cells to growth, proliferate and produce distant metastasis. NK, natural killer cell, TAN, tumor associated neutrophiles, Tregs, regulartoy T cells.

(22). For instance, cortisol has shown a dual role in oral squamous cell carcinoma. At physiological stress levels (i.e., 10 nM) cortisol promoted the expression of IL-6 while higher pharmacological concentration (i.e., 1000 nM) produced the opposite findings (23). The sympathetic nervous system directly modulates cancer cells *via* β-adrenoreceptors-mediated activation of protein kinase A (PKA) (24). β-adrenoreceptors have been found in breast, prostate, lung, esophageal and liver cancer cells among others (25–29). The activation of β-adrenergic signaling by epinephrine or norepinephrine triggers an increase on cyclic adenosine monophosphate (cAMP) which directly modulate cancer cell growth, proliferation, invasiveness, angiogenesis and metastasis (24). One characteristic of cancer cells is the formation of invadopodia (actin-rick protrusions) which are formed to degrade and facilitate migration through the extracellular matrix (30). β-adrenoreceptors activation can promote an increase of invadopodia which correlates with increased tumor invasion in *in vivo* breast cancer models. Importantly, such effect is reversed by β-blockers (31).

Surgery Induces Angiogenesis

A critical step in the metastatic process is the development of new blood vessels (angiogenesis). The vascular endothelial growth factor (VEGF), an extensively studied molecules in angiogenesis, is considered a maker of poor prognosis for some cancers (32, 33). VEGF as well as its receptors (VGFR1 and VGFR2) have been found in cancer cells (34). The activation of VEFGR initiates MAPK signaling pathway with phosphorylation of ERK and ultimately promotion of cell proliferation (35). VEGF has been reported to be higher in cancer patients compared to control groups even before surgery (36–39). It has been theorized that high perioperative levels of VEGF might explain why cancer surgery might facilitate the growth of residual metastases disease early after surgery.

Key Effectors Cells of the Immune Response in Cancer Surgery

Neutrophils are the first line to respond to surgical trauma and defend against invading microorganisms. However, neutrophils have been shown to play a dual role since besides protecting from infection, neutrophils can also lead to cancer progression and tumor dissemination (40). Tumor associated neutrophils (TANs) are associated with poor overall survival in many types of cancers (41–43). Neutrophils can serve as chemotactic factor to attract cancer cells by releasing neutrophil extracellular trap (NETs)(L. 44). Surgery triggers the formation of NETs which can promote formation of metastasis. The inhibition of NETs after surgery powerfully counteract their pro-metastatic effects (45).

Natural killer cells are one of the main effector cells against cancer (46). Upon target cell recognition, NK cells mediate target cell lysis by two different mechanisms. First, the release of cytotoxic granules containing granzyme and perforins, and the induction of Fas ligand and TNF-related apoptosis ligand (TRAIL) (47). Second, activated NK cell secrete several cytokines such as INF- γ, TNF-α and chemokines (i.e., CCL3, CCL 4 and CCL5). Accumulated evidence suggests that NK cell cytotoxicity is decreased immediately after surgery secondary to surgical stress. This effect can last for several weeks (48). Additionally, the surgical stress impair the NK cells' capacity to secrete INF-γ and therefore decreases the activation of the cellular immunity and subsequently antitumor immune response (49). The extent of the surgical insult impacts the function of these cells. For instance, laparoscopically assisted surgery resulted in better preservation of NK cell function compared to open procedures in patients with colon cancer (50).

Lymphocytes are an essential component for maintaining tolerance and preventing excessive inflammation. Postoperative lymphopenia or a high neutrophil-to-lymphocyte ratio (NLR) are independent biomarkers of cancer recurrence (51–53). NLR

appears to be an appealing biomarker in cancer prognosis since its widely available, easily measured and inexpensive. A recent meta-analysis by Cupp et al. suggested an association between high NLR and poor cancer outcomes (54). For instance, Forget *et al.* demonstrated that preoperative high NLR in patients with breast, lung and renal cancer undergoing tumor resection was associated with higher risk or relapse and/or higher mortality (55). Similar findings in term of RFS and OS were found by Choi *et al.* in a cohort of non-small cell lung cancer (NSCLC) patients, however the correlation was only observed in patient with Stage I NSCLC (56). Among lymphocytes, regulatory T cells (Tregs) are also regulators of the anti-tumor immunity (57). Ghiringhelli et al. reported a high Tregs cell levels that correlated with a low number of NK cells that were also dysfunctional in gastrointestinal stromal tumor-bearing patients (58). Peripheral and tumor infiltrating Tregs levels are higher in patients with breast and pancreas cancer compared to healthy subjects. High levels of circulating tumor infiltrating Tregs have been associated with accelerated progression and poor prognosis of those cancers (59). While in the context of low levels of Tregs can predict the presence of postoperative complications, the impact of different peripheral concentrations of these cells after oncological procedures is less understood (60).

In summary, the perioperative period is critical for several steps leading to cancer metastasis. It has been indicated that anesthetics could also influence mechanisms such as NETs formation, EMT and angiogenesis. In the following section, we will summarize the preclinical and clinical evidence regarding the effects of the different types of anesthesia techniques on long-term cancer outcomes.

INHALATIONAL AGENTS AND INTRAVENOUS ANESTHETICS FOR CANCER SURGERY

Preclinical Evidence

Volatile Anesthetics

Volatile anesthetics are commonly used during oncological surgery. There has been increasing interest in investigating the role of volatile anesthetics on cancer recurrence and metastasis. Preclinical data suggest that volatile agents promote the progression of cancer by direct and indirect mechanisms. Firstly, volatile anesthetic can directly modify (by either promoting or inhibiting) intracellular signals involved in key aspect of the cancer cell behavior such as proliferation, migration, invasion and sensitivity to chemotherapeutic agents. For instance, isoflurane (1.2%) increased the proliferation and migration while decreasing apoptosis in glioblastoma stem cells by regulating the expression of hypoxia-inducible factor (HIF) (61, 62). In non-small cell lung cancer, isoflurane at 1%, 2% and 3% promoted proliferation, invasion and invasiveness *via* Akt-mTOR signaling (63). In a colorectal cancer cell line, desflurane (10.3%) induces EMT and metastasis through dysregulation of miR-34/LOXL3 axis a well-known tumor suppressor (64). Sevoflurane (2% for six hours), *in vitro*, increases survival of breast cancer cells *via* modulation of intracellular Ca^{2+} homeostasis (65). Secondly, volatile anesthetics could facilitate cancer progression by inducing immunosuppression. For example, sevoflurane and desflurane attenuated NK cell cytotoxicity *in vitro* by inhibiting the expression of the adhesion molecule leucocyte- function n associated antigen (LFA-1) (66). In addition, isoflurane reduced the ability of NK cells to respond to INF-γ stimulation. A phenomenon that lasted for 11 days (67). Importantly, sevoflurane, isoflurane and enflurane at 1.5 and 2.5 MAC reduced the release of TNF-α and IL-1β in human peripheral blood mononuclear cells (68).

Contrary to this previously cited evidence, a number of preclinical studies indicate that volatile anesthetics might have an anti-tumoral effect. For instance, concentration of sevoflurane from 1.7% to 5.1% significantly inhibits invasion and migration of lung carcinoma cells by decreasing the phosphorylation of p-38 MAPK, reducing HIF-1α activation and downregulating matrix metallopeptidases (MMP) 2 and MMP-9 (69–71). In colon cancer, sevoflurane induced p53-dependent apoptosis while suppressing cell migration and invasion by regulating the ERK/MM-9 pathway (via miR-203) (72, 73). Lastly, sevoflurane at clinical (2.5%) and toxic concentrations (5% and 10%) inhibited viability, migration and invasion of osteosarcoma cells by inactivating PI3K/ATK pathway (74).

In summary, volatile anesthetics regulate important functions in cancer cells. Their inconsistent (pro and anti-tumoral) effects cancer cells and those of the TME could be explained by differences in experimental conditions such as, type of cell line, incubation time (ranged between 30 mins and 6 hours), type and concentration of volatile anesthetics (ranged between 0.5%-10%). For instance, some studies treated cancer cells with very high concentrations that are not usually employed in clinical practice and perhaps the "anti-tumoral" effect is most likely related to toxic concentrations of volatile anesthetics.

Propofol

Propofol based total intravenous anesthesia has gained attention in recent years. Most preclinical studies suggest that propofol inhibits tumor cell viability, proliferation, migration and invasion by regulating different signaling pathways. It inhibits proliferation, migration and invasion in colon cancer cells by upregulating miR-124-3p and downregulating AKT3 (75). Also in colon cancer, propofol decreases cell invasion *via* ERK1/2-depenedent downregulation of MMP-2 and -9 (76). In lung cancer cells, propofol promotes apoptosis also *via* ERK1/2 *via* activation and upregulation of p53 (77), and decreases metastatic cell behaviors by inhibiting HIF-1α (78) and MMPs-2,-7 and -9 (79). Similarly, it inhibits migration of breast cancer cells by inhibiting MMP expression *via* NF-κB pathway (80). In glioma cells, propofol reduced migration and invasion by blocking PI3K/AKT pathways *via* mi-R-206/ROCK1 axis (81). Moreover, propofol reduced oxidative stress and growth in glioma cells by suppressing the Ca^{2+}-permeable α-amino-3-hydroxyl-5methylisoxazole-4-propionic acid (AMPA)receptor and divalent transporter 1(DMT1) (82).

The anti-tumoral effect of propofol in cancer progression also entails indirect mechanisms such as the potentiation of NK cell cytotoxicity and reduction of inflammatory response. For instance, in colon cancer cells, propofol increased expression of activated receptor p30 and p44 in NK cells, which promoted NK cell activation and proliferation (83). Additionally, in esophageal squamous cell carcinoma cells, propofol enhanced the expression of cytotoxic effector molecules like granzyme B and IFN-γ suggesting that NK cytotoxicity was increased (84). In terms of cytokine profile, propofol decreases pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (85) and inhibits PGE2 and COX activity (86). Moreover, propofol decreased NETs formation (through inhibition of p-ERK) without affecting neutrophil killing capacity (87, 88).

Altogether, propofol preferentially promotes anti-metastatic mechanism in cancer cells and those of the TME.

Intravenous Ketamine, Dexmedetomidine and Lidocaine

Ketamine is routinely used during cancer surgery to provide analgesia and reduce the use of volatile anesthetics and opioids. Increasing number of studies suggest that ketamine can modify proliferation and survival of cancer cells (89). For example, ketamine decreased intracellular Ca^{2+}, expression of HIF-1α, p-AKT, p-ERK with subsequent reduction of VEGF expression and cell migration in colorectal cancer cells. Notably, all these changes were associated with NMDA receptor inhibition since D-serine (NMDA activator) reversed the anti-tumoral effect of ketamine (90). Additionally, ketamine promotes apoptosis and inhibits cell growth proliferation in lung adenocarcinoma; throughout CD69 expression (91), hepatic cell carcinoma; throughout Bax-mitochondria-caspase protease pathway (92); pancreatic carcinoma *via* NMDA receptor type R2a (93) and ovarian cancer through the inhibition of long-non-coding RNAs PVT1 expression (89).

Dexmedetomidine has also gained interest due to its sedative and analgesic effects. In esophageal carcinoma, dexmedetomidine inhibits tumor growth and metastasis *via* upregulation of miR-143-3p and reduction of levels of epidermal growth factor receptor 8 (94). Additionally dexmedetomidine enhances immune surveillance by inhibiting the p38 MAPK/NF-κB signaling pathway; however, some authors have indicated that dexmedetomidine can stimulate proliferation of cancer cells (95, 96). For instance, dexmedetomidine induced secretion of IL-6 and promoted progression *via* STAT 3 activation in hepatocellular carcinoma (97). Similarly, it promoted tumor proliferation and migration *via* adrenergic signaling and upregulation of Bcl-2 and Bcl-xL (anti-apoptotic proteins) in neuroglioma and lung carcinomas (98). In a rodent model of breast, lung and cancer colon, dexmedetomidine promoted tumor growth and metastasis (99).

Lidocaine is an amide local anesthetic that has gained popularity because of its anti-ileus effects and suggested beneficial properties in recovery after surgery. Lidocaine suppress tumor cells directly by modifying cancer cells signaling. For instance, lidocaine inhibited metastasis and proliferation of lung cancer cells by up-regulating miR-539 with subsequent blocking of EGFR signaling (100). Furthermore, lidocaine suppressed hepatocellular cell growth and induced apoptosis (via activation of caspase- 3 and regulation of Bax/Bcl-2 proteins through the MAPK pathway)(101). Likewise, lidocaine inhibited cervical cancer cell growth and induced apoptosis by modulating lrnRNA-MEG3/miR-421/BTG1 pathway (102).

Lidocaine has shown potent anti-inflammatory properties by decreasing both; pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and intercellular adhesion molecules (I-CAM) expression (103, 104). Human studies have also confirmed this finding in a randomized controlled trial (RCT) where intravenous lidocaine was associated with significantly less production of IL-1ra, IL-6 with preservation of the lymphocyte proliferation (105). Lidocaine has also stimulated the function of NK cells of patients undergoing cancer surgery (106). Recently, a RCT looking at the effect of intravenous lidocaine infusion in breast cancer patients demonstrated a decrease in postoperative expression of NETosis (which is associated with disease progression) and MMP3 (107). Lastly, lidocaine has shown anti-angiogenic effects. It decreased, in a dose dependent manner (1-10μg/ml) the expression of VEGF-A. The inhibitory effects were the result of inhibition of VEGFR-2 phosphorylation (108).

Taken together, experimental evidence suggests that volatile anesthetics might promote tumor progression by directly modifying intracellular signals involved in key aspects of cancer cell behavior such as proliferation, migration and invasion. Additionally, volatile anesthetics might promote immunosuppression. In contrast, propofol has shown anti-inflammatory properties and potentiation of the immune response. Data for ketamine and dexmedetomidine is inconsistent with some studies showing promotion of tumor progression while other showing opposite findings. On the other hand, lidocaine has shown promising results.

CLINICAL EVIDENCE

Retrospective studies (**Table 1**) indicate that cancer survival and recurrence could be affected by the anesthetic technique. The most recent systematic review and meta-analysis by Chang et al. included 19 retrospective observational studies of patients undergoing surgery for various types of cancer surgery. (130) Pool analysis of OS included 17 studies with 23,489 patients (110, 113–119, 121–124, 126, 128, 131, 132). The study showed that propofol-based TIVA in cancer surgery was associated with better OS compared to volatile agents (HR= 0.79, 95% CI, 0.66-0.94, p= 0.08). Interestingly the results of the subgroup analysis by volatile anesthetics showed that this benefit was statistically significant only when TIVA was compared to desflurane (HR= 0.54, 95% CI, 0.36-0.80, p= 0.03), but not compared to sevoflurane (HR=0.92, 95% CI, 0.74-1.14, p=.436) or other volatile agents (HR=0.83, 96% CI, 0.64-1.07, p=0.156). In terms of RFS, the study pooled the results of 10 studies with 8,980 patients (110, 113, 114, 116, 117, 123, 124, 126, 127, 132).

TABLE 1 | Retrospective trials comparing the effect of TIVA versus volatile anesthesia on long-term cancer outcomes.

Type of Cancer	Author	Overall Survival	Recurrence- Free Survival
Gastrointestinal	(109)	No difference	No difference
Hepatocellular	(110)	No studied	Increased with TIVA
Glioblastoma	(111)	No difference	No difference
Breast	(112)	No difference	No difference
Glioma	(113)	No difference	No difference
Breast	(114)	No difference	No difference
Gastric	(115)	No difference	No difference
Cholangiocarcinoma	(116)	Increased with TIVA	No difference
Hepatocellular	(117)	Increased with TIVA	Increased with TIVA
Breast	(118)	No difference	No difference
Breast, Liver, Lung and Gastrointestinal	(119)	No difference	No difference
Appendiceal	(120)	No difference	No difference
Gastric	(121)	Increased with TIVA	No studied
Colon	(122)	Increased with TIVA	No studied
Lung	(123)	No difference	No difference
Breast	(124)	No difference	No difference
Glioblastoma	(125)	No difference	No difference
Esophageal	(126)	No difference	No difference
Breast	(127)	No difference	No difference
Breast, Sarcoma Gastrointestinal and Urologic	(128)	Increased with TIVA	No studied
Ovarian	(129)	No studied	Increased with volatile anesthetic

The analysis indicated no benefits in survival when using TIVA compared to volatile agents (HR=0.92, 95% CI, 0.74-1.14, p=0.439).

Interestingly the benefits in OS in Chang's work were seen in patients with gastrointestinal malignancies, which is the same type of cancers included in another study done by Yap et al (133). Importantly, this group of investigators found that the use of propofol–based TIVA not only improved OS (HR= 0.76, 95% CI, 0.63-0.92, p <0.01) but also improved RFS (HR=0.78, 95% CI, 0.65-0.94, p<0.01). There are some important study limitations that need to be highlighted when analyzing the available meta-analyses. For example, Wigmore et al. study acknowledged the difference in the baseline characteristics between groups, with more ASA III/IV patients, more complex surgeries and larger metastatic burden in the volatile anesthetics group. Nevertheless after propensity matching to correct potential confunders, the study groups were similar (128). Lai's study presented the same limitation for hepatocellular carcinoma surgery. In that study, the desflurane group had significantly more patients with worse preoperative functional capacity, higher scores of liver disease and tumor grade staging compared to the propofol-based group. Patients in the desflurane group were also more likely to have larger tumors and receive blood transfusions which are all independent factor associated with decreased survival (117).

It is important to point out that the systematic review conducted by Chang et al. included studies published until March 2020 and unfortunately did not include the largest retrospective study done by Makito et al. (which was published later in the same year) (109). In that retrospective study the author investigated the effect of TIVA and volatile agents on long-term oncological outcomes among 196,303 patients with gastrointestinal malignancies and found that OS (HR= 1.02, 95% CI, 0.98-1.07, p= 0.28) and RFS (HR=0.99, 95% CI, 0.96-1.03, P= 0.59) were similar between propofol-based TIVA and volatile anesthetic groups. Similar to Makito's work, other multiple retrospective studies showed no difference between TIVA and volatile in terms of OS and RFS in patients with breast cancer (114, 118, 124, 131). The lack of benefit from propofol-based TIVA has also been described for lung (123, 134) and brain cancer surgeries (111, 113, 125). Subsequent substudies from RCTs in lung and breast cancer indicated the same results (134–136). However, it is important to point out that these RCTs did not have OS and RFS as primary outcome.

Since retrospective studies have significant limitations, RCTs are necessary to determine whether the use of propofol-based anesthesia modifies cancer outcomes in patients undergoing surgery for solid tumors (**Table 2**). The VAPOR-C trial (NCT04074460) has a 2x2 factorial design and will investigate the impact of TIVA vs. inhalational agents and lidocaine vs. placebo on DFS after lung and colorectal cancer surgery with curative intent (stage 1-3) (138). The cancer and anesthesia study (NCT01975064) is also investigating the effect of propofol-based TIVA versus volatile anesthesia in breast and colon cancer patients. Preliminary data for 1-year survival is already available and unsurprisingly no benefit was observed in the propofol-based TIVA group (137). The results from long-term survival (5 years) are expected to be available for 2022-2023. The GA-CARES trial (NCT03034096) will randomize 2,000 patients to assess all-cause mortality and RFS in patient undergoing lung,

TABLE 2 | Randomized control trials comparing the effect of TIVA versus volatile anesthesia on long-term cancer outcomes.

Type of Cancer	Author	Overall Survival	Recurrence- Free Survival
Breast	(137)	*No difference	No published yet
Breast	(135)	No difference	No difference
Breast	(136)	No difference	No difference
Lung	(134)	No difference	No difference

**Preliminary data from 1 year OS.*

TABLE 3 | Retrospective trials assessing the effect of regional anesthesia on long-term cancer outcomes.

Type of Cancer	Author	Intervention	Overall Survival	Cancer Recurrence
Colon	(145)	Epidural	No benefit from RA	No benefit from RA
Colon	(146)	Epidural	No benefit from RA	Benefit from RA
Colon	(147)	Epidural	Benefit from RA	No reported
Colon	(148)	Epidural	Benefit from RA	No reported
Colon	(149)	Epidural	Benefit from RA	No benefit from RA
Colon	(150)	Epidural	No benefit	No benefit
Colorectal	(151)	Epidural	Benefit from RA	No reported
Colon	(152)	Epidural	No reported	No benefit
Breast	(153)	Loco-regional anesthesia	No benefit from RA	No benefit from RA
Breast	(154)	Paravertebral block	No benefit from RA	No benefit from RA
Breast	(155)	Paravertebral block	No benefit from RA	No benefit from RA
Breast	(156)	Paravertebral block	No reported	No benefit from RA
Breast	(157)	Epidural Paravertebral block	No reported	No benefit from RA
Breast	(158)	Paravertebral block	No reported	Benefit from RA
Prostate	(159)	Spinal	No reported	No benefit from RA
Prostate	(160)	Epidural	No benefit from RA	No benefit from RA
Prostate	(161)	Spinal	No reported	No benefit from RA
Prostate	(162)	Spinal	No benefit from RA	No benefit from RA
Prostate	(163)	Spinal	No reported	No benefit from RA
Prostate	(164)	Epidural	No benefit from RA	No benefit from RA
Prostate	(165)	Epidural	No reported	No benefit RA
Prostate	(166)	Epidural	No benefit from RA	Benefit from RA
Prostate	(167)	Epidural	No reported	Benefit from RA
Ovarian	(129)	Epidural	No reported	Benefit from RA
Ovarian	(168)	Epidural	No benefit from RA	No benefit from RA
Ovarian	(169)	Epidural	No benefit from RA	No benefit from RA
Ovarian	(170)	Epidural	Benefit from RA	No reported
Ovarian	(171)	Epidural	No reported	Benefit from RA

TABLE 4 | Randomized control trials assessing the effect of regional anesthesia on long-term cancer outcomes.

Type of Cancer	Author	Intervention	Overall Survival	Cancer Recurrence
Lung	(172)	Epidural	No benefit from RA	No benefit from RA
Thoracic and Abdominal	(173)	Epidural	No benefit from RA	No benefit from RA
Breast	(135)	Paravertebral block	No reported	No benefit from RA
Breast	(174)	Paravertebral block	No benefit from RA	No benefit from RA
Breast	(175)	Paravertebral block	No reported	No benefit from RA
Colon	(176)	Epidural	No benefit from RA	No benefit from RA
Colon	.(177)	Epidural	No benefit from RA	No benefit from RA
Colon	(178)	Epidural	Benefit with RA	No reported
Prostate	(179)	Epidural	No reported	No benefit from RA

bladder, esophagus, pancreas, liver, gastric and biliary duct cancer surgery with propofol-based anesthesia or volatile anesthetics.

The effect of intravenous lidocaine on cancer outcomes was recently investigated in pancreatic surgery. A retrospective study of more than 2,239 patients assessed the effect of intraoperative lidocaine (bolus injection of 1.5 mg/kg followed by continues infusion 2mg/kg/hour) and suggested that intravenous lidocaine was associated with prolonged OS (HR=0.616, 95% CI, 0.290-0.783, p=0.013), but not DFS (HR=0.913, 95% CI, 0.821-1.612, p=0.011) (139).

In conclusion, the current evidence is weak to indicate that propofol-based general anesthesia provides any oncological benefit to patients with cancer requiring surgery.

REGIONAL ANESTHESIA COMPARED TO GENERAL ANESTHESIA FOR CANCER SURGERY

Regional anesthesia (RA) techniques including peripheral nerve blocks and neuraxial anesthesia were associated with a reduction in cancer recurrence in preclinical and observational studies. it was originally theorized that RA could improve oncological outcomes after cancer surgery since RA decreases the neuro-endocrine response to surgical trauma, opioid consumption and the use of volatile anesthetics (140–142). Additionally, RA preserves the function of the immune system and has a direct inhibitory effect on cancer cells (143, 144).

CLINICAL EVIDENCE

Thus far, the evidence regarding the potential benefits of RA in long-term outcomes originates from preclinical, retrospective, *post hoc* analysis of RCT and few RCTs (**Tables 3**, **4**). The most recent RCT enrolled 400 patients to investigate the effect of combined epidural-general or general anesthesia alone in patients undergoing video-assisted thoracoscopic lung cancer resection. The primary outcome was RFS. Secondary outcomes were OS and cancer-specific survival. The median follow-up was after 32 months. Results indicated that epidural-anesthesia for major lung surgery did not improved RFS (HR=0.90, CI 95% 0.60-1.35, p=0.068), cancer–specific survival (HR=1.08, CI 95% 0.61-1.91, p=0.802) or OS (HR=1.12, CI 95% 0.6401.96, p=0.697) compared to general anesthesia alone (172),

The effect of combined epidural-general was also investigated in a large RCT including patients (n= 1,712) undergoing major non-cardiac thoracic or abdominal surgery. The median follow-up time was after 5 years. Again, mortality (HR=1.07, CI 95% 0.92- 1.24, p=0.408), cancer-specific survival (HR=1.09, CI 95% 0.93-1.28, p=0.290) and RFS (HR=0.97, CI 95% 0.84-1.12, p=0.692) was similar between combined epidural-general anesthesia and general anesthesia group. (173) In the setting of breast cancer surgery, two RCTs also failed to demonstrate any benefits from paravertebral blocks in terms of cancer outcomes in patients undergoing breast cancer surgery (135, 174). Other RCTs looking at the effect of RA on colon and prostate cancer surgery also failed to demonstrate any benefits in cancer outcomes (177, 179).

There are multiple RCTs in progress to determine the effects of RA compared to general anesthesia on cancer progression. The study NCT03597087 will assess RFS and PFS in patients undergoing transurethral resection of bladder tumors under spinal anesthesia. NCT03245346 will investigate the effect of epidurals on OS and RFS in patients undergoing pancreatic cancer surgery. This trial will also assess the inflammatory neuro-endocrine response by measuring norepinephrine, epinephrine, cortisol and IL-6, IL-8 levels and by measuring the neutrophil-lymphocyte ratio. Lastly, NCT02786329 will investigate the effect of epidural anesthesia in patients undergoing lung cancer resection.

In conclusion, a growing body of evidence from RCTs consistently demonstrates that cancer-specific mortality and cancer recurrence are not improved by the use of regional anesthesia during oncologic surgery.

CONCLUSION

Cancer surgery remains the standard of care for patients with solid tumors. Despite curative intent, 90% of cancer mortality is secondary to cancer metastasis. Preclinical data suggest that the perioperative stress response to surgical trauma creates a window of opportunity for accelerated tumor growth and metastasis. This effect seems to be secondary to changes in signaling pathways in both-TME and immune response. Total intravenous anesthesia and regional anesthesia have been proposed as strategies to counteract the inflammatory response and the associated immunosuppression associated with cancer surgery. Unfortunately, the majority of the data looking at the relationship of these techniques and cancer outcomes originates from retrospective studies. Whether volatile anesthetics have a deleterious effect of cancer recurrence and survival remains a controversial issue. RCTs are in progress and will explore a causal relationship between volatile anesthetic and cancer outcomes. As far for regional anesthesia, RTCs have consistently shown lack of benefit of this technique in regards to cancer survival and recurrence.

AUTHOR CONTRIBUTIONS

MR and JC: discussed ideas and prepared the manuscript. MR: prepared figures and tables. JC: improved manuscript and edited. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Ahmad FB, Anderson RN. The Leading Causes of Death in the US for 2020. *JAMA* (2021) 325(18):1829–30. doi: 10.1001/jama.2021.5469
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654
4. Kim R. Effects of Surgery and Anesthetic Choice on Immunosuppression and Cancer Recurrence. *J Transl Med* (2018) 16(1):8. doi: 10.1186/s12967-018-1389-7
5. Dillekas H, Rogers MS, Straume O. Are 90% of Deaths From Cancer Caused by Metastases? *Cancer Med* (2019) 8(12):5574–6. doi: 10.1002/cam4.2474
6. Popper H. Primary Tumor and Metastasis-Sectioning the Different Steps of the Metastatic Cascade. *Transl Lung Cancer Res* (2020) 9(5):2277–300. doi: 10.21037/tlcr-20-175
7. Brabletz T, Kalluri R, Nieto MA, Weinberg RA. EMT in Cancer. *Nat Rev Cancer* (2018) 18(2):128–34. doi: 10.1038/nrc.2017.118
8. Hansen E, Wolff N, Knuechel R, Ruschoff J, Hofstaedter F, Taeger K. Tumor Cells in Blood Shed From the Surgical Field. *Arch Surg* (1995) 130(4):387–93. doi: 10.1001/archsurg.1995.01430040049007
9. Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *Int J Mol Sci* (2018) 19(8):1–23. doi: 10.3390/ijms19082164
10. Grivennikov SI, Karin M. Inflammatory Cytokines in Cancer: Tumour Necrosis Factor and Interleukin 6 Take the Stage. *Ann Rheum Dis* (2011) 70 Suppl 1:i104–8. doi: 10.1136/ard.2010.140145
11. Romagnani S. T-Cell Subsets (Th1 Versus Th2). *Ann Allergy Asthma Immunol* (2000) 85(1):9–18; quiz 18, 21. doi: 10.1016/S1081-1206(10)62426-X
12. Huang C, Huang R, Jiang T, Huang K, Cao J, Qiu Z. Laparoscopic and Open Resection for Colorectal Cancer: An Evaluation of Cellular Immunity. *BMC Gastroenterol* (2010) 10:127. doi: 10.1186/1471-230X-10-127
13. Inflammatory Response After Laparoscopic Versus Open Resection of Colorectal Liver Metastases Data From the Oslo-CoMet Trial: Erratum. *Med (Baltimore)* (2016) 95(10):e367e. doi: 10.1097/01.md.0000481801.40636.7e
14. Hogan BV, Peter MB, Shenoy HG, Horgan K, Hughes TA. Surgery Induced Immunosuppression. *Surgeon* (2011) 9(1):38–43. doi: 10.1016/j.surge.2010.07.011
15. Ni Choileain N, Redmond HP. Cell Response to Surgery. *Arch Surg* (2006) 141(11):1132–40. doi: 10.1001/archsurg.141.11.1132

16. Agard M, Asakrah S, Morici LA. PGE(2) Suppression of Innate Immunity During Mucosal Bacterial Infection. *Front Cell Infect Microbiol* (2013) 3:45. doi: 10.3389/fcimb.2013.00045
17. Martinet L, Jean C, Dietrich G, Fournie JJ, Poupot R. PGE2 Inhibits Natural Killer and Gamma Delta T Cell Cytotoxicity Triggered by NKR and TCR Through a cAMP-Mediated PKA Type I-Dependent Signaling. *Biochem Pharmacol* (2010) 80(6):838–45. doi: 10.1016/j.bcp.2010.05.002
18. Karnezis T, Shayan R, Caesar C, Roufail S, Harris NC, Ardipradja K, et al. VEGF-D Promotes Tumor Metastasis by Regulating Prostaglandins Produced by the Collecting Lymphatic Endothelium. *Cancer Cell* (2012) 21(2):181–95. doi: 10.1016/j.ccr.2011.12.026
19. Treffkorn L, Scheibe R, Maruyama T, Dieter P. PGE2 Exerts its Effect on the LPS-Induced Release of TNF-Alpha, ET-1, IL-1alpha, IL-6 and IL-10 *via* the EP2 and EP4 Receptor in Rat Liver Macrophages. *Prostaglandins Other Lipid Mediat* (2004) 74(1-4):113–23. doi: 10.1016/j.prostaglandins.2004.07.005
20. Ellyard JI, Simson L, Parish CR. Th2-Mediated Anti-Tumour Immunity: Friend or Foe? *Tissue Antigens* (2007) 70(1):1–11. doi: 10.1111/j.1399-0039.2007.00869.x
21. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The Surgically Induced Stress Response. *JPEN J Parenter Enteral Nutr* (2013) 37(5 Suppl):21S–9S. doi: 10.1177/0148607113496117
22. Quatrini L, Ugolini S. New Insights Into the Cell- and Tissue-Specificity of Glucocorticoid Actions. *Cell Mol Immunol* (2021) 18(2):269–78. doi: 10.1038/s41423-020-00526-2
23. Bernabe DG, Tamae AC, Biasoli ER, Oliveira SH. Stress Hormones Increase Cell Proliferation and Regulates Interleukin-6 Secretion in Human Oral Squamous Cell Carcinoma Cells. *Brain Behav Immun* (2011) 25(3):574–83. doi: 10.1016/j.bbi.2010.12.012
24. Zhang H, Kong Q, Wang J, Jiang Y, Hua H. Complex Roles of cAMP-PKA-CREB Signaling in Cancer. *Exp Hematol Oncol* (2020) 9(1):32. doi: 10.1186/s40164-020-00191-1
25. Braadland PR, Ramberg H, Grytli HH, Tasken KA. Beta-Adrenergic Receptor Signaling in Prostate Cancer. *Front Oncol* (2014) 375:375. doi: 10.3389/fonc.2014.00375
26. Choy C, Raytis JL, Smith DD, Duenas M, Neman J, Jandial R, et al. Inhibition of Beta2-Adrenergic Receptor Reduces Triple-Negative Breast Cancer Brain Metastases: The Potential Benefit of Perioperative Beta-Blockade. *Oncol Rep* (2016) 35(6):3135–42. doi: 10.3892/or.2016.4710
27. Huang Q, Tan Q, Mao K, Yang G, Ma G, Luo P, et al. The Role of Adrenergic Receptors in Lung Cancer. *Am J Cancer Res* (2018) 8(11):2227–37.
28. Liu J, Qu L, Wan C, Xiao M, Ni W, Jiang F, et al. A Novel Beta2-AR/YB-1/Beta-Catenin Axis Mediates Chronic Stress-Associated Metastasis in Hepatocellular Carcinoma. *Oncogenesis* (2020) 9(9):84. doi: 10.1038/s41389-020-00268-w
29. Liu X, Wu WK, Yu L, Sung JJ, Srivastava G, Zhang ST, et al. Epinephrine Stimulates Esophageal Squamous-Cell Carcinoma Cell Proliferation *via* Beta-Adrenoceptor-Dependent Transactivation of Extracellular Signal-Regulated Kinase/Cyclooxygenase-2 Pathway. *J Cell Biochem* (2008) 105 (1):53–60. doi: 10.1002/jcb.21802
30. Gould CM, Courtneidge SA. Regulation of Invadopodia by the Tumor Microenvironment. *Cell Adh Migr* (2014) 8(3):226–35. doi: 10.4161/cam.28346
31. Creed SJ, Le CP, Hassan M, Pon CK, Albold S, Chan KT, et al. Beta2-Adrenoceptor Signaling Regulates Invadopodia Formation to Enhance Tumor Cell Invasion. *Breast Cancer Res* (2015) 17(1):145. doi: 10.1186/s13058-015-0655-3
32. Karayiannakis AJ, Syrigos KN, Zbar A, Baibas N, Polychronidis A, Simopoulos C, et al. Clinical Significance of Preoperative Serum Vascular Endothelial Growth Factor Levels in Patients With Colorectal Cancer and the Effect of Tumor Surgery. *Surgery* (2002) 131(5):548–55. doi: 10.1067/msy.2002.123011
33. Vidal O, Metges JP, Elizalde I, Valentini M, Volant A, Molina R, et al. High Preoperative Serum Vascular Endothelial Growth Factor Levels Predict Poor Clinical Outcome After Curative Resection of Gastric Cancer. *Br J Surg* (2009) 96(12):1443–51. doi: 10.1002/bjs.6780
34. Sia D, Alsinet C, Newell P, Villanueva A. VEGF Signaling in Cancer Treatment. *Curr Pharm Des* (2014) 20(17):2834–42. doi: 10.2174/13816128113199990590
35. Song M, Finley SD. Mechanistic Insight Into Activation of MAPK Signaling by Pro-Angiogenic Factors. *BMC Syst Biol* (2018) 12(1):145. doi: 10.1186/s12918-018-0668-5
36. Duque JL, Loughlin KR, Adam RM, Kantoff PW, Zurakowski D, Freeman MR. Plasma Levels of Vascular Endothelial Growth Factor Are Increased in Patients With Metastatic Prostate Cancer. *Urology* (1999) 54(3):523–7. doi: 10.1016/s0090-4295(99)00167-3
37. Georgiou GK, Igglezou M, Sainis I, Vareli K, Batsis H, Briasoulis E, et al. Impact of Breast Cancer Surgery on Angiogenesis Circulating Biomarkers: A Prospective Longitudinal Study. *World J Surg Oncol* (2013) 11:213. doi: 10.1186/1477-7819-11-213
38. Niu Q, Tang ZY, Ma ZC, Qin LX, Zhang LH. Serum Vascular Endothelial Growth Factor Is a Potential Biomarker of Metastatic Recurrence After Curative Resection of Hepatocellular Carcinoma. *World J Gastroenterol* (2000) 6(4):565–8. doi: 10.3748/wjg.v6.i4.565
39. Salven P, Perhoniemi V, Tykka H, Maenpaa H, Joensuu H. Serum VEGF Levels in Women With a Benign Breast Tumor or Breast Cancer. *Breast Cancer Res Treat* (1999) 53(2):161–6. doi: 10.1023/a:1006178517505
40. Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil Diversity and Plasticity in Tumour Progression and Therapy. *Nat Rev Cancer* (2020) 20(9):485–503. doi: 10.1038/s41568-020-0281-y
41. Jensen HK, Donskov F, Marcussen N, Nordsmark M, Lundbeck F, von der Maase H. Presence of Intratumoral Neutrophils Is an Independent Prognostic Factor in Localized Renal Cell Carcinoma. *J Clin Oncol* (2009) 27(28):4709–17. doi: 10.1200/JCO.2008.18.9498
42. Schmidt H, Bastholt L, Geertsen P, Christensen IJ, Larsen S, Gehl J, et al. Elevated Neutrophil and Monocyte Counts in Peripheral Blood Are Associated With Poor Survival in Patients With Metastatic Melanoma: A Prognostic Model. *Br J Cancer* (2005) 93(3):273–8. doi: 10.1038/sj.bjc.6602702
43. Shu Q, Hu ZL, Huang C, Yu XW, Fan H, Yang JW, et al. Orexin-A Promotes Cell Migration in Cultured Rat Astrocytes *via* Ca2+-Dependent PKCalpha and ERK1/2 Signals. *PloS One* (2014) 9(4):e95259. doi: 10.1371/journal.pone.0095259
44. Yang L, Liu Q, Zhang X, Liu X, Zhou B, Chen J, et al. DNA of Neutrophil Extracellular Traps Promotes Cancer Metastasis *via* CCDC25. *Nature* (2020) 583(7814):133–8. doi: 10.1038/s41586-020-2394-6
45. Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, et al. Neutrophil Extracellular Traps Sequester Circulating Tumor Cells and Promote Metastasis. *J Clin Invest* (2013), 3446–58. doi: 10.1172/JCI67484
46. Toffoli EC, Sheikhi A, Hoppner YD, de Kok P, Yazdanpanah-Samani M, Spanholtz J, et al. Natural Killer Cells and Anti-Cancer Therapies: Reciprocal Effects on Immune Function and Therapeutic Response. *Cancers (Basel)* (2021) 13(4). doi: 10.3390/cancers13040711
47. Moretta L, Bottino C, Pende D, Vitale M, Mingari MC, Moretta A. Human Natural Killer Cells: Molecular Mechanisms Controlling NK Cell Activation and Tumor Cell Lysis. *Immunol Lett* (2005) 100(1):7–13. doi: 10.1016/j.imlet.2005.07.004
48. Iannone F, Porzia A, Peruzzi G, Birarelli P, Milana B, Sacco L, et al. Effect of Surgery on Pancreatic Tumor-Dependent Lymphocyte Asset: Modulation of Natural Killer Cell Frequency and Cytotoxic Function. *Pancreas* (2015) 44 (3):386–93. doi: 10.1097/MPA.0000000000000288
49. Angka L, Martel AB, Kilgour M, Jeong A, Sadiq M, de Souza CT, et al. Natural Killer Cell IFNgamma Secretion Is Profoundly Suppressed Following Colorectal Cancer Surgery. *Ann Surg Oncol* (2018) 25(12):3747–54. doi: 10.1245/s10434-018-6691-3
50. Shi L, Guo H, Zheng Z, Liu J, Jiang Y, Su Y. Laparoscopic Surgery Versus Open Surgery for Colorectal Cancer: Impacts on Natural Killer Cells. *Cancer Control* (2020) 27(1):1073274820906811. doi: 10.1177/1073274820906811
51. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative Neutrophil-to-Lymphocyte Ratio (NLR) Is Associated With Reduced Disease-Free Survival Following Curative Resection of Pancreatic Adenocarcinoma. *World J Surg* (2011) 35(4):868–72. doi: 10.1007/s00268-011-0984-z
52. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, et al. Effect of Preoperative Neutrophil-Lymphocyte Ratio on the Surgical Outcomes of Stage II Colon Cancer Patients Who do Not Receive Adjuvant Chemotherapy. *Int J Colorectal Dis* (2011) 26(8):1059–65. doi: 10.1007/s00384-011-1192-x
53. Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative Neutrophil to Lymphocyte Ratio as a Prognostic Predictor After Curative Resection for non-Small Cell Lung Cancer. *Anticancer Res* (2011) 31 (9):2995–8. doi: 10.2478/jomb-2019-0031

54. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to Lymphocyte Ratio and Cancer Prognosis: An Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies. *BMC Med* (2020) 18(1):360. doi: 10.1186/s12916-020-01817-1
55. Forget P, Machiels JP, Coulie PG, Berliere M, Poncelet AJ, Tombal B, et al. Neutrophil:lymphocyte Ratio and Intraoperative Use of Ketorolac or Diclofenac Are Prognostic Factors in Different Cohorts of Patients Undergoing Breast, Lung, and Kidney Cancer Surgery. *Ann Surg Oncol* (2013) 20 Suppl 3:S650–60. doi: 10.1245/s10434-013-3136-x
56. Choi JE, Villarreal J, Lasala J, Gottumukkala V, Mehran RJ, Rice D, et al. Perioperative Neutrophil:Lymphocyte Ratio and Postoperative NSAID Use as Predictors of Survival After Lung Cancer Surgery: A Retrospective Study. *Cancer Med* (2015) 4(6):825–33. doi: 10.1002/cam4.428
57. Zhao H, Liao X, Kang Y. Tregs: Where We Are and What Comes Next? *Front Immunol* (2017) 8:1578. doi: 10.3389/fimmu.2017.01578
58. Ghiringhelli FO, Ménard CD, Terme M, Flament C, Taieb J, Chaput N, et al. CD4+CD25+ Regulatory T Cells Inhibit Natural Killer Cell Functions in a Transforming Growth Factor–β–Dependent Manner. *J Exp Med* (2005) 202 (8):1075–85. doi: 10.1084/jem.20051511
59. Liyanage UK, Moore TT, Joo HG, Tanaka Y, Herrmann V, Doherty G, et al. Prevalence of Regulatory T Cells Is Increased in Peripheral Blood and Tumor Microenvironment of Patients With Pancreas or Breast Adenocarcinoma. *J Immunol* (2002) 169(5):2756–61. doi: 10.4049/jimmunol.169.5.2756
60. Scholz AS, Handke J, Gillmann HJ, Zhang Q, Dehne S, Janssen H, et al. Frontline Science: Low Regulatory T Cells Predict Perioperative Major Adverse Cardiovascular and Cerebrovascular Events After Noncardiac Surgery. *J Leukoc Biol* (2019) 107(5):717–30. doi: 10.1002/jlb.5hi1018-392rr
61. Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, et al. Isoflurane, a Commonly Used Volatile Anesthetic, Enhances Renal Cancer Growth and Malignant Potential via the Hypoxia-Inducible Factor Cellular Signaling Pathway *In Vitro*. *Anesthesiology* (2013) 119(3):593–605. doi: 10.1097/ALN.0b013e31829e47fd
62. Zhu M, Li M, Zhou Y, Dangelmajer S, Kahlert UD, Xie R, et al. Isoflurane Enhances the Malignant Potential of Glioblastoma Stem Cells by Promoting Their Viability, Mobility *In Vitro* and Migratory Capacity *In Vivo*. *Br J Anaesth* (2016) 116(6):870–7. doi: 10.1093/bja/aew124
63. Zhang W, Shao X. Isoflurane Promotes Non-Small Cell Lung Cancer Malignancy by Activating the Akt-Mammalian Target of Rapamycin (mTOR) Signaling Pathway. *Med Sci Monit* (2016) 22:4644–50. doi: 10.12659/msm.898434
64. Ren J, Wang X, Wei G, Meng Y. Exposure to Desflurane Anesthesia Confers Colorectal Cancer Cells Metastatic Capacity Through Deregulation of miR-34a/LOXL3. *Eur J Cancer Prev* (2021) 30(2):143–53. doi: 10.1097/CEJ.0000000000000608
65. Deng X, Vipani M, Liang G, Gouda D, Wang B, Wei H. Sevoflurane Modulates Breast Cancer Cell Survival *via* Modulation of Intracellular Calcium Homeostasis. *BMC Anesthesiol* (2020) 20(1):253. doi: 10.1186/s12871-020-01139-y
66. Tazawa K, Koutsogiannaki S, Chamberlain M, Yuki K. The Effect of Different Anesthetics on Tumor Cytotoxicity by Natural Killer Cells. *Toxicol Lett* (2017) 266:23–31. doi: 10.1016/j.toxlet.2016.12.007
67. Markovic SN, Knight PR, Murasko DM. Inhibition of Interferon Stimulation of Natural Killer Cell Activity in Mice Anesthetized With Halothane or Isoflurane. *Anesthesiology* (1993) 78(4):700–6. doi: 10.1097/00000542-199304000-00013
68. Mitsuhata H, Shimizu R, Yokoyama MM. Suppressive Effects of Volatile Anesthetics on Cytokine Release in Human Peripheral Blood Mononuclear Cells. *Int J Immunopharmacol* (1995) 17(6):529–34. doi: 10.1016/0192-0561(95)00026-X
69. Ciechanowicz S, Zhao H, Chen Q, Cui J, Mi E, Mi E, et al. Differential Effects of Sevoflurane on the Metastatic Potential and Chemosensitivity of non-Small-Cell Lung Adenocarcinoma and Renal Cell Carcinoma *In Vitro*. *Br J Anaesth* (2018) 120(2):368–75. doi: 10.1016/j.bja.2017.11.066
70. Liang H, Gu M, Yang C, Wang H, Wen X, Zhou Q. Sevoflurane Inhibits Invasion and Migration of Lung Cancer Cells by Inactivating the P38 MAPK Signaling Pathway. *J Anesth* (2012) 26(3):381–92. doi: 10.1007/s00540-011-1317-y
71. Liang H, Yang CX, Zhang B, Wang HB, Liu HZ, Lai XH, et al. Sevoflurane Suppresses Hypoxia-Induced Growth and Metastasis of Lung Cancer Cells *via* Inhibiting Hypoxia-Inducible Factor-1alpha. *J Anesth* (2015) 29(6):821–30. doi: 10.1007/s00540-015-2035-7
72. Fan L, Wu Y, Wang J, He J, Han X. Sevoflurane Inhibits the Migration and Invasion of Colorectal Cancer Cells Through Regulating ERK/MMP-9 Pathway by Up-Regulating miR-203. *Eur J Pharmacol* (2019) 850:43–52. doi: 10.1016/j.ejphar.2019.01.025
73. Kvolik S, Dobrosevic B, Marczi S, Prlic L, Glavas-Obrovac L. Different Apoptosis Ratios and Gene Expressions in Two Human Cell Lines After Sevoflurane Anaesthesia. *Acta Anaesthesiol Scand* (2009) 53(9):1192–9. doi: 10.1111/j.1399-6576.2009.02036.x
74. Gao K, Su Z, Liu H, Liu Y. Anti-Proliferation and Anti-Metastatic Effects of Sevoflurane on Human Osteosarcoma U2OS and Saos-2 Cells. *Exp Mol Pathol* (2019) 108:121–30. doi: 10.1016/j.yexmp.2019.04.005
75. Li Y, Dong W, Yang H, Xiao G. Propofol Suppresses Proliferation and Metastasis of Colorectal Cancer Cells by Regulating miR-124-3p.1/AKT3. *Biotechnol Lett* (2020) 42(3):493–504. doi: 10.1007/s10529-019-02787-y
76. Miao Y, Zhang Y, Wan H, Chen L, Wang F. GABA-Receptor Agonist, Propofol Inhibits Invasion of Colon Carcinoma Cells. *BioMed Pharmacother* (2010) 64(9):583–8. doi: 10.1016/j.biopha.2010.03.006
77. Xing SG, Zhang KJ, Qu JH, Ren YD, Luan Q. Propofol Induces Apoptosis of non-Small Cell Lung Cancer Cells *via* ERK1/2-Dependent Upregulation of PUMA. *Eur Rev Med Pharmacol Sci* (2018) 22(13):4341–9. doi: 10.26355/eurrev_201807_15431
78. Yang N, Liang Y, Yang P, Ji F. Propofol Suppresses LPS-Induced Nuclear Accumulation of HIF-1alpha and Tumor Aggressiveness in Non-Small Cell Lung Cancer. *Oncol Rep* (2017) 37(5):2611–9. doi: 10.3892/or.2017.5514
79. Wu KC, Yang ST, Hsia TC, Yang JS, Chiou SM, Lu CC, et al. Suppression of Cell Invasion and Migration by Propofol Are Involved in Down-Regulating Matrix Metalloproteinase-2 and P38 MAPK Signaling in A549 Human Lung Adenocarcinoma Epithelial Cells. *Anticancer Res* (2012) 32(11):4833–42.
80. Li Q, Zhang L, Han Y, Jiang Z, Wang Q. Propofol Reduces MMPs Expression by Inhibiting NF-kappaB Activity in Human MDA-MB-231 Cells. *BioMed Pharmacother* (2012) 66(1):52–6. doi: 10.1016/j.biopha.2011.10.006
81. Wang D, Yang T, Liu J, Liu Y, Xing N, He J, et al. Propofol Inhibits the Migration and Invasion of Glioma Cells by Blocking the PI3K/AKT Pathway Through miR-206/ROCK1 Axis. *Onco Targets Ther* (2020) 13:361–70. doi: 10.2147/OTT.S232601
82. Yang C, Xia Z, Li T, Chen Y, Zhao M, Sun Y, et al. Antioxidant Effect of Propofol in Gliomas and Its Association With Divalent Metal Transporter 1. *Front Oncol* (2020) 10:590931. doi: 10.3389/fonc.2020.590931
83. Liu D, Sun X, Du Y, Kong M. Propofol Promotes Activity and Tumor-Killing Ability of Natural Killer Cells in Peripheral Blood of Patients With Colon Cancer. *Med Sci Monit* (2018) 24:6119–28. doi: 10.12659/MSM.911218
84. Zhou M, Dai J, Zhou Y, Wu J, Xu T, Zhou D, et al. Propofol Improves the Function of Natural Killer Cells From the Peripheral Blood of Patients With Esophageal Squamous Cell Carcinoma. *Exp Ther Med* (2018) 16(1):83–92. doi: 10.3892/etm.2018.6140
85. Helmy SA, Al-Attiyah RJ. The Immunomodulatory Effects of Prolonged Intravenous Infusion of Propofol Versus Midazolam in Critically Ill Surgical Patients. *Anaesthesia* (2001) 56(1):4–8. doi: 10.1046/j.1365-2044.2001.01713.x
86. Inada T, Hirota K, Shingu K. Intravenous Anesthetic Propofol Suppresses Prostaglandin E2 and Cysteinyl Leukotriene Production and Reduces Edema Formation in Arachidonic Acid-Induced Ear Inflammation. *J Immunotoxicol* (2015) 12(3):261–5. doi: 10.3109/1547691X.2014.938874
87. Chen MS, Lin WC, Yeh HT, Hu CL, Sheu SM. Propofol Specifically Reduces PMA-Induced Neutrophil Extracellular Trap Formation Through Inhibition of P-ERK and HOCl. *Life Sci* (2019) 221:178–86. doi: 10.1016/j.lfs.2019.02.030
88. Meier A, Chien J, Hobohm L, Patras KA, Nizet V, Corriden R. Inhibition of Human Neutrophil Extracellular Trap (NET) Production by Propofol and Lipid Emulsion. *Front Pharmacol* (2019) 10:323. doi: 10.3389/fphar.2019.00323
89. Li T, Yang J, Yang B, Zhao G, Lin H, Liu Q, et al. Ketamine Inhibits Ovarian Cancer Cell Growth by Regulating the lncRNA-PVT1/EZH2/p57 Axis. *Front Genet* (2020) 11:597467. doi: 10.3389/fgene.2020.597467

90. Duan W, Hu J, Liu Y. Ketamine Inhibits Colorectal Cancer Cells Malignant Potential *via* Blockage of NMDA Receptor. *Exp Mol Pathol* (2019) 107:171–8. doi: 10.1016/j.yexmp.2019.02.004
91. Zhou X, Zhang P, Luo W, Zhang L, Hu R, Sun Y, et al. Ketamine Induces Apoptosis in Lung Adenocarcinoma Cells by Regulating the Expression of CD69. *Cancer Med* (2018) 7(3):788–95. doi: 10.1002/cam4.1288
92. Lee ST, Wu TT, Yu PY, Chen RM. Apoptotic Insults to Human HepG2 Cells Induced by S-(+)-Ketamine Occurs Through Activation of a Bax-Mitochondria-Caspase Protease Pathway. *Br J Anaesth* (2009) 102(1):80–9. doi: 10.1093/bja/aen322
93. Malsy M, Gebhardt K, Gruber M, Wiese C, Graf B, Bundscherer A. Effects of Ketamine, s-Ketamine, and MK 801 on Proliferation, Apoptosis, and Necrosis in Pancreatic Cancer Cells. *BMC Anesthesiol* (2015) 15:111. doi: 10.1186/s12871-015-0076-y
94. Zhang P, He H, Bai Y, Liu W, Huang L. Dexmedetomidine Suppresses the Progression of Esophageal Cancer *via* miR-143-3p/Epidermal Growth Factor Receptor Pathway Substrate 8 Axis. *Anticancer Drugs* (2020) 31 (7):693–701. doi: 10.1097/CAD.0000000000000934
95. Bruzzone A, Pinero CP, Castillo LF, Sarappa MG, Rojas P, Lanari C, et al. Alpha2-Adrenoceptor Action on Cell Proliferation and Mammary Tumour Growth in Mice. *Br J Pharmacol* (2008) 155(4):494–504. doi: 10.1038/bjp.2008.278
96. Szpunar MJ, Burke KA, Dawes RP, Brown EB, Madden KS. The Antidepressant Desipramine and Alpha2-Adrenergic Receptor Activation Promote Breast Tumor Progression in Association With Altered Collagen Structure. *Cancer Prev Res (Phila)* (2013) 6(12):1262–72. doi: 10.1158/1940-6207.CAPR-13-0079
97. Chen P, Luo X, Dai G, Jiang Y, Luo Y, Peng S, et al. Dexmedetomidine Promotes the Progression of Hepatocellular Carcinoma Through Hepatic Stellate Cell Activation. *Exp Mol Med* (2020) 52(7):1062–74. doi: 10.1038/s12276-020-0461-6
98. Wang C, Datoo T, Zhao H, Wu L, Date A, Jiang C, et al. Midazolam and Dexmedetomidine Affect Neuroglioma and Lung Carcinoma Cell Biology *In Vitro* and *In Vivo*. *Anesthesiology* (2018) 129(5):1000–14. doi: 10.1097/ALN.0000000000002401
99. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120(1):188–96. doi: 10.1016/j.bja.2017.11.004
100. Sun H, Sun Y. Lidocaine Inhibits Proliferation and Metastasis of Lung Cancer Cell *via* Regulation of miR-539/EGFR Axis. *Artif Cells Nanomed Biotechnol* (2019) 47(1):2866–74. doi: 10.1080/21691401.2019.1636807
101. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells *In Vitro* and in a Xenograft Model *In Vivo*. *Anesthesiology* (2017) 126(5):868–81. doi: 10.1097/ALN.0000000000001528
102. Zhu J, Han S. Lidocaine Inhibits Cervical Cancer Cell Proliferation and Induces Cell Apoptosis by Modulating the lncRNA-MEG3/miR-421/BTG1 Pathway. *Am J Transl Res* (2019) 11(9):5404–16.
103. Chiu KM, Lu CW, Lee MY, Wang MJ, Lin TY, Wang SJ. Neuroprotective and Anti-Inflammatory Effects of Lidocaine in Kainic Acid-Injected Rats. *Neuroreport* (2016) 27(7):501–7. doi: 10.1097/WNR.0000000000000570
104. Lan W, Harmon DC, Wang JH, Shorten GD, Redmond PH. Activated Endothelial Interleukin-1beta, -6, and -8 Concentrations and Intercellular Adhesion Molecule-1 Expression Are Attenuated by Lidocaine. *Anesth Analg* (2005) 100(2):409–12. doi: 10.1213/01.ANE.0000142113.39092.87
105. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The Effect of Perioperative Intravenous Lidocaine on Postoperative Pain and Immune Function. *Anesth Analg* (2009) 109(5):1464–9. doi: 10.1213/ANE.0b013e3181bab1bd
106. Cata JP, Ramirez MF, Velasquez JF, Di AI, Popat KU, Gottumukkala V, et al. Lidocaine Stimulates the Function of Natural Killer Cells in Different Experimental Settings. *Anticancer Res* (2017) 37(9):4727–32. doi: 10.21873/anticanres.11879
107. Galos EV, Tat TF, Popa R, Efrimescu CI, Finnerty D, Buggy DJ, et al. Neutrophil Extracellular Trapping and Angiogenesis Biomarkers After Intravenous or Inhalation Anaesthesia With or Without Intravenous Lidocaine for Breast Cancer Surgery: A Prospective, Randomised Trial. *Br J Anaesth* (2020) 125(5):712–21. doi: 10.1016/j.bja.2020.05.003
108. Suzuki S, Mori A, Fukui A, Ema Y, Nishiwaki K. Lidocaine Inhibits Vascular Endothelial Growth Factor-A-Induced Angiogenesis. *J Anesth* (2020) 34 (6):857–64. doi: 10.1007/s00540-020-02830-7
109. Makito K, Matsui H, Fushimi K, Yasunaga H. Volatile Versus Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery. *Anesthesiology* (2020) 133(4):764–73. doi: 10.1097/ALN.0000000000003440
110. Koo BW, Lim DJ, Oh AY, Na HS. Retrospective Comparison Between the Effects of Propofol and Inhalation Anesthetics on Postoperative Recurrence of Early- and Intermediate-Stage Hepatocellular Carcinoma. *Med Princ Pract* (2020) 29(5):422–8. doi: 10.1159/000506637
111. Grau SJ, Lohr M, Taurisano V, Trautner H, Timmer M, Schwab SG, et al. The Choice of Anaesthesia for Glioblastoma Surgery Does Not Impact the Time to Recurrence. *Sci Rep* (2020) 10(1):5556. doi: 10.1038/s41598-020-62087-8
112. Enlund M, Berglund A, Ahlstrand R, Wallden J, Lundberg J, Warnberg F, et al. Survival After Primary Breast Cancer Surgery Following Propofol or Sevoflurane General Anesthesia-A Retrospective, Multicenter, Database Analysis of 6305 Swedish Patients. *Acta Anaesthesiol Scand* (2020) 64 (8):1048–54. doi: 10.1111/aas.13644
113. Dong J, Zeng M, Ji N, Hao S, Zhou Y, Gao Z, et al. Impact of Anesthesia on Long-Term Outcomes in Patients With Supratentorial High-Grade Glioma Undergoing Tumor Resection: A Retrospective Cohort Study. *J Neurosurg Anesthesiol* (2020) 32(3):227–33. doi: 10.1097/ANA.0000000000000588
114. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, et al. Total Intravenous Anesthesia Versus Inhalation Anesthesia for Breast Cancer Surgery: A Retrospective Cohort Study. *Anesthesiology* (2019) 130(1):31–40. doi: 10.1097/ALN.0000000000002491
115. Oh TK, Kim HH, Jeon YT. Retrospective Analysis of 1-Year Mortality After Gastric Cancer Surgery: Total Intravenous Anesthesia Versus Volatile Anesthesia. *Acta Anaesthesiol Scand* (2019) 63(9):1169–77. doi: 10.1111/aas.13414
116. Lai HC, Lee MS, Lin KT, Chan SM, Chen JY, Lin YT, et al. Propofol-Based Total Intravenous Anesthesia Is Associated With Better Survival Than Desflurane Anesthesia in Intrahepatic Cholangiocarcinoma Surgery. *Med (Baltimore)* (2019) 98(51):e18472. doi: 10.1097/MD.0000000000018472
117. Lai HC, Lee MS, Lin C, Lin KT, Huang YH, Wong CS, et al. Propofol-Based Total Intravenous Anaesthesia Is Associated With Better Survival Than Desflurane Anaesthesia in Hepatectomy for Hepatocellular Carcinoma: A Retrospective Cohort Study. *Br J Anaesth* (2019) 123(2):151–60. doi: 10.1016/j.bja.2019.04.057
118. Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, et al. Propofol-Based Total Intravenous Anesthesia did Not Improve Survival Compared to Desflurane Anesthesia in Breast Cancer Surgery. *PloS One* (2019) 14(11): e0224728. doi: 10.1371/journal.pone.0224728
119. Hong B, Lee S, Kim Y, Lee M, Youn AM, Rhim H, et al. Anesthetics and Long-Term Survival After Cancer Surgery-Total Intravenous Versus Volatile Anesthesia: A Retrospective Study. *BMC Anesthesiol* (2019) 19(1):233. doi: 10.1186/s12871-019-0914-4
120. Cata JP, Nguyen LT, Ifeanyi-Pillette IC, Van Meter A, Dangler LA, Feng L, et al. An Assessment of the Survival Impact of Multimodal Anesthesia/Analgesia Technique in Adults Undergoing Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy: A Propensity Score Matched Analysis. *Int J Hyperthermia* (2019) 36(1):369–75. doi: 10.1080/02656736.2019.1574985
121. Zheng X, Wang Y, Dong L, Zhao S, Wang L, Chen H, et al. Effects of Propofol-Based Total Intravenous Anesthesia on Gastric Cancer: A Retrospective Study. *Onco Targets Ther* (2018) 11:1141–8. doi: 10.2147/OTT.S156792
122. Wu ZF, Lee MS, Wong CS, Lu CH, Huang YS, Lin KT, et al. Propofol-Based Total Intravenous Anesthesia Is Associated With Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology* (2018) 129 (5):932–41. doi: 10.1097/ALN.0000000000002357
123. Oh TK, Kim K, Jheon S, Lee J, Do SH, Hwang JW, et al. Long-Term Oncologic Outcomes for Patients Undergoing Volatile Versus Intravenous Anesthesia for Non-Small Cell Lung Cancer Surgery: A Retrospective Propensity Matching Analysis. *Cancer Control* (2018) 25 (1):1073274818775360. doi: 10.1177/1073274818775360
124. Kim MH, Kim DW, Kim JH, Lee KY, Park S, Yoo YC. Does the Type of Anesthesia Really Affect the Recurrence-Free Survival After Breast Cancer Surgery? *Oncotarget* (2017) 8(52):90477–87. doi: 10.18632/oncotarget.21014

125. Cata JP, Hagan KB, Bhavsar SD, Arunkumar R, Grasu R, Dang A, et al. The Use of Isoflurane and Desflurane as Inhalational Agents for Glioblastoma Surgery. A Survival Analysis. *J Clin Neurosci* (2017) 35:82–7. doi: 10.1016/j.jocn.2016.10.006
126. Jun IJ, Jo JY, Kim JI, Chin JH, Kim WJ, Kim HR, et al. Impact of Anesthetic Agents on Overall and Recurrence-Free Survival in Patients Undergoing Esophageal Cancer Surgery: A Retrospective Observational Study. *Sci Rep* (2017) 7(1):14020. doi: 10.1038/s41598-017-14147-9
127. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of Propofol-Based Total Intravenous Anesthesia on Recurrence and Overall Survival in Patients After Modified Radical Mastectomy: A Retrospective Study. *Korean J Anesthesiol* (2016) 69(2):126–32. doi: 10.4097/kjae.2016.69.2.126
128. Wigmore TJ, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/ALN.0000000000000936
129. Elias KM, Kang S, Liu X, Horowitz NS, Berkowitz RS, Frendl G. Anesthetic Selection and Disease-Free Survival Following Optimal Primary Cytoreductive Surgery for Stage III Epithelial Ovarian Cancer. *Ann Surg Oncol* (2015) 22(4):1341–8. doi: 10.1245/s10434-014-4112-9
130. Chang CY, Wu MY, Chien YJ, Su IM, Wang SC, Kao MC. Anesthesia and Long-Term Oncological Outcomes: A Systematic Review and Meta-Analysis. *Anesth Analg* (2021) 132(3):623–34. doi: 10.1213/ANE.0000000000005237
131. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The Choice of Anaesthetic–Sevoflurane or Propofol–and Outcome From Cancer Surgery: A Retrospective Analysis. *Ups J Med Sci* (2014) 119(3):251–61. doi: 10.3109/03009734.2014.922649
132. Sung CH, Tsuang FY, Shih CC, Chang JL, Liao MH, Yang YW, et al. Scalp Block Is Associated With Improved Recurrence Profiles in Patients Undergoing Primary Glioma Resection Surgery. *J Neurosurg Anesthesiol* (2021) 33(3):239–46. doi: 10.1097/ANA.0000000000000664
133. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel BGlobal Onco-Anesthesia Research Collaboration, G. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anaesth* (2019) 66(5):546–61. doi: 10.1007/s12630-019-01330-x
134. Xu Q, Shi NJ, Zhang H, Zhu YM. Effects of Combined General-Epidural Anesthesia and Total Intravenous Anesthesia on Cellular Immunity and Prognosis in Patients With Nonsmall Cell Lung Cancer: A Comparative Study. *Mol Med Rep* (2017) 16(4):4445–54. doi: 10.3892/mmr.2017.7144
135. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X
136. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of Propofol/Remifentanil-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Release of VEGF-C and TGF-Beta and Prognosis After Breast Cancer Surgery: A Prospective, Randomized and Controlled Study. *BMC Anesthesiol* (2018) 18(1):131. doi: 10.1186/s12871-018-0588-3
137. Enlund M. Is It Definitely Clear That Long-Term Survival After Breast Cancer Surgery Is Not Affected by Anaesthetics? *Cancers (Basel)* (2021) 13 (14). doi: 10.3390/cancers13143390
138. Dubowitz JA, Cata JP, De Silva AP, Braat S, Shan D, Yee K, et al. Volatile Anaesthesia and Peri-Operative Outcomes Related to Cancer: A Feasibility and Pilot Study for a Large Randomised Control Trial. *Anaesthesia* (2021) 76 (9):1198–206. doi: 10.1111/anae.15354
139. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association Between Intraoperative Intravenous Lidocaine Infusion and Survival in Patients Undergoing Pancreatectomy for Pancreatic Cancer: A Retrospective Study. *Br J Anaesth* (2020) 125(2):141–8. doi: 10.1016/j.bja.2020.03.034
140. Calvo-Soto P, Martinez-Contreras A, Hernandez BT, And FP, Vasquez C. Spinal-General Anaesthesia Decreases Neuroendocrine Stress Response in Laparoscopic Cholecystectomy. *J Int Med Res* (2012) 40(2):657–65. doi: 10.1177/147323001204000228
141. Ingelmo PM, Ferri F, Fumagalli R. Interactions Between General and Regional Anesthesia. *Minerva Anestesiol* (2006) 72(6):437–45.
142. Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. *Anesth Analg* (2017) 125(5):1749–60. doi: 10.1213/ANE.0000000000002497
143. Perez-Gonzalez O, Cuellar-Guzman LF, Soliz J, Cata JP. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature. *Reg Anesth Pain Med* (2017) 42(6):751–6. doi: 10.1097/AAP.0000000000000662
144. Zhang Y, Peng X, Zheng Q. Ropivacaine Inhibits the Migration of Esophageal Cancer Cells *via* Sodium-Channel-Independent But Prenylation-Dependent Inhibition of Rac1/JNK/Paxillin/FAK. *Biochem Biophys Res Commun* (2018) 501(4):1074–9. doi: 10.1016/j.bbrc.2018.05.110
145. Tai YH, Chang WK, Wu HL, Chan MY, Chen HH, Chang KY. The Effect of Epidural Analgesia on Cancer Progression in Patients With Stage IV Colorectal Cancer After Primary Tumor Resection: A Retrospective Cohort Study. *PloS One* (2018) 13(7):e0200893. doi: 10.1371/journal.pone.0200893
146. Zimmitti G, Soliz J, Aloia TA, Gottumukkala V, Cata JP, Tzeng CW, et al. Positive Impact of Epidural Analgesia on Oncologic Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. *Ann Surg Oncol* (2016) 23(3):1003–11. doi: 10.1245/s10434-015-4933-1
147. Vogelaar FJ, Abegg R, van der Linden JC, Cornelisse HG, van Dorsten FR, Lemmens VE, et al. Epidural Analgesia Associated With Better Survival in Colon Cancer. *Int J Colorectal Dis* (2015) 30(8):1103–7. doi: 10.1007/s00384-015-2224-8
148. Holler JP, Ahlbrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, et al. Peridural Analgesia may Affect Long-Term Survival in Patients With Colorectal Cancer After Surgery (PACO-RAS-Study): An Analysis of a Cancer Registry. *Ann Surg* (2013) 258(6):989–93. doi: 10.1097/SLA.0b013e3182915f61
149. Cummings KC3rd, Xu F, Cummings LC, Cooper GS. A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence After Colectomy: A Population-Based Study. *Anesthesiology* (2012) 116(4):797–806. doi: 10.1097/ALN.0b013e31824674f6
150. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective Analysis of the Effect of Postoperative Analgesia on Survival in Patients After Laparoscopic Resection of Colorectal Cancer. *Br J Anaesth* (2012) 109 (2):185–90. doi: 10.1093/bja/aes106
151. Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in Mortality After Epidural Anaesthesia and Analgesia in Patients Undergoing Rectal But Not Colonic Cancer Surgery: A Retrospective Analysis of Data From 655 Patients in Central Sweden. *Br J Anaesth* (2011) 107(2):164–70. doi: 10.1093/bja/aer100
152. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association Between Epidural Analgesia and Cancer Recurrence After Colorectal Cancer Surgery. *Anesthesiology* (2010) 113(1):27–34. doi: 10.1097/ALN.0b013e3181de6d0d
153. Tsigonis AM, Al-Hamadani M, Linebarger JH, Vang CA, Krause FJ, Johnson JM, et al. Are Cure Rates for Breast Cancer Improved by Local and Regional Anesthesia? *Reg Anesth Pain Med* (2016) 41(3):339–47. doi: 10.1097/AAP.0000000000000379
154. Kairaluoma P, Mattson J, Heikkila P, Pere P, Leidenius M. Perioperative Paravertebral Regional Anaesthesia and Breast Cancer Recurrence. *Anticancer Res* (2016) 36(1):415–8. doi: 10.2165/00128413-200615610-00023
155. Cata JP, Chavez-MacGregor M, Valero V, Black W, Black DM, Goravanchi F, et al. The Impact of Paravertebral Block Analgesia on Breast Cancer Survival After Surgery. *Reg Anesth Pain Med* (2016) 41(6):696–703. doi: 10.1097/AAP.0000000000000479
156. Starnes-Ott K, Goravanchi F, Meininger JC. Anesthetic Choices and Breast Cancer Recurrence: A Retrospective Pilot Study of Patient, Disease, and Treatment Factors. *Crit Care Nurs Q* (2015) 38(2):200–10. doi: 10.1097/CNQ.0000000000000062
157. Koonce SL, McLaughlin SA, Eck DL, Porter S, Bagaria S, Clendenen SR, et al. Breast Cancer Recurrence in Patients Receiving Epidural and Paravertebral Anesthesia: A Retrospective, Case-Control Study. *Middle East J Anaesthesiol* (2014) 22(6):567–71.
158. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008

159. Tseng KS, Kulkarni S, Humphreys EB, Carter HB, Mostwin JL, Partin AW, et al. Spinal Anesthesia Does Not Impact Prostate Cancer Recurrence in a Cohort of Men Undergoing Radical Prostatectomy: An Observational Study. *Reg Anesth Pain Med* (2014) 39(4):284–8. doi: 10.1097/AAP.0000000000000108
160. Sprung J, Scavonetto F, Yeoh TY, Kramer JM, Karnes RJ, Eisenach JH, et al. Outcomes After Radical Prostatectomy for Cancer: A Comparison Between General Anesthesia and Epidural Anesthesia With Fentanyl Analgesia: A Matched Cohort Study. *Anesth Analg* (2014) 119(4):859–66. doi: 10.1213/ANE.0000000000000320
161. Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, et al. Association Between Neuraxial Analgesia, Cancer Progression, and Mortality After Radical Prostatectomy: A Large, Retrospective Matched Cohort Study. *Br J Anaesth* (2014) 113 Suppl 1:i95–102. doi: 10.1093/bja/aet467
162. Roiss M, Schiffmann J, Tennstedt P, Kessler T, Blanc I, Goetz A, et al. Oncological Long-Term Outcome of 4772 Patients With Prostate Cancer Undergoing Radical Prostatectomy: Does the Anaesthetic Technique Matter? *Eur J Surg Oncol* (2014) 40(12):1686–92. doi: 10.1016/j.ejso.2014.02.223
163. Ehdaie B, Sjoberg DD, Dalecki PH, Scardino PT, Eastham JA, Amar D. Association of Anesthesia Technique for Radical Prostatectomy With Biochemical Recurrence: A Retrospective Cohort Study. *Can J Anaesth* (2014) 61(12):1068–74. doi: 10.1007/s12630-014-0221-y
164. Wuethrich PY, Thalmann GN, Studer UE, Burkhard FC. Epidural Analgesia During Open Radical Prostatectomy Does Not Improve Long-Term Cancer-Related Outcome: A Retrospective Study in Patients With Advanced Prostate Cancer. *PloS One* (2013) 8(8):e72873. doi: 10.1371/journal.pone.0072873
165. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, et al. Do Intraoperative Analgesics Influence Oncological Outcomes After Radical Prostatectomy for Prostate Cancer? *Eur J Anaesthesiol* (2011) 28(12):830–5. doi: 10.1097/EJA.0b013e32834b7d9a
166. Wuethrich PY, Hsu Schmitz SF, Kessler TM, Thalmann GN, Studer UE, Stueber F, et al. Potential Influence of the Anesthetic Technique Used During Open Radical Prostatectomy on Prostate Cancer-Related Outcome: A Retrospective Study. *Anesthesiology* (2010) 113(3):570–6. doi: 10.1097/ALN.0b013e3181e4f6ec
167. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence: A Retrospective Analysis. *Anesthesiology* (2008) 109(2):180–7. doi: 10.1097/ALN.0b013e31817f5b73
168. Lacassie HJ, Cartagena J, Branes J, Assel M, Echevarria GC. The Relationship Between Neuraxial Anesthesia and Advanced Ovarian Cancer-Related Outcomes in the Chilean Population. *Anesth Analg* (2013) 117(3):653–60. doi: 10.1213/ANE.0b013e3182a07046
169. Capmas P, Billard V, Gouy S, Lhomme C, Pautier P, Morice P, et al. Impact of Epidural Analgesia on Survival in Patients Undergoing Complete Cytoreductive Surgery for Ovarian Cancer. *Anticancer Res* (2012) 32(4):1537–42.
170. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic Technique may Affect Prognosis for Ovarian Serous Adenocarcinoma: A Retrospective Analysis. *Br J Anaesth* (2011) 106(6):814–22. doi: 10.1093/bja/aer055
171. de Oliveira GSJr., Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. Intraoperative Neuraxial Anesthesia But Not Postoperative Neuraxial Analgesia Is Associated With Increased Relapse-Free Survival in Ovarian Cancer Patients After Primary Cytoreductive Surgery. *Reg Anesth Pain Med* (2011) 36(3):271–7. doi: 10.1097/AAP.0b013e318217aada
172. Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anesthesia-Analgesia and Recurrence-Free Survival After Lung Cancer Surgery: A Randomized Trial. *Anesthesiol* (2021). doi: 10.1097/ALN.0000000000003873
173. Du YT, Li YW, Zhao BJ, Guo XY, Feng Y, Zuo MZ, et al. Long-Term Survival After Combined Epidural-General Anesthesia or General Anesthesia Alone: Follow-Up of a Randomized Trial. *Anesthesiology* (2021) 135(2):233–45. doi: 10.1097/ALN.0000000000003835
174. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival Analysis of Patients With Breast Cancer Undergoing a Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: A 5-Year Follow-Up of a Randomized Controlled Trial. *Anticancer Res* (2017) 37(10):5813–20. doi: 10.21873/anticanres.12024
175. Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NPS, et al. Post-Mastectomy Cancer Recurrence With and Without a Continuous Paravertebral Block in the Immediate Postoperative Period: A Prospective Multi-Year Follow-Up Pilot Study of a Randomized, Triple-Masked, Placebo-Controlled Investigation. *J Anesth* (2017) 31(3):374–9. doi: 10.1007/s00540-017-2345-z
176. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major Abdominal Surgery for Cancer: Does Epidural Analgesia Have a Long-Term Effect on Recurrence-Free and Overall Survival? *Ann Fr Anesth Reanim* (2013) 32(5):e81–88. doi: 10.1016/j.annfar.2013.02.027
177. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI, et al. Perioperative Epidural Analgesia for Major Abdominal Surgery for Cancer and Recurrence-Free Survival: Randomised Trial. *BMJ* (2011) 342:d1491. doi: 10.1136/bmj.d1491
178. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-Term Survival After Colon Cancer Surgery: A Variation Associated With Choice of Anesthesia. *Anesth Analg* (2008) 107(1):325–32. doi: 10.1213/ane.0b013e3181770f55
179. Tsui BC, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, et al. Epidural Anesthesia and Cancer Recurrence Rates After Radical Prostatectomy. *Can J Anaesth* (2010) 57(2):107–12. doi: 10.1007/s12630-009-9214-7

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Targeting Myeloid-Derived Suppressor Cells Derived From Surgical Stress: The Key to Prevent Post-surgical Metastasis

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Myeloid-derived suppressor cells (MDSCs) are known to play an essential part in tumor progression under chronic stress settings through their manipulation of adaptive and innate immune systems. Previous researches mainly focus on MDSC's role in the chronic tumor immune environment. In addition, surgery can also serve as a form of acute stress within the patient's internal environment. Nevertheless, the part that MDSCs play in post-surgical tumor development has not gained enough attention yet. Although surgery is known to be an effective definite treatment for most localized solid tumors, there are still plenty of cancer patients who experience recurrence or metastasis after radical resection of the primary tumor. It is believed that surgery has the paradoxical capability to enhance tumor growth. Many possible mechanisms exist for explaining post-surgical metastasis. We hypothesize that surgical resection of the primary tumor can also facilitate the expansion of MDSCs and their pro-tumor role since these surgery-induced MDSCs can prepare the pre-metastatic niche (the "soil") and at the same time interact with circulating tumor cells (the "seeds"). This vicious, reciprocal mechanism is a crucial point in the emergence of post-surgical metastasis. According to our hypothesis, MDSCs can be the precise target to prevent cancer patients from post-surgical recurrence and metastasis during the perioperative phase to break the wretched cycle and provide better long-term survival for these patients. Future studies are needed to validate this hypothesis.

Keywords: myeloid-derived suppressor cells, stress, surgery, tumor recurrence, metastasis

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INTRODUCTION

Myeloid-derived suppressor cells' (MDSCs) existence in pathologic conditions such as sepsis, stress, and trauma can be considered a reflection of emergency myelopoiesis. However, the tumor can utilize this phenomenon to create long-lasting abnormal myelopoiesis in favor of tumor growth and progression. Previous researches mainly focus on MDSC's role in chronic tumor environment: MDSCs can participate directly in both the adaptive and innate immune systems *via* a plethora of mechanisms, including the deprivation of arginine, the release of oxidizing molecules, the modulation of regulatory T cells (Tregs), and the interfere with T cell functions (1); and MDSC level correlates with primary tumor growth and poor prognosis (2–4).

MDSCs' function during trauma and sepsis processes has been reviewed in detail (5). In their review, Alex G Cuenca et al. believe that they may play a protective role in the host's acute stress reaction by suppressing the cytokine responses and inherent immunity. As in an acute inflammatory response process, there has been a question for quite a time: is the role of MDSC beneficial or detrimental, which has not been a satisfying answer yet. But at least the expansion in MDSCs could possibly either contributes to sepsis immune suppression or prevent it, depending on the conditions, illustrating its complexity. Ulteriorly, we are more interested in the role of MDSCs in the setting of an organism-environment where the tumor already exists.

Surgical resection is the mainstay for radically removing the primary tumor. Admittedly, surgical removal of the primary tumor is widely acknowledged as the best option in treating almost all localized solid tumors; surgery is still a significant disturbance to a living organism. Tumor recurrence and metastasis after complete resection of the primary tumor exists, resulting in a rather unsatisfactory long-term survival. Growing evidence indicates that surgery on the tumor mass can paradoxically promote post-surgical metastasis risk through complex processes that include multiple factors interplaying simultaneously (6).

Researchers have been wondering about the possible mechanism for post-surgical metastasis. MDSCs in the tumor microenvironment (TME) play a significant role in tumor metastasis (7, 8). Studies show acute stress-like surgery is likely to stimulate MDSCs growth in the TME, which then regulate the immune suppression and participate in the formation of the pre-metastatic niche (PMN) (the "soil") (7, 9). Not only can MDSCs be induced by surgical stress, being the most obviously increased immune-related cells immediately before and after the resection of tumor lesions, post-operatively induced MDSCs are also a very potent contributor to metastases. In addition, the combination of primary tumor resection and low-dose adjuvant epigenetic modifiers or gemcitabine (which targets MDSCs) can restrain subsequent metastatic growth. This further reinforces the critical value of MDSCs in post-surgical metastasis development (8, 10). Besides their ability to forge fertile "soil" for metastasis lesions, MDSCs can also influence the fate of circulating tumor cells (CTCs) (the "seeds").

The reasons behind post-surgical metastasis are very complicated, with metabolic, inflammatory, neural, endocrine, and immunologic factors all inseparably intertwined. We hypothesize that surgical-induced MDSCs are potent causes of post-surgical metastasis by interacting with CTCs and augmenting the PMN for CTCs to colonize and grow. In other words, MDSCs can fertilize the "soil" as well as the "seeds" at the same time. Therefore, targeting this pivotal factor and the leading source of the following cascade from surgical insult to metastasis during the perioperative period can significantly improve cancer patients' prognosis after tumor resection surgery.

EVALUATION OF THE HYPOTHESIS

Surgery Can Induce the Expansion of MDSCs

Surgery has the paradoxical capability to enhance tumor growth (11–13). Early in 1982, Uchida A has reported the possibility that circulating "suppressor monocytes" might have contributed to the inhibition of NK activity in post-operative tumor patients (14); these cells, later, were believed to be MDSCs actually. Recent endeavors have been abundant but fragmentary, spanning from inflammation, tumor cell shedding, and tumor immunity. Studies using the acute infection and sepsis model show that MDSCs increase through the expansion and activation of immature myeloid cells through the acute inflammatory process (15, 16). Surgery can also be perceived as a kind of acute stress. Evidence validates that it can induce the expansion and accumulation of MDSCs in a tumor-host, as in numerous studies in mice (17, 18) and humans (8, 19–21).

Also, the MDSCs concentration seems to correlate with the surgical procedure intensity (22, 23). In a study within breast cancer patients, research has reported that targeting the overall tumor burden through resection of the primary tumor lesions contributed to the inhibition of MDSCs, therefore promoting survival benefits (24). At the same time, there are also studies showing no significant difference in MDSC levels in different operative types, id est the surgical stress intensity (25). We have several possible explanations for this phenomenon. Firstly, the surgery itself may have reached the ceiling level of surgical stress; thus, more aggressive procedures do not necessarily result in higher MDSC-related cytokines. On the other hand, carbon dioxide (CO_2) pneumoperitoneum could be an important factor in enhancing the metastasis-promoting ability of laparoscopic surgery (26). We suppose that besides causing peritoneal damage, CO_2 could also facilitate tumor metastases through increasing MDSC in the local environment, as MDSC percentage increases along with the growth of arterial CO_2 pressure (27).

Surgery possibly promotes the numerical expansion of MDSCs *via* the stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), as well as their associated increased soluble factors and proinflammatory cytokines (IL-4, IL-10, TGF-β, and VEGF IL-6, IL-8, CXCR, CCL) (7, 28). These changes collectively create a favorable environment for the expansion and accumulation of MDSCs (29).

Surgery-Induced MDSCs Can Augment the PMN (Soil) and Interact With CTCs (Seeds)

The previously most accepted mechanism of metastases formation is CTC being disseminated into the blood during the procedure (30). However, this is controversial since reduced or nearly unaltered CTC counts following complete tumor resection are more often observed (31, 32). Also, some researchers claim that the CTC change is not related to patient prognosis (32). Thus, tumor resection surgery promotes post-surgical metastasis, which is yet to be debated, since surgery itself does not necessarily increase the CTC numbers. Regarding this question, there is evidence showing that MDSCs can enhance

the survival and metastatic function of CTCs by soluble factors as well as direct contact (9, 33). This interaction between MDSCs and CTCs is mainly composed of two aspects: direct cell-to-cell interaction and soluble factors. Firstly, MDSCs can protect CTCs in circulation from a hostile environment and facilitate their extravasation through secreting reactive oxygen species (ROS) (34, 35). Furthermore, MDSCs can directly adhere to CTCs *in vivo* and *in vitro*, form a CTC/PMN-MDSC complex, and enhance their pro-tumorigenic differentiation (36).

In addition to the interaction with CTCs, which are disseminated during the surgical procedures or discharged into the circulation before, and promote their ability to colonize and survive in the PMN, MDSCs can renovate CTCs' living conditions (PMN) as well. Surgical trauma-inflicted MDSC expansion and host immunity suppression facilitate the development of PMN (37) through releasing various MDSC-derived factors, including TGF-β, VEGF, S100A8/9, HMGB1, MMP9, TIMP-1, Arg-1, ROS, and exosomes. These factors interact as a complex network to fertile the PMN for CTCs regarding many aspects such as the colonization of CTCs, ECM remodeling, inflammation, and immunosuppressive TME (38).

Although the interference of anesthesia could confound the possible mechanisms behind the relation of surgery and post-surgical metastasis, psychological stress, surgical eradication of surrounding nerves, etc. (39–44), we hypothesize that MDSCs inflicted by surgical stress are the key players connecting these complicated mechanisms for post-surgical metastasis. In other words, MDSCs can be perceived as an orchestration of the effects of circulating cancer cells, the suppressed antitumor immunity, and the PMN of the organisms with cancer who undergo surgical resection. Thus, MDSCs should be valued as a potential target for preventing metastases from happening during the perioperative period.

CONSEQUENCES OF THE HYPOTHESIS AND DISCUSSION

If the extent of surgery-induced immunosuppression manages to counteract the positive effect of primary tumor removal, surgery will fail to meet our expectations to prolong patient survival. These unwanted processes, such as MDSC expansion and its following cascade reactions, should be noted and avoided in the future. Currently, we have several methods to tackle MDSCs in cancer *via* targeting its expansion, infiltration, migration, activation, differentiation, Arg1 and iNOS induction, and so forth, which is reviewed detailedly in related reviews (45). Nevertheless, this crucial perioperative period is not given enough attention from the pharmacological intervention perspective. According to our hypothetical model, targeting MDSCs is very likely the key to preventing MDSCs induced/related post-surgical recurrence and metastasis.

Future studies are encouraged to first verify the change of MDSCs in various cancer types at a different time (before and after surgery), providing a concentration curve preferably to pinpoint a more accurate window phase for future intervention.

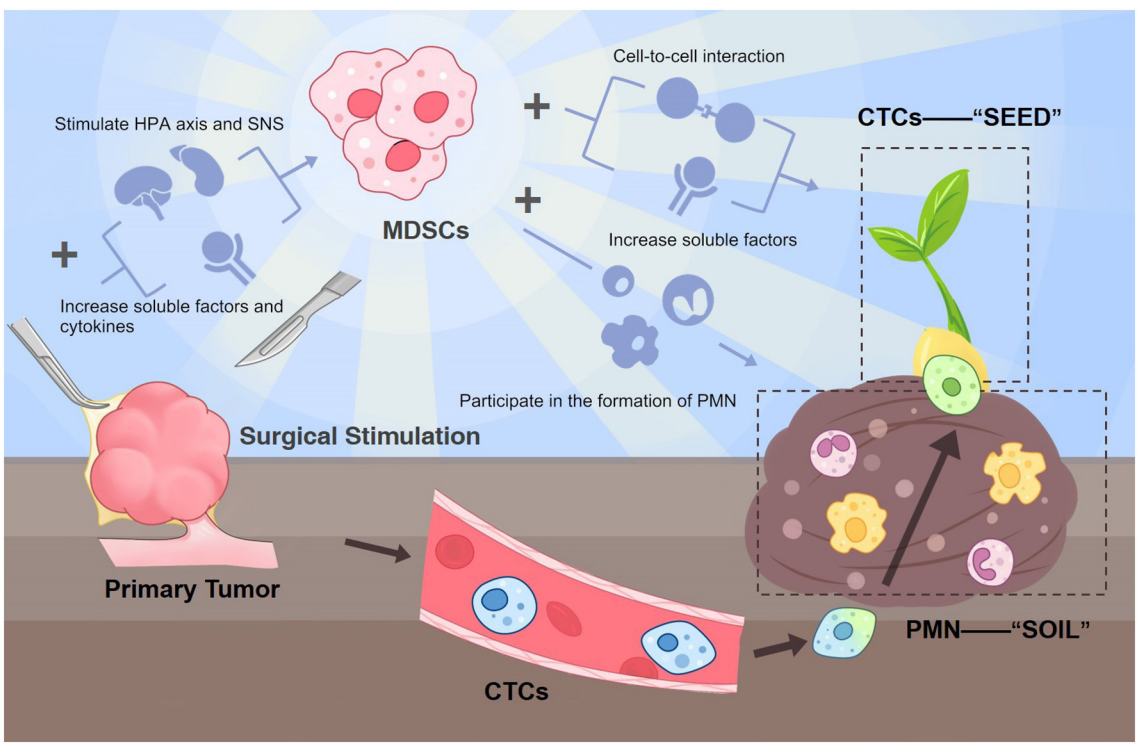

FIGURE 1 | A schematic diagram of this whole hypothesis.

The possible existence form and structure of the MDSC-CTC complex should also be measured. *In vivo* experiments testing whether precisely removing MDSCs can reverse their effects on CTC and PMN and the following prognosis difference is also needed. Also, researchers can use flow cytometry sorting to capture CTCs and co-culture them with MDSCs extracted after emergency surgical stimulation to verify MDSC's impact on CTCs and comparing to the blank control group. Under this circumstance, when the aforementioned tests proved true, we can promisingly move on to the time when surgeons can interrupt tumor progression during the perioperative phase. A schematic diagram of this whole hypothesis is shown in **Figure 1**.

LIMITATIONS

Here we propose a general model to explain what happens in the perioperative period may pre-dispose impacts on the long-time prognosis of the tumor resection procedures, mainly discussing the change and consequences of surgery-induced MDSCs. However, different primary solid tumors are likely to differ in the peripheral responses after surgery slightly, It is still needed to explore further this model in well-designed basic and clinical researches in different cancers.

CONCLUSIONS

We hypothesize that surgical resection of the primary tumor can also facilitate the expansion of MDSCs and their pro-tumor role since these surgery-induced MDSCs can prepare the pre-metastatic niche (the "soil") and at the same time interact with circulating tumor cells (the "seeds"). This vicious, reciprocal mechanism is a crucial point in the emergence of post-surgical metastasis. According to our hypothesis, MDSCs have the potential to be the precise target to prevent cancer patients from post-surgical recurrence and metastasis during the perioperative phase in order to break the wretched cycle and provide better long-term survival for these patients. Future studies are needed to validate this hypothesis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SZ wrote this manuscript. YZ created the figure. XM was involved in the idea formation and manuscript revision. YQ contributed to the reviewing and manuscript editing process. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.783218/full#supplementary-material

REFERENCES

1. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol.* (2012) 12:253–68. doi: 10.1038/nri3175
2. Porembka MR, Mitchem JB, Belt BA, Hsieh C-S, Lee H-M, Herndon J, et al. Pancreatic adenocarcinoma induces bone marrow mobilization of myeloid-derived suppressor cells which promote primary tumor growth. *Cancer Immunol Immunother.* (2012) 61:1373–85. doi: 10.1007/s00262-011-1178-0
3. Wang L, Chang EWY, Wong SC, Ong S-M, Chong DQY, Ling KL. Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage and plasma S100A8/A9 proinflammatory proteins. *J Immunol.* (2013) 190:794–804. doi: 10.4049/jimmunol.1202088
4. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol Immunother.* (2009) 58:49–59. doi: 10.1007/s00262-008-0523-4
5. Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moreno C, Scumpia PO, Laface DM, et al. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. *Mol Med (Cambridge, Mass).* (2011) 17:281–92. doi: 10.2119/molmed.2010.00178
6. Benish M, Ben-Eliyahu S. Surgery as a double-edged sword: a clinically feasible approach to overcome the metastasis-promoting effects of surgery by blunting stress and prostaglandin responses. *Cancers (Basel).* (2010) 2:1929–51. doi: 10.3390/cancers2041929
7. Wang J, Su X, Yang L, Qiao F, Fang Y, Yu L, et al. The influence of myeloid-derived suppressor cells on angiogenesis and tumor growth after cancer surgery. *Int J Cancer.* (2016) 138:2688–99. doi: 10.1002/ijc.29998
8. Lu Z, Zou J, Li S, Topper MJ, Tao Y, Zhang H, et al. Epigenetic therapy inhibits metastases by disrupting premetastatic niches. *Nature.* (2020) 579:284–90. doi: 10.1038/s41586-020-2054-x
9. Trovato R, Canè S, Petrova V, Sartoris S, Ugel S, De Sanctis F. The engagement between MDSCs and metastases: partners in crime. *Front Oncol.* (2020) 10:165. doi: 10.3389/fonc.2020.00165
10. Bosiljcic M, Cederberg RA, Hamilton MJ, LePard NE, Harbourne BT, Collier JL, et al. Targeting myeloid-derived suppressor cells in combination with primary mammary tumor resection reduces metastatic growth in the lungs. *Breast Cancer Res.* (2019) 21:103. doi: 10.1186/s13058-019-1189-x
11. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The effects of surgery on tumor growth: a century of investigations. *Ann Oncol.* (2008) 19:1821–8. doi: 10.1093/annonc/mdn386
12. Murthy SM, Goldschmidt RA, Rao LN, Ammirati M, Buchmann T, Scanlon EF. The influence of surgical trauma on experimental metastasis. *Cancer.* (1989). 64:2035–44. doi: 10.1002/1097-0142(19891115)64:10<2035::aid-cncr2820641012>3.0.co;2-l
13. van der Bij GJ, Oosterling SJ, Beelen RH, Meijer S, Coffey JC, van Egmond M. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. *Ann Surg.* (2009) 249:727–34. doi: 10.1097/SLA.0b013e3181a3ddbd

14. Uchida A, Kolb R, Micksche M. Generation of suppressor cells for natural killer activity in cancer patients after surgery. *J Natl Cancer Inst.* (1982) 68:735–41.
15. Arocena AR, Onofrio LI, Pellegrini AV, Carrera Silva AE, Paroli A, Cano RC, et al. Myeloid-derived suppressor cells are key players in the resolution of inflammation during a model of acute infection. *Eur J Immunol.* (2014) 44:184–94. doi: 10.1002/eji.201343606
16. Schrijver IT, Théroude C, Roger T. Myeloid-derived suppressor cells in sepsis. *Front Immunol.* (2019) 10:327. doi: 10.3389/fimmu.2019.00327
17. Pyter LM, Suarez-Kelly LP, Carson WE, III, Kaur J, Bellisario J, Bever SR. Novel rodent model of breast cancer survival with persistent anxiety-like behavior and inflammation. *Behav Brain Res.* (2017) 330:108–17. doi: 10.1016/j.bbr.2017.05.011
18. Ananth AA, Tai LH, Lansdell C, Alkayyal AA, Baxter KE, Angka L, et al. Surgical stress abrogates pre-existing protective T cell mediated anti-tumor immunity leading to postoperative cancer recurrence. *PLoS ONE.* (2016) 11:e0155947. doi: 10.1371/journal.pone.0155947
19. Li W, Wu K, Zhao E, Shi L, Li R, Zhang P, et al. HMGB1 recruits myeloid derived suppressor cells to promote peritoneal dissemination of colon cancer after resection. *Biochem Biophys Res Commun.* (2013) 436:156–61. doi: 10.1016/j.bbrc.2013.04.109
20. Ma X, Wang M, Yin T, Zhao Y, Wei X. Myeloid-derived suppressor cells promote metastasis in breast cancer after the stress of operative removal of the primary cancer. *Front Oncol.* (2019) 9:855. doi: 10.3389/fonc.2019.00855
21. Xu P, He H, Gu Y, Wang Y, Sun Z, Yang L, et al. Surgical trauma contributes to progression of colon cancer by downregulating CXCL4 and recruiting MDSCs. *Exp Cell Res.* (2018) 370:692–8. doi: 10.1016/j.yexcr.2018.07.035
22. Coffey JC, Wang JH, Smith MJ, Bouchier-Hayes D, Cotter TG, Redmond HP. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol.* (2003) 4:760–8. doi: 10.1016/S1470-2045(03)01282-8
23. Da Costa ML, Redmond P, Bouchier-Hayes DJ. The effect of laparotomy and laparoscopy on the establishment of spontaneous tumor metastases. *Surgery.* (1998) 124:516–25. doi: 10.1016/S0039-6060(98)70098-4
24. Rashid OM, Nagahashi M, Ramachandran S, Graham L, Yamada A, Spiegel S, et al. Resection of the primary tumor improves survival in metastatic breast cancer by reducing overall tumor burden. *Surgery.* (2013) 153:771–8. doi: 10.1016/j.surg.2013.02.002
25. Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol.* (2009) 10:44–52. doi: 10.1016/S1470-2045(08)70310-3
26. Gupta A, Watson DI, Ellis T, Jamieson GG. Tumour implantation following laparoscopy using different insufflation gases. *ANZ J Surg.* (2002) 72:254–7. doi: 10.1046/j.1445-2197.2002.02385.x
27. Brajer-Luftmann B, Nowicka A, Kaczmarek M, Grabicki M, Kuznar-Kamińska B, Bromińska B, et al. Myeloid-derived suppressor cells in bronchoalveolar lavage fluid in patients with chronic obstructive pulmonary disease. *Pol Arch Med Wewn.* (2016) 126:980–8. doi: 10.20452/pamw.3718
28. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. *J Transl Med.* (2018) 16:8. doi: 10.1186/s12967-018-1389-7
29. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. *Nat Immunol.* (2018) 19:108–19. doi: 10.1038/s41590-017-0022-x
30. Yamaguchi K, Takagi Y, Aoki S, Futamura M, Saji S. Significant detection of circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. *Ann Surg.* (2000) 232:58–65. doi: 10.1097/00000658-200007000-00009
31. Juratli MA, Siegel ER, Nedosekin DA, Sarimollaoglu M, Jamshidi-Parsian A, Cai C, et al. *In vivo* long-term monitoring of circulating tumor cells fluctuation during medical interventions. *PLoS ONE.* (2015) 10:e0137613. doi: 10.1371/journal.pone.0137613
32. van Dalum G, van der Stam GJ, Tibbe AGJ, Franken B, Mastboom WJB, Vermes I, et al. Circulating tumor cells before and during follow-up after breast cancer surgery. *Int J Oncol.* (2015) 46:407–13. doi: 10.3892/ijo.2014.2694
33. Szczerba BM, Castro-Giner F, Vetter M, Krol I, Gkountela S, Landin J, et al. Neutrophils escort circulating tumour cells to enable cell cycle progression. *Nature.* (2019) 566:553–7. doi: 10.1038/s41586-019-0915-y
34. Ohl K, Tenbrock K. Reactive oxygen species as regulators of MDSC-mediated immune suppression. *Front Immunol.* (2018) 9:2499. doi: 10.3389/fimmu.2018.02499
35. Wang L, Leite de Oliveira R, Huijberts S, Bosdriesz E, Pencheva N, Brunen D, et al. An acquired vulnerability of drug-resistant melanoma with therapeutic potential. *Cell.* (2018) 173:1413–25.e14. doi: 10.1016/j.cell.2018.04.012
36. Sprouse ML, Welte T, Boral D, Liu HN, Yin W, Vishnoi M, et al. PMN-MDSCs enhance CTC metastatic properties through reciprocal interactions *via* ROS/Notch/Nodal signaling. *Int J Mol Sci.* (2019) 20:1916. doi: 10.3390/ijms20081916
37. Ceelen W, Pattyn P, Mareel M. Surgery, wound healing, and metastasis: recent insights and clinical implications. *Crit Rev Oncol Hematol.* (2014) 89:16–26. doi: 10.1016/j.critrevonc.2013.07.008
38. Wang Y, Ding Y, Guo N, Wang S. MDSCs: key criminals of tumor pre-metastatic niche formation. *Front Immunol.* (2019) 10:172. doi: 10.3389/fimmu.2019.00172
39. Weber M, Moebius P, Büttner-Herold M, Amann K, Preidl R, Neukam FW, et al. Macrophage polarisation changes within the time between diagnostic biopsy and tumour resection in oral squamous cell carcinomas–an immunohistochemical study. *Br J Cancer.* (2015) 113:510–9. doi: 10.1038/bjc.2015.212
40. Yan T, Zhang G-H, Cheng Y-Z, Wu L-X, Liu X-Y, Sun Y-L, et al. Effects of anesthetic technique and surgery on myeloid-derived suppressor cells and prognosis in women who underwent breast cancer surgery: a prospective study. *Cancer Manag Res.* (2019) 11:5513–22. doi: 10.2147/CMAR.S183519
41. Mundy-Bosse BL, Thornton LM, Yang H-C, Andersen BL, Carson WE. Psychological stress is associated with altered levels of myeloid-derived suppressor cells in breast cancer patients. *Cell Immunol.* (2011) 270:80–7. doi: 10.1016/j.cellimm.2011.04.003
42. Koo KC, Park SU, Kim KH, Rha KH, Hong SJ, Yang SC, et al. Prognostic impacts of metastatic site and pain on progression to castrate resistance and mortality in patients with metastatic prostate cancer. *Yonsei Med J.* (2015) 56:1206–12. doi: 10.3349/ymj.2015.56.5.1206
43. van den Beuken-van Everdingen MHJ, de Graeff A, Jongen JLM, Dijkstra D, Mostovaya I, Vissers KC. Pharmacological treatment of pain in cancer patients: the role of adjuvant analgesics, a systematic review. *Pain Pract.* (2017) 17:409–19. doi: 10.1111/papr.12459
44. Page GG. Surgery-induced immunosuppression and postoperative pain management. *AACN Clin Issues.* (2005) 16:302–9. doi: 10.1097/00044067-200507000-00004
45. Liu Y, Wei G, Cheng WA, Dong Z, Sun H, Lee VY, et al. Targeting myeloid-derived suppressor cells for cancer immunotherapy. *Cancer Immunol Immunother.* (2018) 67:1181–95. doi: 10.1007/s00262-018-2175-3

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REVIEW
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Can Acute Postoperative Pain Management After Tumour Resection Surgery Modulate Risk of Later Recurrence or Metastasis?

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Background: Cancer is a leading cause of mortality worldwide, but death is rarely from the primary tumour: Rather it is multi-organ dysfunction from metastatic disease that is responsible for up to 90% of cancer-related deaths. Surgical resection of the primary tumour is indicated in 70% of cases. The perioperative stress response, tissue hypoxia at the site of surgery, and acute pain contribute to immunosuppression and neo-angiogenesis, potentially promoting tumour survival, proliferation, and metastasis. Poorly controlled acute postoperative pain decreases Natural Killer (NK) immune cell activity, which could potentially facilitate circulating tumour cells from evading immune detection. This consequently promotes tumour growth and distal metastasis.

Methods: We conducted a comprehensive literature search for links between acute pain and cancer outcomes using multiple online databases. Relevant articles from January 1st, 2010 to September 1st, 2021 were analysed and appraised on whether postoperative pain control can modulate the risk of recurrence, metastasis, and overall cancer survival.

Results: Although experimental and retrospective clinical data suggest a plausible role for regional anaesthesia in cancer outcome modulation, this has not been supported by the single, largest prospective trial to date concerning breast cancer. While there are mixed results on anaesthesiology drug-related interventions, the most plausible data relates to total intravenous anaesthesia with propofol, and to systemic administration of lidocaine.

Conclusion: The hypothesis that anaesthetic and analgesic technique during cancer surgery could influence risk of subsequent recurrence or metastasis has been prevalent for >15 years. The first, large-scale definitive trial among women with breast cancer found robust equivalent findings between volatile anaesthesia with opioid analgesia and regional anaesthesia. Therefore, while regional anaesthesia during tumour resection does not seem to have any effect on cancer outcomes, it remains plausible that other anaesthetic techniques (e.g. total intravenous anaesthesia and systemic lidocaine infusion) might influence oncologic outcome in other major tumour resection surgery (e.g. colorectal and lung).

Therefore, another large trial is needed to definitively answer these specific research questions. Until such evidence is available, perioperative analgesia for cancer surgery of curative intent should be based on patient co-morbidity and non-cancer endpoints, such as optimising analgesia and minimising postoperative complications.

Keywords: acute pain, cancer, cancer recurrence, metastasis, anaesthesia

INTRODUCTION

In 2020, it was estimated that 18 million new cancer cases were diagnosed, (excluding nonmelanoma skin cancer). This was associated with approximately 10 million cancer related deaths (1). The incidence of female breast cancer has exceeded lung cancer and is now the most prevalent cancer among women. Furthermore, it is estimated that by 2040, the global overall cancer burden will rise by 47%, which approximates to 28 million cases (1). The value of surgery in the treatment of solid tumours is evident, because they are amenable to surgical resection. Surgery offers the best chance of a cure and improves prognosis. This is particularly true for early-stage disease (2). Metastasis is defined as a complex multistep process in which tumour cells disseminate from the primary neoplasm to secondary sites (3). The primary tumour is rarely the cause of death for cancer patients. In reality, the metastatic process and resultant organ dysfunction is accountable for 70-90% of cancer related deaths (4, 5).

Minimal residual cancer is defined as an undetectable group of malignant cells that persist after surgical resection (6). This occurs as a result of inadequate surgical clearance, incomplete surgical margins or seeding of cancerous cells into the surgical field, blood or lymphatic system during the intraoperative period. Alternatively, these cells may already exist prior to surgery as subclinical micro-metastatic disease. Survival of these cancerous cells depends on an array of factors, such as surgical stress response, tissue hypoxia, inflammation, and pain. All of these elements suppress the immune system during cancer surgery. Therefore, host immunosuppression will assist these tumour cells to escape cellular destruction and thus aid metastasis (7). Additionally, other factors such as perioperative blood transfusion, hypothermia, and more aggressive cancer types may negatively influence the risk of cancer recurrence (8, 9). Analgesic agents are used along with both general and regional anaesthesia techniques during surgery, to obtund the surgical stress response and manage perioperative pain. Moreover, a large number of preclinical and experimental data over the past 30 years have suggested that various anaesthetic and analgesic agents may exhibit potentially beneficial cancer-resisting effects, while others may demonstrate potentially harmful cancer-promoting effects (10). The perioperative period during cancer surgery is a critical time of immunological susceptibility. Therefore, anaesthetic and analgesic techniques may have a role in modulating this risk, consequently potentially affecting postoperative oncologic outcomes (11). In the past few decades, only one high quality randomised controlled trial has been conducted to test this hypothesis. In this review article, we will explore how sub-optimal management of acute perioperative pain may be associated with cancer recurrence, and whether or not common analgesic agents and strategies used during the perioperative period may influence the risk of cancer recurrence or metastasis.

METHODS

A literature search for links between acute pain and cancer outcomes was conducted using the following databases: Medline/Pubmed, EMBASE, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and CINAHL. Key search terms such as 'acute pain'; 'cancer'; 'cancer recurrence'; 'regional anaesthesia and cancer'; 'postoperative analgesia and cancer recurrence'; 'analgesia and metastasis'; 'opioids and cancer recurrence', and 'perioperative pain control', were used to analyse the relevant literature. Studies from 1 January 2010 until 1 September 2021 were included. This comprised of randomised controlled trials, retrospective studies, meta-analyses, systematic reviews, relevant review articles and any referenced articles deemed important regardless of the publication date. Articles were assessed for importance and significance by all named authors. For the purpose of this review article, we included what were, in our opinion, the most notable, relevant and recent data.

PAIN AND CANCER RECURRENCE

At an anatomical level, cancer is made up of tumour cells surrounded by the tumour microenvironment. This microenvironment consists of an extracellular matrix, blood vessels and various host cells (fibroblasts, mesenchymal and various immune cells) (12). Additionally, a subset of tumour cells called 'cancer stem cells', that play an important role in facilitating tumour metastasis, are found within this environment (13). Cancer surgery can easily disrupt this environment and inevitably may promote spread of residual cancer cells. Postoperative cancer recurrence may occur *via* the following mechanisms (8):

1. Local recurrence at the surgical resection site.
2. Lymph node metastasis.
3. Secondary organ metastasis as a result of circulating tumour cells (CTCs) seeding before or during the perioperative period.

The likelihood for CTCs to survive and lodge in distant tissues during the perioperative period is not fully understood, but can be influenced by numerous immunomodulating factors. These include pain, surgical stress response, and degree of inflammation caused by the surgery itself (10). Interleukin (IL)-6, IL-1-beta, tumour necrosis

factor (TNF)-alpha, and vascular endothelia growth factor (VEGF) are important inflammatory mediators that are released during surgery and the postoperative period. These all have significant implications in survival of residual cancer cells (14). Moreover, distal inflammatory sites may provide the ideal site for CTCs to collect during the perioperative period, a process called inflammatory oncotaxis (15). In addition, the inflammatory response depresses the host immune function by impairing natural killer (NK) cells cytotoxicity (16). NK cells are particularly important in preventing tumorigenesis and metastasis (17). The surgical stress response results in activation of the sympathetic and neuroendocrine system to stimulate the release of catecholamines and cortisol. Again, this impairs the immune system by inhibiting the antitumour activity of NK cells and CD8+T cells. These humoral factors promote the proliferation of T regulatory and Type 2 helper T cells (Th2), which supports cancer cell growth (18). Early laboratory data has demonstrated that surgical trauma increases host susceptibility to experimental metastasis formation (19, 20). The impaired immune system, in particular cell mediated immune function, can result in circulating tumour cells evading host detection. Therefore, it is plausible to speculate that the stronger and more uncontrolled the surgical stress response is, the greater the risk of distal metastasis occurring during the perioperative period.

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' (21). It is a multidimensional experience and personalised to each patient (22). Acute pain refers to pain that does not persist for longer than three months (22). Acute perioperative pain is a consequence of surgical trauma, inflammation, and sympathetic system over-reactivity, the latter being an important factor that contributes to the transition from acute to chronic persistent post-surgical pain (23). Animal experimental data consistently suggests that poorly controlled pain following surgical trauma promotes postoperative immunosuppression, and, in turn may enhance malignant processes (24–26). The most notable immunosuppressive effect demonstrated in these studies was decreased NK cell count and activity (24–26). Moreover, uncontrolled acute perioperative pain may exacerbate the surgical stress response, due to enhanced activity to both the sympathetic nervous system and neuroendocrine responses. Therefore, this may additionally increase the risk of postoperative cancer recurrence/metastasis by further decreasing NK cell activity. This sequence of events is summarised in **Figure 1**.

Theoretically, satisfactory acute perioperative pain control and associated obtundation of the surgical stress response may potentially reduce cancer recurrence risk. A recent systematic review and meta-analysis of experimental animal data compared the risk of cancer metastasis between two groups, analgesic versus control treatment. The authors suggested that analgesics, in particular NSAIDs, significantly reduce the risk of metastasis in various animal models (n=7,000) (27). However,

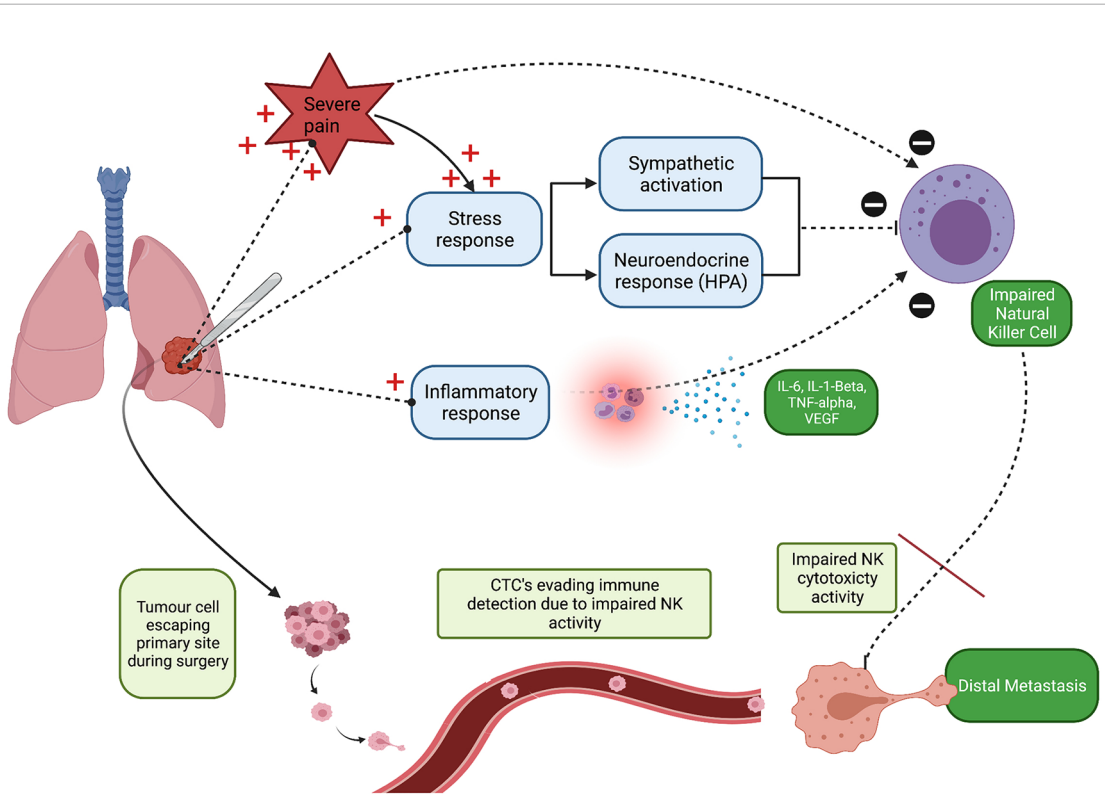

FIGURE 1 | Schematic illustration highlighting that poorly controlled acute perioperative pain may promote tumour cell seeding and consequently increase the risk of distal metastasis. NK, Natural Killer cell; CTCs, Circulating Tumour Cell's. Created with BioRender.com.

translatability of these experimental findings (27) to the clinical situation remains unclear. It would undoubtedly be unethical to test this hypothesis in a prospective, randomised control trial in patients undergoing cancer surgery. It would involve purposely withholding effective analgesia strategies in one group and not in the other. Instead this is limited to retrospective data, a (28) retrospective review of 2,401 patients who underwent colorectal cancer resection included 13,931 pain score observations. Results showed that approximately 10% of these surgical patients had persistent moderate to severe pain up to five days postoperatively. This group had the highest risk of cancer recurrence and mortality when compared to patients from the same cohort who only experienced mild postoperative pain (28).

Figure 2 illustrates the pain pathway and site of action of common analgesia adjuvant agents used during the perioperative period. We will review each of these analgesic agents used during cancer surgery and summarise the current evidence relating to their effect on potential cancer recurrence.

REGIONAL ANAESTHESIA: ACUTE PAIN MANAGEMENT AND CANCER RECURRENCE

Regional anaesthesia is defined as applying local anaesthetic agents to an individual nerve, plexus of nerves, or to an anatomical plane through which nerves pass, in order to render a distal site anaesthetised (29). Use of regional anaesthesia techniques is increasing worldwide. In the operating theatre, regional anaesthesia can be used solely to achieve surgical anaesthesia, and may also be used to complement general anaesthesia to effectively manage acute pain and postoperative recovery after various types of surgery (30, 31). There are many different regional anaesthesia techniques including: spinal anaesthesia, epidural anaesthesia, fascial plane blocks and peripheral nerve blocks (32)

Local anaesthetic agents are the principal drugs used in regional anaesthesia procedures. These drugs are water-soluble salts, or lipid soluble alkaloids, and are made up of three

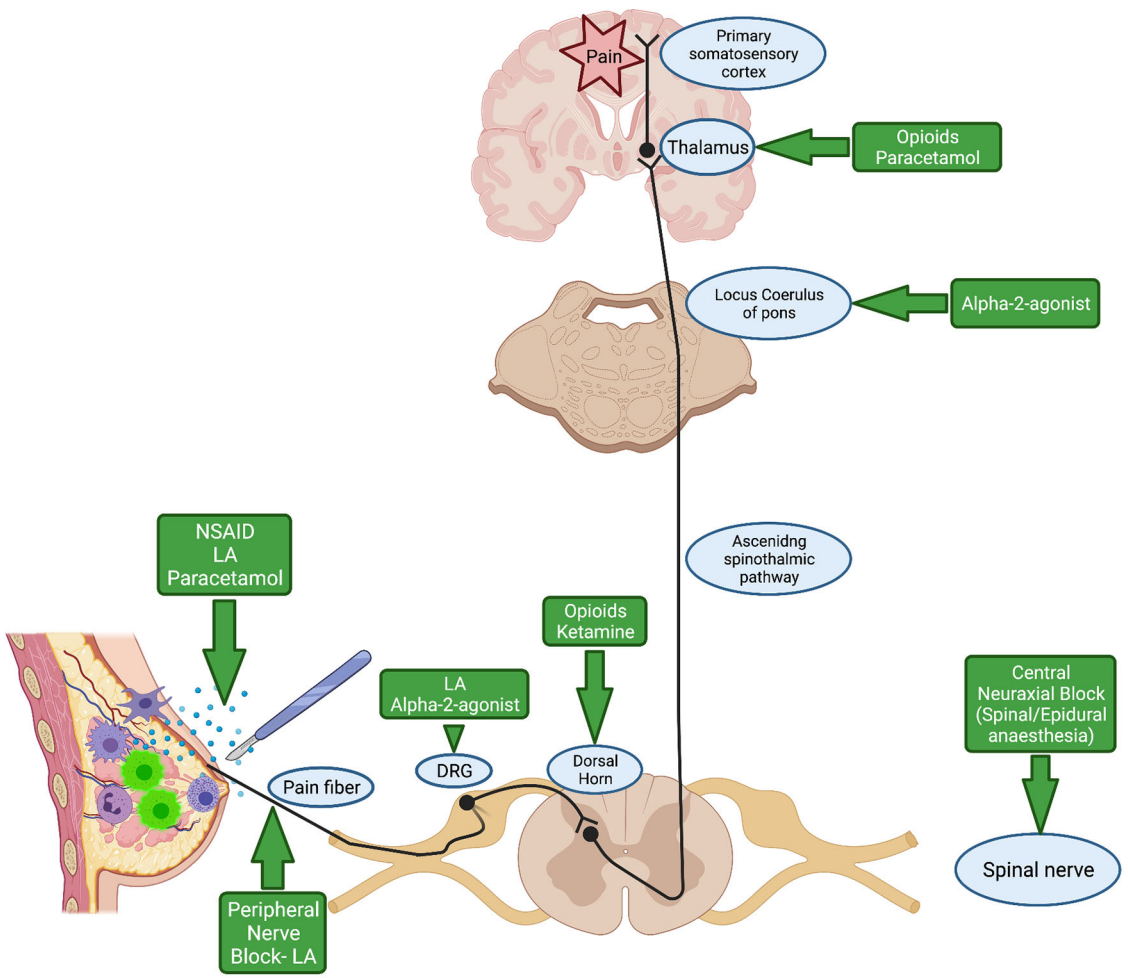

FIGURE 2 | Pain pathway and site of action of commonly used analgesic agents during the perioperative period. NSAID, Non-steroidal anti-inflammatory drug; LA, Local Anaesthetic; DRG, Dorsal Root Ganglion. Created with BioRender.com.

structures: a hydrophilic amine group, a hydrocarbon link and a lipophilic aromatic group (33). Local anaesthetic agents are categorised into esters or amides, depending on the structure of this hydrocarbon intermediary link chain (33). *In vitro* experiments involving ropivacaine, an amide local anaesthetic agent, have demonstrated antimetastatic effects by inhibiting migration of cancer cells (34) and interfering with cell differentiation and tumorigenesis (35).

Lidocaine is an amide local anaesthetic agent and is commonly used during cancer surgery (36). It contains potent analgesic, anti-hyperalgesia and anti-inflammatory properties (36). Alternatively, an additional benefit to lidocaine's analgesic effects, are its potential antitumour properties. Therefore, it has been suggested that the use of lidocaine during and after surgery could improve oncological outcomes, by reducing the ability of cancer cells to recur and metastasise (37). The anticancer effects of lidocaine have been extensively demonstrated in multiple *in vitro* studies. At various concentrations (0.1 mM-10 mM), it manifests antitumour effects by inhibiting proliferation (38, 39), migration (39, 40) and invasion of cancer cells (39), and by inducing cell cycle arrest (41). Lidocaine's inhibitory action on voltage-gated-sodium-channels plays a significant role in the process of cancer metastasis (42). In addition, at clinically relevant doses, lidocaine has been shown to demonstrate anti-DNA tumour replication activity in oestrogen receptor negative and positive breast cancer cell lines (43). Furthermore, *in vivo* studies have indicated that lidocaine inhibits metastasis in murine cancer models by multiple mechanisms (44–48). It also appears that lidocaine has a greater affect at attenuating the development of pulmonary metastasis as compared to other organ sites. **Table 1** summaries the findings of the most recent animal experiments on lidocaine and its effect on cancer metastasis.

Unfortunately, the translation of these laboratory findings to the clinical setting is limited (44–48). Zhang Hao et al. (49) conducted a retrospective study of 2,239 patients who underwent pancreatectomy for pancreatic cancer. They reported that the use of intraoperative intravenous lidocaine infusion was associated with improved overall survival, but not disease-free survival, compared to the non-lidocaine group.

Neutrophil extracellular trapping (NETosis) is a process where neutrophils degranulate when exposed to tumour antigens, and is a potential biomarker for metastatic risk (50). A randomised controlled trial investigated the addition of intravenous (IV) perioperative lidocaine during breast cancer surgery, and concluded that IV lidocaine decreased postoperative expression of NETosis, therefore potentially reducing the rate of cancer recurrence (51).

Large prospective, well-designed, randomised controlled clinical trials are urgently needed to assess the protective effect of lidocaine on recurrence after cancer surgery to achieve a "proof of concept". At present, the VAPOR-C Trial (Volatile Anaesthesia and Perioperative Outcomes Related to Cancer, NCT04316013) aims to accomplish this. This large, multicentre trial is a pragmatic randomised controlled trial, with a 2x2 factorial design, comparing volatile anaesthesia with sevoflurane versus total intravenous anaesthesia with propofol. Within these two arms, patients will be further randomised to receive perioperative lidocaine according to standard use, or saline control. The study aims to enrol a total of 5,763 participants globally, with its primary outcome being disease free survival. A feasibility and pilot study were recently completed (52). The authors demonstrated a successful adherence to randomisation in 99.3% of their study cohort. Recruitment for VAPOR-C has begun, and its' estimated completion date is 2027. In addition, the 'ALLEGRO RCT

TABLE 1 | Selected summary of recent *in vivo* studies investigating the antitumour effects of lidocaine.

Author	Year	Lidocaine dosage	Finding	Proposed mechanism of action
Freeman et al. (44)	2018	1.5mg/kg bolus followed by a 30-40 minute infusion at 2mg/kg/hr	lidocaine combined with Cisplatin significantly decreased metastatic lung colony count in a murine model of breast cancer surgery.	Lidocaine enhanced the metastasis-inhibiting action of cisplatin.
Goa et al. (45)	2018	Co-loading of lidocaine and cisplatin by ligand-modified nanogels.	Targeted delivery of co-loaded lidocaine and cisplatin inhibited the primary tumour growth but also alleviated lung metastasis.	Co-loaded lidocaine and cisplatin by ligand-modified nanogels exhibited higher selective cellular uptake and enhanced the apoptosis activity of cisplatin.
Johnson et al. (46)	2018	Combination of 1.5mg/kg lidocaine bolus followed by 25 minute infusion at 2mg/kg/hr and inhalational sevoflurane during the perioperative period.	Lidocaine reduced lung metastatic colony count and proportion of pulmonary metastasis versus sevoflurane inhalational anaesthesia alone in a murine model of breast cancer.	Reduced anti-inflammatory and anti-angiogenic effects when lidocaine was introduced.
Wall et al. (47)	2019	1.5mg/kg bolus followed by a 25 minute infusion at 2mg/kg/hr	Lidocaine reduced pulmonary metastasis in a murine model of breast cancer surgery model but was ineffective against liver metastatic colonies	Inhibitory effect on Matrix Metallopeptidase 2.
Liu et al. (48)	2021	Intraperitoneal injection of (0.5%, 50 μl) lidocaine into murine model once a day for three days	Lidocaine retarded the metastasis and induced apoptosis in ovarian cancer tissues of a murine ovarian cancer model.	Lidocaine blocked the NaV1.5 channel and subsequently malignancy through inactivation of FAK/Paxillin signalling pathway

(ISRCTN 52352431), another ongoing multicentre RCT, will examine the effect of Intravenous lidocaine bolus followed by an infusion during colorectal cancer surgery. Cancer outcomes up to 10 years post patient surgery will be assessed.

Regional anaesthesia offers numerous benefits during the peri-operative period. These include superior analgesia, reduced length of hospital stay, improved quality of early recovery and fewer postoperative cardiorespiratory complications (30, 53, 54). Moreover, regional anaesthesia-analgesic regimes attenuate the surgical stress response and diminishes the amount of opioids required during the perioperative period (55, 56). As discussed below, the findings of some laboratory and preclinical studies suggest that opioids may be associated with immunosuppressive properties and thus promote tumorigenesis. Impaired host resistance may increase the risk of cancer metastasis during the perioperative period. Experimental data from murine models have suggested that perioperative pain control may play a crucial role in preventing impairment in host resistance after surgery (24). It has been postulated that incorporating regional anaesthesia regimes into cancer surgery to provide excellent perioperative analgesia and to blunt the surgical stress response, may have a role in modulating the risk of cancer recurrence or metastasis. An original retrospective review conducted by Exadaktylos and colleagues, suggested an association between paravertebral anaesthesia and analgesia for breast cancer surgery and a reduced risk of metastasis (57). However, the first multicentre randomised controlled trial on the effect of anaesthetic and analgesic techniques on long term oncologic outcome, published in The Lancet by our group (58) demonstrated robust equivalent findings, regardless of anaesthetic technique. Over 11 years (2007–2018), the authors randomised 2,132 patients to receive either regional anaesthesia-analgesia (paravertebral combined with propofol IV general anaesthesia), or general anaesthesia (sevoflurane) and opioid analgesia. The rate of cancer recurrence between the two groups was similar, at approximately 10%. We concluded that paravertebral regional anaesthesia-analgesia did not reduce cancer recurrence after intended curative surgery.

Neuraxial anaesthesia includes both epidural and spinal anaesthesia procedures. Both techniques are widely used for acute pain management after thoracic and abdominal cancer surgeries. Epidural analgesia is achieved by placing an epidural catheter into the epidural space, which is used to administer a continuous infusion of local anaesthetic agents with or without opioids into this space. This catheter is usually left *in situ* for up to four days to achieve satisfactory analgesia in the early postoperative period when acute pain is most intense. The catheter is not left in the epidural space for longer than four days as the risk of infection significantly increases beyond this time frame (59). In contrast, spinal anaesthesia involves a single dose of local anaesthetic, usually 15-20mg of bupivacaine/ Levobupivacaine with/without opioids administered into the intrathecal space. This provides surgical anaesthesia and analgesia for up to 6 hours (60).

Numerous retrospective studies have been performed to determine if there is an association between neuraxial anaesthesia and cancer recurrence. The results from these reviews are conflicting. To date there have been five meta-analyses conducted to answer this question. These meta-analyses dated between 2014 and 2020 (61–65). **Table 2** summarises the findings from these meta-analyses. These retrospective analyses suggests that perioperative neuraxial anaesthesia techniques may be associated with an improved overall survival in patients undergoing cancer surgeries, especially for colorectal and prostate cancer. However, the majority of these studies failed to demonstrate a decrease in cancer recurrence rates.

A recent small RCT aimed to investigate the effect of epidurals on cancer recurrence. The authors randomised 400 patients undergoing lung cancer surgery, to receive a combined epidural-general anaesthetic or a general anaesthetic with opioid analgesia. This trial was adequately powered to detect a relative reduction in cancer recurrence. The authors concluded that the insertion of an epidural as an adjuvant to general anaesthesia and for acute postoperative pain management, did not improve cancer recurrence rate and overall survival, for patients undergoing lung cancer surgery compared to general anaesthesia alone (66).

TABLE 2 | Summary of recent meta-analysis of neuraxial anaesthesia and cancer recurrence.

Author	Year	Regional anaesthesia	Total Number of studies analysed	Findings
Lee et al. (65)	2020	Epidural and paravertebral anaesthesia	6 (3,139 patients in the regional anaesthesia group)	Adjunctive use of epidural or paravertebral anaesthesia with general anaesthesia did not reduce the rate of cancer recurrence following cancer surgery.
Weng et al. (61)	2016	Epidural and Spinal anaesthesia	20 (15,160 patients in regional anaesthesia group)	Neuraxial anaesthesia appears to improve overall survival, specifically in colorectal cancer surgery and may be associated with reduced risk of cancer recurrence.
Sun et al. (62)	2015	Epidural and Spinal anaesthesia	20 (16,618 patients in regional anaesthesia group)	Perioperative neuraxial anaesthesia may improve overall survival after cancer surgery but it had no positive influence in the reduction of cancer recurrence.
Lee et al. (64)	2015	Epidural and Spinal anaesthesia	10 (7,504 patients in regional anaesthesia group)	Neuraxial anaesthesia during prostate cancer surgery appears to improve overall survival but was not associated with longer recurrence-free-survival.
Pej et al. (63)	2014	Epidural anaesthesia	10 (3,254 patients in regional anaesthesia group)	Perioperative epidural anaesthesia did not influence postoperative cancer recurrence and metastasis rate. However, epidural anaesthesia may be associated with improvement in prognosis of prostate cancer surgery with a follow-up of less than or equal to two years.

OPIOIDS

Opioids are primarily used for cancer patients to provide analgesia in both the acute and chronic settings. While they have known beneficial analgesic properties, they also have non-analgesic effects, including direct and indirect effects on cancer cells. Laboratory studies have investigated numerous mechanisms by which opioids may influence cancer cells, however, results of these studies are inconsistent. Clinical studies investigating perioperative opioids have not shown consistent links between their use and increased risk of tumour growth and metastasis (58).

Preclinical studies have investigated the effects of opioids on immunosuppression and inflammation. Opioids have been shown to have direct and indirect effects on cancer cells and on anti-tumour immunity, (NK cells, macrophages and T-cells). Direct effects on immune cells are materialised *via* opioid and non-opioid toll-like receptors. Cancer cells show an overexpression of μ opioid receptors (MOR), therefore opioids may directly influence their growth (67). MOR overexpression has been linked with the development of metastases in patients with lung, prostate and oesophageal cancer (67–69). Subclasses of opioids have been shown to have varying effects on cancer cells; specifically morphine has been shown to influence the proliferation and survival of cancer cells *via* direct effects on tumour cell DNA cleavage, Akt, PlK, MAPK, Src, GRB2-associated binding protein 1 (Gab-1) and STAT3 signalling pathways (70–72). A study of patients with breast cancer found that those with an MOR gene polymorphism had reduced cancer-related mortality over a ten-year period (73). Methylnaltrexone, which is a MOR antagonist, has shown consistent findings in the role of MOR in cancer progression, in that it may have beneficial effects in stopping cancer progression and metastasis. In the laboratory setting, a study of non-small cell lung cancer (NSCLC) cell lines, revealed that treatment with methylnaltrexone inhibited invasion of cancer cells (70). In the clinical setting, *post hoc* analysis of two randomized trials, revealed that patients with end stage cancer treated with methylnaltrexone for opioid induced constipation had improved overall survival in contrast to patients who did not receive methylnaltrexone (74).

As previously mentioned, indirect effects of opioids on cancer cells occur *via* the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis (75). Acute opioid administration enhances activity in the periaqueductal grey matter which activates the SNS. The SNS innervates lymphoid organs, such as the spleen, and this activation causes the release of biological amines which reduce splenic lymphocyte proliferation and NK cell cytotoxicity (76). Additionally, prolonged use of opioids increases HPA axis activity and glucocorticoid production, which decrease NK cell cytotoxicity (76). Animal models have shown that this is not a class effect and that it varies between opioid subgroups. These studies have shown morphine and fentanyl to suppress NK cell cytotoxicity whereas buprenorphine does not affect NK cell cytotoxicity (77) and tramadol increases NK cell cytotoxicity, reducing metastasis (78). Differences between opioid subclasses are also evident in clinical trials. However, we could not find any high quality randomised control clinical trials that support these preclinical findings.

Clinical studies investigating the effects of perioperative opioid administration on cancer recurrence displayed conflicting results. Similar to previous data, a more recent retrospective study (2020) comprising of 2,775 patients undergoing surgery for renal cell carcinoma, revealed that higher intraoperative oral morphine milligram equivalent (MME) administration was associated with worse recurrence free survival (RFS) (79). The authors demonstrated that on multivariable analysis, the hazard ratio (HR) was 1.04 per 10 MME (95% CI: 1.01-1.07; P=0.018). Therefore, the trend over the past few decades in experimental and observational studies, has been that the perioperative use of opioids during cancer surgery is associated with negative oncological outcomes. Consequently, this may encourage anaesthesiologists to change their clinical practice in relation to caring for patients undergoing cancer surgery, i.e. by providing an 'opioid free' anaesthesia.

However, recent randomised data published in the past few years have not identified such links in large scale clinical practice. In a recent randomised control trial (2021), 146 patients with prostate cancer scheduled for radical prostatectomy were randomised into opioid-free anaesthesia or opioid-based anaesthesia. The authors concluded that intraoperative opioid use did not alter biochemical recurrence free survival in this cohort of patients (80). Similarly, our RCT cited above, of 2,132 women in 13 countries compared regional, (paravertebral blocks and propofol), with general, (sevoflurane and opioid-based analgesia), anaesthesia on breast cancer recurrence. We concluded that regional anaesthesia and the avoidance of opioids did not reduce cancer recurrence after surgery for primary breast cancer compared with general anaesthesia (58). Furthermore, a meta-analysis of thirteen studies regarding perioperative opioids and colorectal cancer indicated that there is no robust evidence to avoid the use of opioids with the primary goal of reducing risk of cancer recurrence (81).

On the other hand it is interesting to note, a more recent observational study suggests a possible beneficial effect of intraoperative opioids on cancer recurrence. A retrospective database study of 1,143 patients with triple negative breast cancer (TNBC), analysed opioid receptor expression patterns in the tumour microenvironment using publicly available bulk and single-cell RNA-sequence data. The investigators identified opioid receptor expression in the TNBC tumours and analysed it alongside its corresponding clinical anaesthesia management and oncologic outcomes. The use of higher doses of intraoperative opioids correlated with improved recurrence free survival but was not significantly associated with improved overall survival (82).

While evidence from laboratory, healthy volunteer, clinical and surgical studies suggest that different opioids variably influence protective anti-tumour immunity, inconsistencies remain in the results of these studies. These may be explained in part by the different methodologies, species, and opioids used,

and the dose and duration of their administration. Timing of opioid administration, along with differences in opioid dose and duration of administration, can influence outcome. Large clinical trials have not revealed consistent links between cancer recurrence and perioperative opioid administration. In this growing era of personalised medicine, efforts to differentiate the effects of opioids across cancer subtypes, (and ultimately individual patients), should continue. Given that current data from patients with cancer are inconclusive, categorical recommendations about how acceptable analgesia is best delivered cannot be made and opioids for cancer-related pain will continue to be recommended.

KETAMINE

Ketamine is a phencyclidine derivative that was first synthesised in 1960's and this racemic compound has been widely adopted in clinical practice. It is used as an induction agent for general anaesthesia and for procedural sedation. In addition, it has potent analgesia properties and is widely used for both acute and chronic pain management. Its anaesthesia and analgesia effects are achieved by acting as a competitive antagonist to N-Methyl-D-Aspartate (NMDA) receptors located in the dorsal horn of the spinal cord (83).

Subanaesthetic doses of ketamine are used for the management of acute perioperative pain. This low dose ranges between 0.5-1mg/kg for a bolus dose, and less than 1.2mg/kg/hr for continuous intravenous administration (84). A Cochrane analysis of the use of intravenous ketamine in the perioperative setting, highlighted that when used as an adjuvant analgesic agent, it reduces postoperative pain scores and opioid consumption (85).

The theoretical concept of ketamine modulating immune function and therefore tumorigenesis dates back to experimental data in the early twenty-first century. These pre-clinical trials demonstrated that ketamine significantly suppressed important pro-inflammatory cytokines that promote tumour production and metastasis; IL-6, IL-8 and TNF-Alpha production (86, 87). In addition, it has been demonstrated that $CD4^+$ T-Helper Lymphocyte (Th) cells play a key role in immune protection, these cells are crucial for effective anti-tumour immunity (88). There are two subsets of T-Helper Lymphocytes, Th1 and Th2. In a recent experimental study, Hou et al. (89) highlighted that patients diagnosed with colorectal cancer (CRC) exhibit decreased ratio of Th1/Th2. This imbalance inhibits the hosts immunological response and in turn hastens tumour metastasis. The authors also concluded that morphine further decreases this ratio but the use of ketamine shifted this balance towards Th1, suggesting that ketamine may have a protective immunoregulatory mechanism in patients with CRC (89). Nevertheless, it is worthwhile to note that early experimental data suggests that ketamine significantly suppressed natural killer cell activity and therefore promoted tumour metastasis (90).

A recent randomised control trial (91) disputes this data. The authors randomly assigned 100 patients undergoing colorectal surgery to a control or ketamine group. This clinical trial did not convey any favourable effect on postoperative NK cell activity or diminish pro-inflammatory cytokine levels. The incidence of cancer recurrence or metastasis within two years after surgery were the same between the experimental (Ketamine) and control groups. However, this study was not statistically powered to examine cancer prognosis after surgery as a primary outcome (91). Two recent large retrospective studies in patients with early-stage lung adenocarcinoma (2021) (92) and renal cell carcinoma (2020) (79), found an association between the use of ketamine as an analgesic agent, and reduced perioperative opioid consumption. Furthermore, on multivariable analysis of these retrospective studies, using ketamine as an analgesic adjuvant versus no adjuvant improved the RFS in both renal cell carcinoma (HR = 0.4, 95% CI 0.16-1.00; P=0.050) (79) and in lung adenocarcinoma (HR = 0.44, 95% CI: 0.24-0.80; P=0.007) (92).

The immunomodulatory effects of ketamine may depend on the tumour type, stage and grade. Administration of ketamine as an adjuvant in combination with other opioid sparring analgesia techniques, such as regional anaesthesia and intravenous lidocaine, may also have an influence on immunomodulation. Whether the analgesic effects of ketamine on the observed improved RFS in renal and lung carcinoma, are due to its direct effect on tumour biology or indirect effect (i.e. opioid sparring) remains debatable. This is novel and merits further high quality clinical trials to guide perioperative physicians.

DEXMEDETOMIDINE

Dexmedetomidine is an alpha-2-adrenoceptor agonist drug, and it was first introduced into clinical practice in 1999 as a sedative for mechanically ventilated patients in ICU (93). Pharmacologically, it is D-isomer of medetomidine, a full agonist to alpha-2-adrenergic receptors and in comparison to clonidine, another alpha-2-adrenoreceptor, dexmedetomidine is more selective towards these receptors. Dexmedetomidine has a specificity of 1620:1 (alpha-2: alpha-1), whereas clonidine affinity is 220:1 (alpha-2: alpha-1) (93). It can be administered *via* various routes; intravenous, intranasal, intrathecal and as an adjuvant in peripheral nerve blocks. At present, its clinical application extends beyond the critical care environment. It is now used during the perioperative period to reduce anaesthesia requirements, as a sedative agent, to attenuate the surgical stress response and as an acute analgesic agent. The analgesic mechanism of action of dexmedetomidine is not fully understood but it is thought to produce analgesia by the following pathways (94): 1. Dose-dependent inhibition of C pain fibres, 2. Inhibition of neurotransmission through the dorsal horn of the spinal cord *via* activation of alpha-2-adrergic receptors in the locus coeruleus area of the rostral pons and 3. Promotion of the release of acetylcholine from spinal interneurons. The blunting of systemic sympathetic activation and opioid sparing effects of alpha-2-adrenoceptor agonists (95) are of particular interest in cancer surgery. It is hypothesised that these effects may influence cancer prognosis.

A recent meta-analysis highlighted that intraoperative use of dexmedetomidine may be a favourable analgesic adjuvant in breast cancer surgery, which in turn could reduce both postoperative pain and incidence of postoperative nausea and vomiting (96). Despite this, there is growing concern that its use may negatively impact cancer prognosis. Experimental data have demonstrated that expression of alpha-1 and alpha-2 adrenergic receptors on basal-like breast cancer cells were associated with a poor prognosis (97), and subsequent adrenergic receptor activation by dexmedetomidine may promote proliferation, migration and invasion of breast (98–100), lung (100, 101) and colon (100) cancer cells. However, one study found that dexmedetomidine alone or in combination with propofol had minimal effect on the migration of colorectal cancer cells (102). In addition, recent retrospective data did not demonstrate that intraoperative use of dexmedetomidine was associated with a reduction in recurrence free survival after lung cancer surgery (103) or affect biochemical recurrence and radiological progression following prostate cancer surgery (104). Therefore, the use of adrenergic receptor agonists, notably dexmedetomidine, in cancer surgery could do more harm than good and remains debatable. High quality randomised control trials are warranted before a change of practice is recommended. At present, there are two ongoing randomised control trials (NCT03109990 & NCT03012971: clinicaltrials.gov) which aim to examine overall cancer survival and recurrence in patients receiving an intravenous dexmedetomidine infusion as an analgesic adjuvant versus placebo during cancer surgery.

NON-STEROIDAL INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are commonly used as analgesics in the perioperative setting and may also provide supplementary anticancer benefits. NSAIDs can be either non-selective, (aspirin, diclofenac, naproxen, ibuprofen, ketorolac), or selective for either the cyclooxygenase 1 (COX1) isoform (ketoprofen) or the COX2 isoform (celecoxib, parecoxib, etodolac, rofecoxib) and have been demonstrated to play an important role in multimodal analgesia for oncological surgery. NSAIDs may prolong the recurrence-free survival of patients after cancer surgery by three distinct mechanisms; first, NSAIDs can reduce the postoperative tumour burden by having a direct effect on cancer cells. For example, celecoxib has been shown to inhibit the formation of surgery-induced metastasis in animal models of colorectal cancer by inhibiting the prostaglandin E2 (PGE2)-glycogen synthase kinase-B catenin pathway (105). Secondly, as inflammation influences the metastatic process, methods of regulating systemic and local inflammatory responses to surgery, may prevent the escape of cancer cells from immunosurveillance in the tumour microenvironment. Lastly, NSAIDs have significant opioid-sparing effects. Opioids have been implicated in postoperative cancer recurrence as discussed previously in this article. In animal models, the use of NSAIDS during surgery has been shown to reduce NK cell numbers and prevent the growth of metastases in murine models (106). By reducing tumour associated inflammation, NSAIDs have also been shown to reduce the extent of angiogenesis and lymphangiogenesis in animal models (107, 108).

Clinical trials indicate that NSAIDs have both local and systemic anti-inflammatory effects. Preoperative use of NSAIDs has been shown to reduce intra-tumoral levels of VEGF expression, lymphangiogenesis, and Treg cell infiltration (109, 110). A study of perioperatively delivered COX2 inhibitors revealed a reduction in prostaglandin levels at the surgical site and in the systemic circulation. Similarly COX2 inhibitors have been shown to suppress increases in systemic catecholamine, cytokine and T-cell levels, and to also buffer the reduction in NK cell counts in the postoperative period (111–115). Data from these prospective clinical studies (2014–2017) suggest an indirect anticancer effect.

There has been considerable effort spent in investigating oncological outcomes related to long term NSAID use prior to, or after diagnosis in cancer patients. Observational studies have shown that regular NSAID use has been associated with improved cancer recurrence rates in colorectal cancer (116) and breast cancer (117). However, perioperative administration of NSAIDs during cancer surgery at analgesic doses have demonstrated variable results in terms of any association with cancer recurrence and overall survival outcomes (118–122). **Table 3** summaries these retrospective studies.

TABLE 3 | Selected retrospective studies examining the association between perioperative administration of NSAID and cancer recurrence and overall survival rates.

Author	Year	NSAID	Number of patients	Cancer type	Findings
Forget et al. (118)	2011	Ketorolac	1,111	Prostate cancer	Intraoperative use of Ketorolac did not significantly improve the incidence of biochemical recurrence-free survival rates
Forget et al. (119)	2014	Ketorolac and Diclofenac	720	Breast cancer	Intraoperative use of ketorolac or diclofenac was associated with improved outcomes in cancer recurrence and overall survival rates.
Yeh et al. (120)	2015	Non-specific	15,574	Hepatocellular carcinoma	The use of NSAIDS was associated with a reduced risk of early HCC recurrence within 2 years after liver surgery.
Lee et al. (121)	2016	Ketorolac, ibuprofen, rofecoxib or celecoxib.	1,637	Non-small-cell lung cancer	Perioperative use of NSAID did not significantly improve cancer recurrence and overall survival rates.
Huang et al. (122)	2018	Flurbiprofen and dexamethasone combination	588	Non-small-cell lung cancer	Perioperative combined administration of dexamethasone and flubiprofen was associated with longer survival rates.

Finally, a systematic review on NSAIDs in the oncological surgical population, included studies up to 2017 and concluded that the evidence is equivocal regarding the short-term effects of these analgesic/inflammatory agents on cancer recurrence after cancer surgery (123). Furthermore, two recent prospective RCTs examining these effects have not provided definitive conclusions. A 2019 study comprising of 203 patients scheduled to undergo curative surgery for breast cancer, revealed that a single administration of 30mg of ketorolac preoperatively does not increase disease-free survival in high-risk breast cancer patients. The authors conceded however, that this study was hugely underpowered due to lower recurrence rates than initially anticipated (124). In addition, a 2021 multicentre study of 2639 patients conducted in 160 centres in Germany and the UK, revealed no evidence of a disease-free benefit for 2 years' treatment with celecoxib compared with placebo, as adjuvant treatment of ERBB2-negative breast cancer. The authors concluded that longer-term treatment or use of a higher dose of celecoxib may lead to a disease-free benefit. Further high-powered clinical trials would be required to further investigate this (125).

SUMMARY

The hypothesis that anaesthetic and analgesic technique during cancer surgery could influence risk of subsequent recurrence or metastasis has been topical for more than 15 years. Although there is some supportive *in vitro* and *in vivo* experimental data, and also observational clinical data suggesting such an association, only prospective randomised clinical trials can prove a causal link between perioperative analgesia and long-term oncologic outcomes. The first and only large trial available to date has shown robust equivalent findings with regional or volatile general anaesthesia with opioid analgesia. A number of other prospective RCTs evaluating the effect of various analgesic drugs during surgery for cancer resection on disease free survival are ongoing, especially the VAPOR-C trial. These will provide crucial evidence over the coming 5 years which will definitively answer this urgent research question of our time: whether this hypothesis has any meaningful clinical implications for the perioperative care of our cancer resection patients?

AUTHOR CONTRIBUTIONS

Conceptualization of this article was performed by DB. Literature search, selection of relevant original investigations for inclusion, and initial writing synthesis: AM and AE. Writing- original draft preparation: AM, AE, and DB. Writing-review and editing: AM, AE, and DB. All named authors contributed to the intellectual content and approved the final submitted version.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Ward ZJ, Scott AM, Hricak H, Abdel-Wahab M, Paez D, Lette MM, et al. Estimating the Impact of Treatment and Imaging Modalities on 5-Year Net Survival of 11 Cancers in 200 Countries: A Simulation-Based Analysis. *Lancet Oncol* (2020) 21(8):1077–88. doi: 10.1016/S1470-2045(20)30317-X
3. Welch DR, Hurst DR. Defining the Hallmarks of Metastasis. *Cancer Res* (2019) 79(12):3011–27. doi: 10.1158/0008-5472.CAN-19-0458
4. Riggio AI, Varley KE, Welm AL. The Lingering Mysteries of Metastatic Recurrence in Breast Cancer. *Br J Cancer* (2021) 124(1):13–26. doi: 10.1038/s41416-020-01161-4
5. Dillekas H, Rogers MS, Straume O. Are 90% of Deaths From Cancer Caused by Metastases? *Cancer Med* (2019) 8(12):5574–6. doi: 10.1002/cam4.2474
6. Luskin MR, Murakami MA, Manalis SR, Weinstock DM. Targeting Minimal Residual Disease: A Path to Cure? *Nat Rev Cancer* (2018) 18(4):255–63. doi: 10.1038/nrc.2017.125
7. Tohme S, Simmons RL, Tsung A. Surgery for Cancer: A Trigger for Metastases. *Cancer Res* (2017) 77(7):1548–52. doi: 10.1158/0008-5472.CAN-16-1536
8. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative Events Influence Cancer Recurrence Risk After Surgery. *Nat Rev Clin Oncol* (2018) 15(4):205–18. doi: 10.1038/nrclinonc.2017.194
9. Cata JP, Lasala J, Pratt G, Feng L, Shah JB. Association Between Perioperative Blood Transfusions and Clinical Outcomes in Patients Undergoing Bladder Cancer Surgery: A Systematic Review and Meta-Analysis Study. *J Blood Transfus* (2016) 2016:9876394. doi: 10.1155/2016/9876394
10. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of Perioperative Anaesthetic and Analgesic Interventions on Oncological Outcomes: A Narrative Review. *Br J Anaesth* (2019) 123(2):135–50. doi: 10.1016/j.bja.2019.04.062
11. Forget P, Aguirre JA, Bencic I, Borgeat A, Cama A, Condron C, et al. How Anesthetic, Analgesic and Other Non-Surgical Techniques During Cancer Surgery Might Affect Postoperative Oncologic Outcomes: A Summary of Current State of Evidence. *Cancers (Basel)* (2019) 11(5):592–607. doi: 10.3390/cancers11050592
12. Jin MZ, Jin WL. The Updated Landscape of Tumor Microenvironment and Drug Repurposing. *Signal Transduct Target Ther* (2020) 5(1):166. doi: 10.1038/s41392-020-00280-x
13. Lee G, Hall RR3rd, Ahmed AU. Cancer Stem Cells: Cellular Plasticity, Niche, and its Clinical Relevance. *J Stem Cell Res Ther* (2016) 6(10):363–72. doi: 10.4172/2157-7633.1000363
14. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and Tumor Progression: Signaling Pathways and Targeted Intervention. *Signal Transduct Target Ther* (2021) 6(1):263. doi: 10.1038/s41392-021-00658-5
15. Walter ND, Rice PL, Redente EF, Kauvar EF, Lemond L, Aly T, et al. Wound Healing After Trauma may Predispose to Lung Cancer Metastasis: Review of Potential Mechanisms. *Am J Respir Cell Mol Biol* (2011) 44(5):591–6. doi: 10.1165/rcmb.2010-0187RT
16. Angka L, Khan ST, Kilgour MK, Xu R, Kennedy MA, Auer RC. Dysfunctional Natural Killer Cells in the Aftermath of Cancer Surgery. *Int J Mol Sci* (2017) 18(8):1787–807. doi: 10.3390/ijms18081787
17. Wu SY, Fu T, Jiang YZ, Shao ZM. Natural Killer Cells in Cancer Biology and Therapy. *Mol Cancer* (2020) 19(1):120. doi: 10.1186/s12943-020-01238-x

18. Behrenbruch C, Shembrey C, Paquet-Fifield S, Molck C, Cho HJ, Michael M, et al. Surgical Stress Response and Promotion of Metastasis in Colorectal Cancer: A Complex and Heterogeneous Process. *Clin Exp Metastasis* (2018) 35(4):333–45. doi: 10.1007/s10585-018-9873-2
19. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The Effects of Surgery on Tumor Growth: A Century of Investigations. *Ann Oncol* (2008) 19(11):1821–8. doi: 1093/annonc/mdn386.
20. Murthy SM, Goldschmidt RA, Rao LN, Ammirati M, Buchmann T, Scanlon EF. The Influence of Surgical Trauma on Experimental Metastasis. *Cancer* (1989) 64(10):2035–44. doi: 10.1002/1097-0142(19891115)64:10<2035::aid-cncr2820641012>3.0.co;2-l
21. Treede RD. The International Association for the Study of Pain Definition of Pain: As Valid in 2018 as in 1979, But in Need of Regularly Updated Footnotes. *Pain Rep* (2018) 3(2):e643. doi: 10.1097/PR9.0000000000000643
22. Small C, Laycock H. Acute Postoperative Pain Management. *Br J Surg* (2020) 107(2):e70–80. doi: 10.1002/bjs.11477
23. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. *Anesthesiology* (2018) 129(2):343–66. doi: 10.1097/ALN.0000000000002130
24. Page GG, Blakely WP, Ben-Eliyahu S. Evidence That Postoperative Pain is a Mediator of the Tumor-Promoting Effects of Surgery in Rats. *Pain* (2001) 90 (1-2):191–9. doi: 10.1016/s0304-3959(00)00403-6
25. Shavit Y, Terman GW, Lewis JW, Zane CJ, Gale RP, Liebeskind JC. Effects of Footshock Stress and Morphine on Natural Killer Lymphocytes in Rats: Studies of Tolerance and Cross-Tolerance. *Brain Res* (1986) 372(2):382–5. doi: 10.1016/0006-8993(86)91149-2
26. Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G. Evidence that Stress and Surgical Interventions Promote Tumor Development by Suppressing Natural Killer Cell Activity. *Int J Cancer* (1999) 80(6):880–8. doi: 10.1002 (sici)1097-0215(19990315)80:6<880::aid-ijc14>3.0.co;2-y
27. Hooijmans CR, Geessink FJ, Ritskes-Hoitinga M, Scheffer GJ. A Systematic Review and Meta-Analysis of the Ability of Analgesic Drugs to Reduce Metastasis in Experimental Cancer Models. *Pain* (2015) 156(10):1835–44. doi: 10.1097/j.pain.0000000000000296
28. Chang WK, Tai YH, Lin SP, Wu HL, Tsou MY, Chang KY. An Investigation of the Relationships Between Postoperative Pain Trajectories and Outcomes After Surgery for Colorectal Cancer. *J Chin Med Assoc* (2019) 82(11):865–71. doi: 10.1097/JCMA.0000000000000166
29. Chin KJ, Mariano ER, El-Boghdadly K. Advancing Towards the Next Frontier in Regional Anaesthesia. *Anaesthesia* (2021) 76(Suppl 1):3–7. doi: 10.1111/anae.15321
30. Pack E, Saha S. Regional Anaesthesia and Perioperative Medicine. *Br J Hosp Med (Lond)* (2020) 81(8):1–2. doi: 10.12968/hmed.2020.0111
31. Albrecht E, Chin KJ. Advances in Regional Anaesthesia and Acute Pain Management: A Narrative Review. *Anaesthesia* (2020) 75(Suppl 1):e101–e10. doi: 10.1111/anae.14868
32. Torpy JM, Lynm C, Golub RM. Regional Anesthesia. *JAMA* (2011) 306 (7):781. doi: 10.1001/jama.306.7.781
33. Taylor A, McLeod G. Basic Pharmacology of Local Anaesthetics. *BJA Educ* (2020) 20(2):34–41. doi: 10.1016/j.bjae.2019.10.002
34. Piegeler T, Votta-Velis EG, Liu G, Place AT, Schwartz DE, Beck-Schimmer B, et al. Antimetastatic Potential of Amide-Linked Local Anesthetics: Inhibition of Lung Adenocarcinoma Cell Migration and Inflammatory Src Signaling Independent of Sodium Channel Blockade. *Anesthesiology* (2012) 117(3):548–59. doi: 10.1097/ALN.0b013e3182661977
35. Lucchinetti E, Awad AE, Rahman M, Feng J, Lou PH, Zhang L, et al. Antiproliferative Effects of Local Anesthetics on Mesenchymal Stem Cells: Potential Implications for Tumor Spreading and Wound Healing. *Anesthesiology* (2012) 116(4):841–56. doi: 10.1097/ALN.0b013e31824babfe
36. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, et al. Molecular Mechanisms of Action of Systemic Lidocaine in Acute and Chronic Pain: A Narrative Review. *Br J Anaesth* (2019) 123 (3):335–49. doi: 10.1016/j.bja.2019.06.014
37. Zhou DP, Wang L, Cui QB, Iftikhar R, Xia YF, Xu P. Repositioning Lidocaine as an Anticancer Drug: The Role Beyond Anesthesia. *Front Cell Dev Biol* (2020) 8:565. doi: 10.3389/fcell.2020.00565
38. Yang W, Cai J, Zhang H, Wang G, Jiang W. Effects of Lidocaine and Ropivacaine on Gastric Cancer Cells Through Down-Regulation of ERK1/2 Phosphorylation *In Vitro*. *Anticancer Res* (2018) 38(12):6729–35. doi: 10.21873/anticanres.13042
39. Ye L, Zhang Y, Chen YJ, Liu Q. Anti-Tumor Effects of Lidocaine on Human Gastric Cancer Cells *In Vitro*. *Bratisl Lek Listy* (2019) 120(3):212–7. doi: 10.4149/BLL_2019_036
40. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, et al. Antitumor Effects of Lidocaine on Human Breast Cancer Cells: An *In Vitro* and *In Vivo* Experimental Trial. *Anticancer Res* (2018) 38 (1):95–105. doi: 10.21873/anticanres.12196
41. Bundscherer AC, Malsy M, Bitzinger DI, Wiese CH, Gruber MA, Graf BM. Effects of Lidocaine on HT-29 and SW480 Colon Cancer Cells *In Vitro*. *Anticancer Res* (2017) 37(4):1941–5. doi: 10.21873/anticanres.11534
42. Fraser SP, Ozerlat-Gunduz I, Brackenbury WJ, Fitzgerald EM, Campbell TM, Coombes RC, et al. Regulation of Voltage-Gated Sodium Channel Expression in Cancer: Hormones, Growth Factors and Auto-Regulation. *Philos Trans R Soc Lond B Biol Sci* (2014) 369(1638):20130105. doi: 10.1098/rstb.2013.0105
43. Lirk P, Hollmann MW, Fleischer M, Weber NC, Fiegl H. Lidocaine and Ropivacaine, But Not Bupivacaine, Demethylate Deoxyribonucleic Acid in Breast Cancer Cells *In Vitro*. *Br J Anaesth* (2014) 113(Suppl 1):i32–8. doi: 10.1093/bja/aeu201
44. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. *Anticancer Res* (2018) 38(10):5599–606. doi: 10.21873/anticanres.12894
45. Gao X, Yang H, Wu M, Shi K, Zhou C, Peng J, et al. Targeting Delivery of Lidocaine and Cisplatin by Nanogel Enhances Chemotherapy and Alleviates Metastasis. *ACS Appl Mater Interf* (2018) 10(30):25228–40. doi: 10.1021/acsami.8b09376
46. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Ketamine-Xylazine Anaesthesia for Breast Tumour Resection in a Murine Model. *Br J Anaesth* (2018) 121(1):76–85. doi: 10.1016/j.bja.2017.12.043
47. Wall TP, Crowley PD, Sherwin A, Foley AG, Buggy DJ. Effects of Lidocaine and Src Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers (Basel)* (2019) 11(10):1414–24. doi: 10.3390/cancers11101414
48. Liu C, Yu M, Li Y, Wang H, Xu C, Zhang X, et al. Lidocaine Inhibits the Metastatic Potential of Ovarian Cancer by Blocking NaV 1.5-Mediated EMT and FAK/Paxillin Signaling Pathway. *Cancer Med* (2021) 10(1):337–49. doi: 10.1002/cam4.3621
49. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association Between Intraoperative Intravenous Lidocaine Infusion and Survival in Patients Undergoing Pancreatectomy for Pancreatic Cancer: A Retrospective Study. *Br J Anaesth* (2020) 125(2):141–8. doi: 10.1016/j.bja.2020.03.034
50. Park J, Wysocki RW, Amoozgar Z, Maiorino L, Fein MR, Jorns J, et al. Cancer Cells Induce Metastasis-Supporting Neutrophil Extracellular DNA Traps. *Sci Transl Med* (2016) 8(361):361ra138. doi: 10.1126/scitranslmed.aag1711
51. Galos EV, Tat TF, Popa R, Efrimescu CI, Finnerty D, Buggy DJ, et al. Neutrophil Extracellular Trapping and Angiogenesis Biomarkers After Intravenous or Inhalation Anaesthesia With or Without Intravenous Lidocaine for Breast Cancer Surgery: A Prospective, Randomised Trial. *Br J Anaesth* (2020) 125(5):712–21. doi: 10.1016/j.bja.2020.05.003
52. Dubowitz JA, Cata JP, De Silva AP, Braat S, Shan D, Yee K, et al. Volatile Anaesthesia and Peri-Operative Outcomes Related to Cancer: A Feasibility and Pilot Study for a Large Randomised Control Trial. *Anaesthesia* (2021) 76 (9):1198–206. doi: 10.1111/anae.15354
53. Jakobsson J, Johnson MZ. Perioperative Regional Anaesthesia and Postoperative Longer-Term Outcomes. *F1000Res* (2016) 5:2501–8. doi: 10.12688/f1000research.9100.1
54. Johnston DF, Turbitt LR. Defining Success in Regional Anaesthesia. *Anaesthesia* (2021) 76 Suppl 1:40–52. doi: 10.1111/anae.15275
55. Desborough JP. The Stress Response to Trauma and Surgery. *Br J Anaesth* (2000) 85(1):109–17. doi: 10.1093/bja/85.1.109
56. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. *JAMA Surg* (2017) 152(7):691–7. doi: 10.1001/jamasurg.2017.0898

57. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008
58. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X
59. Bomberg H, Bayer I, Wagenpfeil S, Kessler P, Wulf H, Standl T, et al. Prolonged Catheter Use and Infection in Regional Anesthesia: A Retrospective Registry Analysis. *Anesthesiology* (2018) 128(4):764–73. doi: 10.1097/ALN.0000000000002105
60. del-Rio-Vellosillo M, Garcia-Medina JJ, Pinazo-Duran MD, Abengochea-Cotaina A. Doses and Effects of Levobupivacaine and Bupivacaine for Spinal Anaesthesia. *Br J Anaesth* (2014) 113(3):521–2. doi: 10.1093/bja/aeu276
61. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The Effect of Neuraxial Anesthesia on Cancer Recurrence and Survival After Cancer Surgery: An Updated Meta-Analysis. *Oncotarget* (2016) 7(12):15262–73. doi: 10.18632/oncotarget.7683
62. Sun Y, Li T, Gan TJ. The Effects of Perioperative Regional Anesthesia and Analgesia on Cancer Recurrence and Survival After Oncology Surgery: A Systematic Review and Meta-Analysis. *Reg Anesth Pain Med* (2015) 40 (5):589–98. doi: 10.1097/AAP.0000000000000273
63. Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, et al. Comparison of Combined General-Epidural Anesthesia With General Anesthesia Effects on Survival and Cancer Recurrence: A Meta-Analysis of Retrospective and Prospective Studies. *PloS One* (2014) 9(12):e114667. doi: 10.1371/journal.pone.0114667
64. Lee BM, Singh Ghotra V, Karam JA, Hernandez M, Pratt G, Cata JP. Regional Anesthesia/Analgesia and the Risk of Cancer Recurrence and Mortality After Prostatectomy: A Meta-Analysis. *Pain Manage* (2015) 5 (5):387–95. doi: 10.2217/pmt.15.30
65. Lee ZX, Ng KT, Ang E, Wang CY, Binti SII. Effect of Perioperative Regional Anesthesia on Cancer Recurrence: A Meta-Analysis of Randomized Controlled Trials. *Int J Surg* (2020) 82:192–9. doi: 10.1016/j.ijsu.2020.08.034
66. Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anesthesia-Analgesia and Recurrence-Free Survival After Lung Cancer Surgery: A Randomized Trial. *Anesthesiology* (2021) 135:419–32. doi: 10.1097/ALN.0000000000003873
67. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased Mu-Opioid Receptor Expression in Metastatic Lung Cancer. *Br J Anaesth* (2014) 113 Suppl 1:i103–8. doi: 10.1093/bja/aeu165
68. Zhang YF, Xu QX, Liao LD, Xu XE, Wu JY, Wu ZY, et al. Association of Mu-Opioid Receptor Expression With Lymph Node Metastasis in Esophageal Squamous Cell Carcinoma. *Dis Esophagus* (2015) 28(2):196–203. doi: 10.1111/dote.12165
69. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid Requirement, Opioid Receptor Expression, and Clinical Outcomes in Patients With Advanced Prostate Cancer. *Cancer* (2013) 119(23):4103–10. doi: 10.1002/cncr.28345
70. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The Novel Role of the Mu Opioid Receptor in Lung Cancer Progression: A Laboratory Investigation. *Anesth Analg* (2011) 112 (3):558–67. doi: 10.1213/ANE.0b013e31820568af
71. Lennon FE, Mirzapoiazova T, Mambetsariev B, Poroyko VA, Salgia R, Moss J, et al. The Mu Opioid Receptor Promotes Opioid and Growth Factor-Induced Proliferation, Migration and Epithelial Mesenchymal Transition (EMT) in Human Lung Cancer. *PloS One* (2014) 9(3):e91577. doi: 10.1371/journal.pone.0091577
72. Lennon FE, Mirzapoiazova T, Mambetsariev B, Salgia R, Moss J, Singleton PA. Overexpression of the Mu-Opioid Receptor in Human Non-Small Cell Lung Cancer Promotes Akt and mTOR Activation, Tumor Growth, and Metastasis. *Anesthesiology* (2012) 116(4):857–67. doi: 10.1097/ALN.0b013e31824babe2
73. Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. Mu-Opioid Receptor Gene A118G Polymorphism Predicts Survival in Patients With Breast Cancer. *Anesthesiology* (2012) 116(4):896–902. doi: 10.1097/ALN.0b013e31824b96a1
74. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment With Methylnaltrexone Is Associated With Increased Survival in Patients With Advanced Cancer. *Ann Oncol* (2016) 27(11):2032–8. doi: 10.1093/annonc/mdw317
75. Boland JW, Pockley AG. Influence of Opioids on Immune Function in Patients With Cancer Pain: From Bench to Bedside. *Br J Pharmacol* (2018) 175(14):2726–36. doi: 10.1111/bph.13903
76. Capellino S, Claus M, Watzl C. Regulation of Natural Killer Cell Activity by Glucocorticoids, Serotonin, Dopamine, and Epinephrine. *Cell Mol Immunol* (2020) 17(7):705–11. doi: 10.1038/s41423-020-0477-9
77. Franchi S, Moschetti G, Amodeo G, Sacerdote P. Do All Opioid Drugs Share the Same Immunomodulatory Properties? A Review From Animal and Human Studies. *Front Immunol* (2019) 10:2914. doi: 10.3389/fimmu.2019.02914
78. Gaspani L, Bianchi M, Limiroli E, Panerai AE, Sacerdote P. The Analgesic Drug Tramadol Prevents the Effect of Surgery on Natural Killer Cell Activity and Metastatic Colonization in Rats. *J Neuroimmunol* (2002) 129(1-2):18–24. doi: 10.1016/s0165-5728(02)00165-0
79. Silagy AW, Hannum ML, Mano R, Attalla K, Scarpa JR, DiNatale RG, et al. Impact of Intraoperative Opioid and Adjunct Analgesic Use on Renal Cell Carcinoma Recurrence: Role for Onco-Anaesthesia. *Br J Anaesth* (2020) 125 (5):e402–e4. doi: 10.1016/j.bja.2020.06.036
80. Rangel FP, Auler JOCJr., Carmona MJC, Cordeiro MD, Nahas WC, Coelho RF, et al. Opioids and Premature Biochemical Recurrence of Prostate Cancer: A Randomised Prospective Clinical Trial. *Br J Anaesth* (2021) 126 (5):931–9. doi: 10.1016/j.bja.2021.01.031
81. Diaz-Cambronero O, Mazzinari G, Cata JP. Perioperative Opioids and Colorectal Cancer Recurrence: A Systematic Review of the Literature. *Pain Manage* (2018) 8(5):353–61. doi: 10.2217/pmt-2018-0029
82. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative Opioids are Associated With Improved Recurrence-Free Survival in Triple-Negative Breast Cancer. *Br J Anaesth* (2021) 126 (2):367–76. doi: 10.1016/j.bja.2020.10.021
83. Mion G, Villevieille T. Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). *CNS Neurosci Ther* (2013) 19(6):370–80. doi: 10.1111/cns.12099
84. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clin Pharmacokinet* (2016) 55(9):1059–77. doi: 10.1007/s40262-016-0383-6
85. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, et al. Perioperative Intravenous Ketamine for Acute Postoperative Pain in Adults. *Cochrane Database Syst Rev* (2018) 12:CD012033. doi: 10.1002/14651858.CD012033.pub4
86. Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greemberg L, Yardeni IZ, et al. Low-Dose Ketamine Affects Immune Responses in Humans During the Early Postoperative Period. *Br J Anaesth* (2007) 99(4):522–7. doi: 10.1093/bja/aem218
87. Kawasaki C, Kawasaki T, Ogata M, Nandate K, Shigematsu A. Ketamine Isomers Suppress Superantigen-Induced Proinflammatory Cytokine Production in Human Whole Blood. *Can J Anaesth* (2001) 48(8):819–23. doi: 10.1007/BF03016701
88. Tay RE, Richardson EK, Toh HC. Revisiting the Role of CD4(+) T Cells in Cancer Immunotherapy-New Insights Into Old Paradigms. *Cancer Gene Ther* (2021) 28(1-2):5–17. doi: 10.1038/s41417-020-0183-x
89. Hou M, Zhou N, Li H, Wang B, Wang X, Wang X, et al. Morphine and Ketamine Treatment Suppress the Differentiation of T Helper Cells of Patients With Colorectal Cancer *In Vitro*. *Exp Ther Med* (2019) 17 (1):935–42. doi: 10.3892/etm.2018.7035
90. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, But Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth Analg* (2003) 97(5):1331–9. doi: 10.1213/01.ANE.0000082995.44040.07
91. Cho JS, Kim NY, Shim JK, Jun JH, Lee S, Kwak YL. The Immunomodulatory Effect of Ketamine in Colorectal Cancer Surgery: A Randomized-Controlled Trial. *Can J Anaesth* (2021) 68(5):683–92. doi: 10.1007/s12630-021-01925-3
92. Connolly JG, Tan KS, Mastrogiacomo B, Dycoco J, Caso R, Jones GD, et al. Intraoperative Opioid Exposure, Tumour Genomic Alterations, and Survival

Differences in People With Lung Adenocarcinoma. *Br J Anaesth* (2021) 127 (1):75–84. doi: 10.1016/j.bja.2021.03.030
93. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet* (2017) 56(8):893–913. doi: 10.1007/s40262-017-0507-7
94. Tang C, Xia Z. Dexmedetomidine in Perioperative Acute Pain Management: A non-Opioid Adjuvant Analgesic. *J Pain Res* (2017) 10:1899–904. doi: 10.2147/JPR.S139387
95. Ju JY, Kim KM, Lee S. Effect of Preoperative Administration of Systemic Alpha-2 Agonists on Postoperative Pain: A Systematic Review and Meta-Analysis. *Anesth Pain Med (Seoul)* (2020) 15(2):157–66. doi: 10.17085/apm.2020.15.2.157
96. Liu C, Wang W, Shan Z, Zhang H, Yan Q. Dexmedetomidine as an Adjuvant for Patients Undergoing Breast Cancer Surgery: A Meta-Analysis. *Med (Baltimore)* (2020) 99(50):e23667. doi: 10.1097/MD.0000000000023667
97. Powe DG, Voss MJ, Habashy HO, Zanker KS, Green AR, Ellis IO, et al. Alpha- and Beta-Adrenergic Receptor (AR) Protein Expression is Associated With Poor Clinical Outcome in Breast Cancer: An Immunohistochemical Study. *Breast Cancer Res Treat* (2011) 130(2):457–63. doi: 10.1007/s10549-011-1371-z
98. Xia M, Ji NN, Duan ML, Tong JH, Xu JG, Zhang YM, et al. Dexmedetomidine Regulate the Malignancy of Breast Cancer Cells by Activating Alpha2-Adrenoceptor/ERK Signaling Pathway. *Eur Rev Med Pharmacol Sci* (2016) 20(16):3500–6.
99. Liu Y, Sun J, Wu T, Lu X, Du Y, Duan H, et al. Effects of Serum From Breast Cancer Surgery Patients Receiving Perioperative Dexmedetomidine on Breast Cancer Cell Malignancy: A Prospective Randomized Controlled Trial. *Cancer Med* (2019) 8(18):7603–12. doi: 10.1002/cam4.2654
100. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120(1):188–96. doi: 10.1016/j.bja.2017.11.004
101. Su X, Fan Y, Yang L, Huang J, Qiao F, Fang Y, et al. Dexmedetomidine Expands Monocytic Myeloid-Derived Suppressor Cells and Promotes Tumour Metastasis After Lung Cancer Surgery. *J Transl Med* (2018) 16 (1):347. doi: 10.1186/s12967-018-1727-9
102. Deng F, Ouyang M, Wang X, Yao X, Chen Y, Tao T, et al. Differential Role of Intravenous Anesthetics in Colorectal Cancer Progression: Implications for Clinical Application. *Oncotarget* (2016) 7(47):77087–95. doi: 10.18632/oncotarget.12800
103. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, et al. Intraoperative Use of Dexmedetomidine Is Associated With Decreased Overall Survival After Lung Cancer Surgery. *J Anaesthesiol Clin Pharmacol* (2017) 33(3):317–23. doi: 10.4103/joacp.JOACP_299_16
104. Yoo YC, Jang WS, Kim KJ, Hong JH, Yang S, Kim NY. Effect of Dexmedetomidine on Biochemical Recurrence in Patients After Robot-Assisted Laparoscopic Radical Prostatectomy: A Retrospective Study. *J Pers Med* (2021) 11(9):912–22. doi: 10.3390/jpm11090912
105. Zhang S, Da L, Yang X, Feng D, Yin R, Li M, et al. Celecoxib Potentially Inhibits Metastasis of Lung Cancer Promoted by Surgery in Mice, *via* Suppression of the PGE2-Modulated Beta-Catenin Pathway. *Toxicol Lett* (2014) 225(2):201–7. doi: 10.1016/j.toxlet.2013.12.014
106. Glasner A, Avraham R, Rosenne E, Benish M, Zmora O, Shemer S, et al. Improving Survival Rates in Two Models of Spontaneous Postoperative Metastasis in Mice by Combined Administration of a Beta-Adrenergic Antagonist and a Cyclooxygenase-2 Inhibitor. *J Immunol* (2010) 184 (5):2449–57. doi: 10.4049/jimmunol.0903301
107. Dillekas H, Demicheli R, Ardoino I, Jensen SAH, Biganzoli E, Straume O. The Recurrence Pattern Following Delayed Breast Reconstruction After Mastectomy for Breast Cancer Suggests a Systemic Effect of Surgery on Occult Dormant Micrometastases. *Breast Cancer Res Treat* (2016) 158 (1):169–78. doi: 10.1007/s10549-016-3857-1
108. Karnezis T, Shayan R, Caesar C, Roufail S, Harris NC, Ardipradja K, et al. VEGF-D Promotes Tumor Metastasis by Regulating Prostaglandins Produced by the Collecting Lymphatic Endothelium. *Cancer Cell* (2012) 21 (2):181–95. doi: 10.1016/j.ccr.2011.12.026
109. Lonnroth C, Andersson M, Arvidsson A, Nordgren S, Brevinge H, Lagerstedt K, et al. Preoperative Treatment With a non-Steroidal Anti-Inflammatory Drug (NSAID) Increases Tumor Tissue Infiltration of Seemingly Activated Immune Cells in Colorectal Cancer. *Cancer Immun* (2008) 8:5.
110. Sooriakumaran P, Coley HM, Fox SB, Macanas-Pirard P, Lovell DP, Henderson A, et al. A Randomized Controlled Trial Investigating the Effects of Celecoxib in Patients With Localized Prostate Cancer. *Anticancer Res* (2009) 29(5):1483–8.
111. Hiller JG, Sampurno S, Millen R, Kuruvilla N, Ho KM, Ramsay R, et al. Impact of Celecoxib on Inflammation During Cancer Surgery: A Randomized Clinical Trial. *Can J Anaesth* (2017) 64(5):497–505. doi: 10.1007/s12630-017-0818-z
112. Zhu Y, Wang S, Wu H, Wu Y. Effect of Perioperative Parecoxib on Postoperative Pain and Local Inflammation Factors PGE2 and IL-6 for Total Knee Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Study. *Eur J Orthop Surg Traumatol* (2014) 24(3):395–401. doi: 10.1007/s00590-013-1203-4
113. Wang LD, Gao X, Li JY, Yu HY, Su HW, Liu LZ, et al. Effects of Preemptive Analgesia With Parecoxib Sodium on Haemodynamics and Plasma Stress Hormones in Surgical Patients With Thyroid Carcinoma. *Asian Pac J Cancer Prev* (2015) 16(9):3977–80. doi: 10.7314/apjcp.2015.16.9.3977
114. Ma W, Wang K, Du J, Luan J, Lou G. Multi-Dose Parecoxib Provides an Immunoprotective Effect by Balancing T Helper 1 (Th1), Th2, Th17 and Regulatory T Cytokines Following Laparoscopy in Patients With Cervical Cancer. *Mol Med Rep* (2015) 11(4):2999–3008. doi: 10.3892/mmr.2014.3003
115. Shen JC, Sun HL, Zhang MQ, Liu XY, Wang Z, Yang JJ. Flurbiprofen Improves Dysfunction of T-Lymphocyte Subsets and Natural Killer Cells in Cancer Patients Receiving Post-Operative Morphine Analgesia. *Int J Clin Pharmacol Ther* (2014) 52(8):669–75. doi: 10.5414/CP202027
116. Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, et al. Aspirin and COX-2 Inhibitor Use in Patients With Stage III Colon Cancer. *J Natl Cancer Inst* (2015) 107(1):345. doi: 10.1093/jnci/dju345
117. Huang XZ, Gao P, Sun JX, Song YX, Tsai CC, Liu J, et al. Aspirin and Nonsteroidal Anti-Inflammatory Drugs After But Not Before Diagnosis are Associated With Improved Breast Cancer Survival: A Meta-Analysis. *Cancer Causes Control* (2015) 26(4):589–600. doi: 10.1007/s10552-015-0539-y
118. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, et al. Do Intraoperative Analgesics Influence Oncological Outcomes After Radical Prostatectomy for Prostate Cancer? *Eur J Anaesthesiol* (2011) 28(12):830–5. doi: 10.1097/EJA.0b013e32834b7d9a
119. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative Use of Ketorolac or Diclofenac is Associated With Improved Disease-Free Survival and Overall Survival in Conservative Breast Cancer Surgery. *Br J Anaesth* (2014) 113 Suppl 1:i82–7. doi: 10.1093/bja/aet464
120. Yeh CC, Lin JT, Jeng LB, Ho HJ, Yang HR, Wu MS, et al. Nonsteroidal Anti-Inflammatory Drugs are Associated With Reduced Risk of Early Hepatocellular Carcinoma Recurrence After Curative Liver Resection: A Nationwide Cohort Study. *Ann Surg* (2015) 261(3):521–6. doi: 10.1097/SLA.0000000000000746
121. Lee BM, Rodriguez A, Mena G, Gottumukkala V, Mehran RJ, Rice DC, et al. Platelet-To-Lymphocyte Ratio and Use of NSAIDs During the Perioperative Period as Prognostic Indicators in Patients With NSCLC Undergoing Surgery. *Cancer Control* (2016) 23(3):284–94. doi: 10.1177/107327481602300312
122. Huang WW, Zhu WZ, Mu DL, Ji XQ, Nie XL, Li XY, et al. Perioperative Management May Improve Long-Term Survival in Patients After Lung Cancer Surgery: A Retrospective Cohort Study. *Anesth Analg* (2018) 126 (5):1666–74. doi: 10.1213/ANE.0000000000002886
123. Cata JP, Guerra CE, Chang GJ, Gottumukkala V, Joshi GP. Non-Steroidal Anti-Inflammatory Drugs in the Oncological Surgical Population: Beneficial or Harmful? A Systematic Review of the Literature. *Br J Anaesth* (2017) 119 (4):750–64. doi: 10.1093/bja/aex225
124. Forget P, Bouche G, Duhoux FP, Coulie PG, Decloedt J, Dekleermaker A, et al. Intraoperative Ketorolac in High-Risk Breast Cancer Patients. A Prospective, Randomized, Placebo-Controlled Clinical Trial. *PloS One* (2019) 14(12):e0225748. doi: 10.1371/journal.pone.0225748
125. Coombes RC, Tovey H, Kilburn L, Mansi J, Palmieri C, Bartlett J, et al. Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival

Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. *JAMA Oncol* (2021) 7(9):1291–301. doi: 10.1001/jamaoncol.2021.2193

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Anesthesia and Cancer, Friend or Foe? A Narrative Review

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Cancer remains the leading cause of death worldwide with close to 10 million deaths reported annually. Due to growth of the advanced age cohort in our population, it is predicted that the number of new cancer cases diagnosed between now until 2035 is to reach potentially 24 million individuals, a staggering increase in a relatively short time period. For many solid tumors, surgical resection along with chemotherapy is the best available approach to a potential cure which leads to almost 80% of cancer patients undergoing at least one surgical procedure during the course of their disease. During surgical intervention, the exposure to general anesthesia can be lengthy, complex and often involves various modalities resulting in an important question as to the role, if any, anesthesia may play in primary recurrence or metastatic conversion. Many components of the stress and inflammatory responses exhibited in the perioperative period can contribute to cancer growth and invasion. The agents used to induce and maintain general anesthesia have variable interactions with the immune and neuroendocrine systems and can influence the stress response during surgery. Thus, debating the best type of anesthesia that would help to attenuate sympathetic and/or pro-inflammatory responses while modulating cytokine release and transcription factors/oncogenes remains at the forefront. This may affect inducible cancer cell survival and migratory abilities not only intra-operatively, but also during the immediate post-operative phase of recovery. The ultimate question becomes how and whether the choice of anesthesia may influence the outcomes of cancer surgery with two major approaches being considered, i.e., regional and general anesthesia as well as the various hypnotics, analgesics and sympatholytics commonly used. In this review, we will address the latest information as to the role that anesthesia may play during cancer surgery with specific focus on primary recurrence and metastasis.

Keywords: cancer recurrence, metastatic conversion, general anesthesia, regional anesthesia, total intravenous anesthesia, dexmedetomidine, lidocaine infusion

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INTRODUCTION

Although more is known about cancer biology and treatment today than ever before, cancer remains the leading cause of death worldwide and it is predicted that this death toll will only continue to increase owed to our ever-aging population (1–3). The perioperative period presents a unique conundrum for the perioperative care team; patients present for surgery to be cured of their disease and yet find themselves

at risk of recurrence and metastatic conversion, two major sources of morbidity for patients having tumor resection with curative intent (3). The perioperative period is well known for activating the body's natural stress response starting with upregulated neuroendocrine signaling, increased release of pro-inflammatory mediators and heightened immunomodulation (4). Additionally, surgical resection of solid tumors leads to increased sympathetic output and invites a pro-inflammatory response to tissue damage which is necessary for tissue repair and healing. This biological response to surgical stress can be hijacked and used for the benefit of any remaining cancer cells to ensure their survival and possibly allow them to migrate. Metastatic disease is the most common cause of death for cancer patients and it can be a source of great financial burden and emotional distress for patients and their families (5).

The biology of cancer cell survival and migration in the perioperative period is frequently studied and is extremely complex (4); hence, much time and effort have been spent to examine two important considerations, the effects of anesthetic techniques and drug choices on the risk of primary recurrence and metastatic conversion for these patients. To date there have been numerous *in vitro*, *in vivo* and retrospective studies as well as several prospective randomized controlled trials performed in hopes of addressing these considerations (2, 4, 6–14). In this review, we will report the latest data investigating the role of anesthesia in cancer recurrence and metastatic conversion. It is important to note that to date, there are no official recommendations for best practice in this area. Many studies have suggested some anesthetic agents have the potential to be harmful and increase the risk of recurrence or disease progression while others have been shown to decrease these risks.

A literature search was performed using public databases with the following key words: cancer recurrence, metastatic conversion, general anesthesia, regional anesthesia, total intravenous anesthesia, dexmedetomidine and systemic local anesthetics. Appropriateness for inclusion in the narrative was determined by the authors to include a wide and unbiased range of recent and pertinent studies. Thus in order to examine how anesthesia may affect patient outcomes we will discuss basic tumor biology and some of the potential targets available for modulation. Then we will report and comment on recent studies comparing outcomes for patients undergoing solid tumor resections under general anesthesia *vs* regional anesthesia followed by outcome data comparing two major types of general anesthesia—volatile anesthesia (e.g., isoflurane, sevoflurane, desflurane) *vs* propofol based TIVA (Total Intravenous Anesthesia). Lastly, some recent data on the oncogenic effects of various commonly used anesthetic agents will be discussed.

CURRENT STATE

There have been tremendous advances in the field of cancer biology over the past decade and though our understanding has deepened, there is much that remains a mystery (1). Factors affecting cancer recurrence and metastatic conversion at the time of primary resection are two facets of cancer biology that remain incompletely understood.

There are three basic mechanisms by which recurrence and metastatic conversion occur (15, 16). The first is local recurrence where surviving cancer cells may proliferate at the primary site of resection *via* mechanisms involving pro-inflammatory cytokines, pro-oncogenes and angiogenic factors. Second, cancer cells may transform and acquire the ability to travel to distant sites through either vascular or lymphatic spread due activation and mutation of oncogenes. And third, body cavity seeding during primary tumor resection. The use of intraperitoneal chemotherapy during cytoreductive surgery or primary resection of cancer is one tool aimed at destroying microscopic disease (17–19).

As previously noted, surgical resection of tumors induces an expected state of systemic inflammation and local hypoxia as a result of tissue damage and immunomodulation that may facilitate the conversion of solid tumors into metastatic disease, otherwise known as the epithelial to mesenchymal conversion (20–22). At the same time this pro-inflammatory state exerts a myriad of effects on the body's own cell mediated immune response. There is an intricate interplay between the release of cortisol and catecholamines and the function of immune cells including but not limited to natural killer (NK) cells and CD8+ T cells, both of which are stunted in their antitumor activity. Additionally pro-oncogenic cell lines, regulatory T cells and type 2 helper T cells are activated and encouraged to proliferate in such a state (4).

It is therefore only logical that anesthesiologists would look to take advantage of the sympatholytic, anti-inflammatory and immunomodulatory effects of anesthetic drugs in an attempt to modify this process and improve patient outcomes. In essence, the ideal anesthetic for cancer patients would:

I. Attenuate sympathetic response while maintaining adequate tissue perfusion to avoid tissue hypoxia
II. Attenuate pro-inflammatory milieu while maintaining an adequate healing response
III. Modulate cytokine release and cellular function to lean toward promoting NK and CD8+ cell activity
IV. Modulate transcription factors and oncogenes to prevent inducible cell survival and migration

Unfortunately, despite promising *in vitro* and *in vivo* studies it appears that this process is far more complex than originally thought, likely owed to both the heterogeneous biology of different malignancies and patient populations. Recent prospective randomized clinical trials (RCTs) have shown little promise at elucidating the perfect anti-oncogenic anesthetic, however there are dozens of active multicenter RCTs aimed at shedding light on this topic (1, 23).

USE OF GENERAL ANESTHESIA *VS* REGIONAL ANESTHESIA

Volatile anesthetics and other hypnotics used to induce and maintain general anesthesia have several anti-inflammatory and

immunomodulatory effects (2, 24–30). Regional anesthetic techniques, ranging from peripheral nerve blocks to neuraxial analgesia, are already employed in many primary tumor resections in order to reduce post-surgical pain and decrease opioid consumption (31–35). From a physiologic point of view, it is logical that one would expect an improvement in recurrence or conversion outcomes, owed to the powerful sympatholytic effects of regional anesthesia in addition to avoidance of the potentially detrimental immunosuppressive effects of volatile anesthetics and opioids. In 2019, one of the largest RCTs to date, evaluated the use of paravertebral nerve blocks (PVB) combined with propofol TIVA in women undergoing primary mastectomy for breast cancer and compared it to volatile anesthesia and conventional opioid analgesia (25). Recurrence occurred in 102 (9.8%) *vs* 111 (10.4%) women in the regional anesthesia *vs* volatile general anesthesia groups, which was found to be statistically significant and passed the study's futility threshold. The study was aborted at that time and no further data was collected. In this study, it was concluded that the use of regional-propofol anesthesia does not impact breast cancer recurrence (25). Although, this study was appropriately powered and the results seem compelling, we must not forget about the extreme heterogeneity of oncologic disease and should apply caution when generalizing studies such as this to other patient populations. More studies are needed in order to definitively recommend regional *vs* general anesthesia for any given malignancy or patient population. Although with recent advances in surgical technique more and more surgeries can be performed under regional anesthesia (36) it should be noted that nearly all oncological surgeries require general anesthesia in order to be feasible and safe.

TIVA *VS* VOLATILE GAS ANESTHESIA

An interesting question remains whether the known effects of volatile anesthetics on immune function are detrimental for cancer recurrence and metastatic conversion. *In vitro and in vivo* studies have shown that when breast, ovarian and renal cell carcinoma cells are exposed to volatile gases there is increased cytokine release (IL-1/6/8 and TNF), NK and T-cell modulation as well as an increase in growth, angiogenic and migration factors (3, 7, 37–39). However, for other cancer types such as non-small cell lung cancer (NSCLC) exposure to volatile anesthetics has been shown to be suppressive of growth and migration (40). The Cancer and Anesthesia Study (CAN NCT01975064), one of the largest RCTs to study recurrence and survival in breast cancer patients following exposure to general anesthesia, recently published its analysis of first year survival data for 1705 patients with breast cancer (41). These patients were randomized to either a volatile anesthetic *vs* TIVA with propofol and no difference in survival was observed between the two groups at one year; patients will continue to be followed until 2022. The CAN trial contains two other arms which include patients undergoing primary resection of colorectal cancer which are still in progress. This study points to some important complexities which include the heterogeneity of tumor biology including different cancer types, length of surgery and patient factors such as race and other environmental factors. It was noted in this study that patients of Chinese descent had improved survival rates at one year than other groups (41). To date there has been one RCT that showed propofol decreased local recurrence of breast intraductal carcinoma for patients undergoing primary resection with the goal of breast conservation (42). This study included 2036 women of Asian descent randomized to receive either propofol TIVA and PVB *vs* volatile anesthesia and PVB. Women who received propofol showed a significant reduction in local recurrence risk; however, there was no difference in risk of metastatic conversion. In short, more data is needed to definitively say whether exposure to one type of anesthetic is beneficial or harmful for the survival of cancer patients.

OPIOIDS

Due to the world-wide opioid epidemic, the use of opioids in anesthesia has long been under question as there are more and more pharmacologic agents that can be used to manage intraoperative and post-operative pain as well as achieve sympatholysis during general anesthesia. Opioids are powerful immunomodulators which are known to affect innate cell immunity by downregulating NK cell activity and decreasing cytokine production (31, 43). This effect is thought to be due to mu-opioid receptor activity as evidenced in one study by improved survival in colorectal and breast cancer patients receiving mu-opioid receptor antagonists, such as naloxone (44, 45). Other cell and animal studies have shown that opioids have a direct effect on tumor growth *via* activation of transcription factors (46). Additionally, opioids have been shown to be pro-angiogenic through activation of VEGF-receptors (30, 45, 47). For decades it was thought that opioids were largely ubiquitous in their immunomodulatory effects and morphine was used as the prototypical opioid profile; however, with recent data it is becoming clear that different opioids exert different effects on the immune system. For example, morphine and fentanyl have been shown to have similar effects on NK-cell activity and lymphocyte proliferation; however, oxycodone has been shown to have minimal immunosuppressive properties (48). Despite this data, it would be naïve to think that it might be possible to completely eliminate the use of opioids in the treatment of pain in cancer patients as they are the most commonly employed analgesic drugs in the post-operative period (33). Frustratingly, opioid sparing techniques do not seem to affect short term survival as noted in one study that randomized patients to receive remifentanil infusions (47). Thus, the question becomes whether there is a balance of pharmacologic effects between anesthetic and analgesic agents that could be found to improve patient disease free survival.

ALPHA-2 AGONISTS

Clonidine and dexmedetomidine are powerful α2-adrenoceptor agonists used in general anesthesia and ICU care for their analgesic effects, opioid sparing properties as well as powerful

sedative and anxiolytic effects. Some studies have found dexmedetomidine to be neuroprotective and an improvement in postoperative cognitive dysfunction through reduction of serum TNF-α, IL-6, PI3K and AKT, which would also suggest that dexmedetomidine is anti-inflammatory (49–51). Because of its analgesic properties and excellent performance as a sympatholytic, dexmedetomidine is an alluring choice for use in general anesthesia for cancer patients. Even when compared to clonidine, dexmedetomidine is significantly more efficacious with fewer side effects. There is however, much evidence to suggest the contrary.

There have been numerous *in vivo* and *in vitro* studies showing that dexmedetomidine may in fact increase the risk for recurrence by modulating cell survival through activation of HIF-1α as well as increased secretion of metalloproteinases (MMP) which have been implicated in cell migration and metastatic conversion (6, 9–11, 14, 38, 50, 52–56). The transcription factor HIF-1 α has been shown to confer a survival advantage to cells when exposed to hypoxic conditions, such as when vascular supply is removed during resection (9, 52, 54, 56). Bruzzone et al. first found that α2-adrenoceptors have a positive effect on the proliferation of a mouse mammary tumor cell line *in vitro* (57). In addition to already discussed effects of HIF-1α, dexmedetomidine induces the proliferation of myeloid-derived suppressor cells associated with significant proangiogenic potential, promoting tumor metastasis through increasing production of VEGF (9). Furthermore, dexmedetomidine upregulates the expression of survivin, MMP −2, MMP−9, all implicated in metastatic conversion of lung adenocarcinoma (56). A recent retrospective study for patients with NSCLC showed that the use of dexmedetomidine had no benefit on recurrence free survival and a significantly lower overall-survival for patients who underwent primary surgical resection (56). These effects have been noted in other cancer types such as esophageal, colorectal and hepatocellular carcinoma (6, 7).

As with previous hypotheses involving the effects of anesthesia on cancer recurrence and metastatic conversion these data are not practice altering. Quality evidence in support of or against use of dexmedetomidine in clinical practice for cancer patients is lacking. More prospective RCTs are needed to determine whether effects seen in cell and animal studies will pan out. However, with the number of studies suggesting potential harm from dexmedetomidine it is probably prudent to avoid using it if "safer" alternatives are available. There are several RCTs aimed at studying the effects of dexmedetomidine on cancer recurrence. One trial examining the impact of dexmedetomidine on breast cancer recurrence is due to be completed in 2024 (NCT03109990) (23).

LOCAL ANESTHETICS

Amide local anesthetics, specifically lidocaine, have long been a useful tool in the management of pain during general anesthesia, employed both as systemic intravenous infusions and during neuraxial and peripheral nerve blocks. Lidocaine is a short acting minimally toxic sodium channel blocker that acts to decrease nerve conduction and results in reduction of pain scores in patients receiving intravenous infusions intraoperatively and postoperatively (35, 58–60). In addition to its analgesic properties, lidocaine exhibits anti-oncogenic and anti-inflammatory effects through various pathways (61–64). Dozens of laboratory studies have been performed to flesh out the biological pathways responsible for lidocaine's observed effects (12, 13, 32, 65–68). Unfortunately, clinical data including retrospective analyses are sparce. To date there has been one study reporting on the observed clinical effects of lidocaine on recurrence of pancreatic cancer, which showed that patients treated with intravenous infusions of lidocaine had better survival rates at 1 and 3 years with no difference in disease-free survival (65). These anti-inflammatory effects have been observed even through alternative methods of local anesthetic administration including intraperitoneal lavage. In one prospective randomized controlled study of patients undergoing ovarian tumor resection, it was observed that patients who received intraperitoneal washings of ropivacaine had a shortened time to chemotherapy administration vs patients in the placebo arm (69). Though the mechanism by which this was achieved is unclear, the authors proposed it could be due to an attenuated inflammatory response, local anesthetic cytotoxicity for microscopic disease in the peritoneum and improved wound healing. While not a direct effect on cancer recurrence, the effect noted in this study could suggest an alternative use for local anesthetics that could hasten a patient's treatment course—several studies have concluded that early chemotherapy administration is associated with improved outcomes although the timeline is still under debate (70).

An upcoming RCT, Volatile Anesthesia and Perioperative Outcomes Related to Cancer trial (VAPOR-C, NCT04316013) set to complete in 2025, will examine the effects of lidocaine in patients with lung or colorectal adenocarcinoma (71). It is important to remember that using intravenous lidocaine as an analgesic is off-label. To date there have been no studies to show that lidocaine infusions are harmful to cancer patients so long as they are employed judiciously and there are no contraindications or conditions that would increase toxicity, such as severe liver disease or low protein states (32, 60, 61, 71). Centers using intravenous lidocaine infusions should have safety protocols and dosing guidelines to avoid harm in patients receiving this treatment (60). Time and care should be applied to training personnel in the recognition of lidocaine toxicity and treatment both intraoperatively and in the post-operative period (61). At our institution, it is common to use intravenous lidocaine infusions for patients that have undergone colorectal surgery, not always to treat oncologic disease, as part of an enhanced recovery after surgery (ERAS) protocol to aid in gut motility and decrease opioid consumption.

CONCLUSION

Optimization of the care of cancer patients is in constant flux and evolution. The perioperative period has been identified as a unique intersection of intent to treat with potential harm coming to the patient due to that treatment. Anesthesiologists and surgeons are in

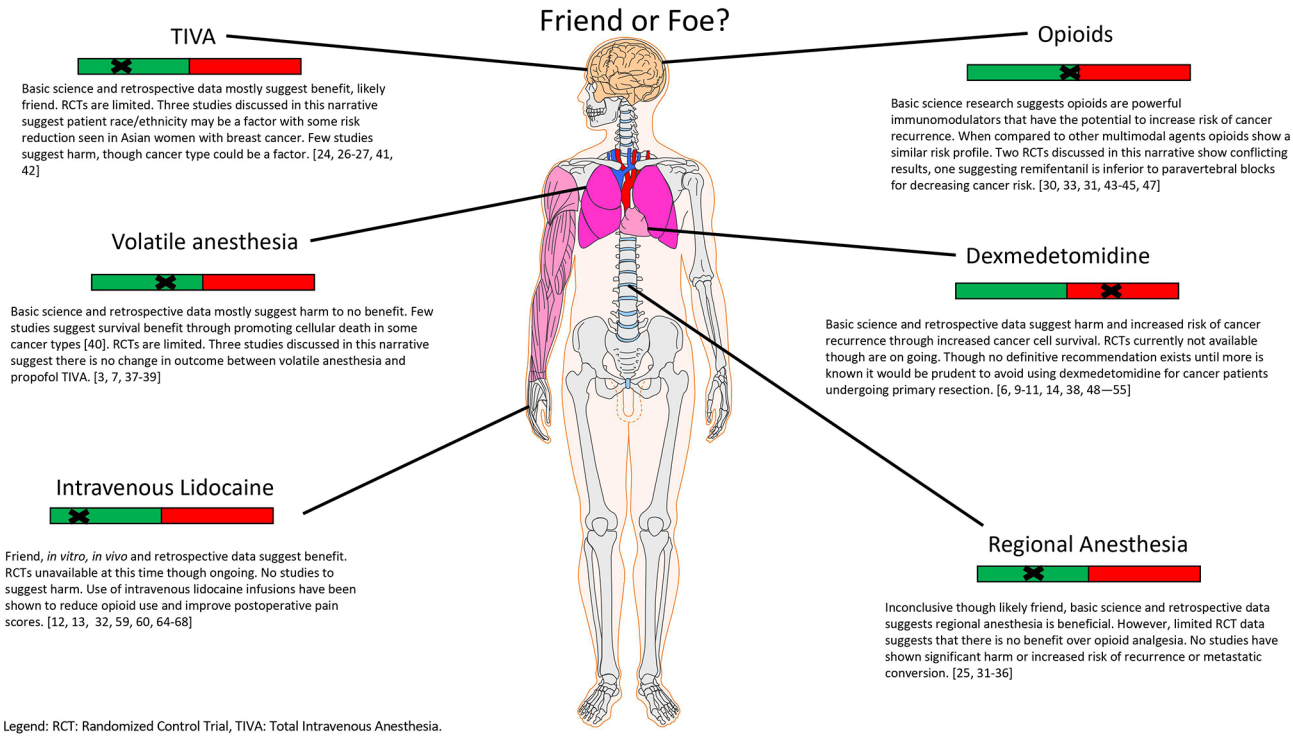

FIGURE 1 | A summary of findings depicted in this narrative review.

the unique position to affect a patient's postoperative course and survival outcome. Specifically, the agents chosen to induce and maintain general anesthesia while surgical intervention is performed have the potential to bring benefit or harm to these patients (**Figure 1**). In this review, we have briefly discussed cancer cell biology and how recurrence and metastatic conversion may occur as a result of the interplay between circulating tumor cells, cytokines, the HPA axis, the immune system, growth and migration factors and catecholamines as well as the effects of several commonly used hypnotics and analgesics. Despite the numerous studies performed to date, the data currently available is insufficient to form a definitive recommendation for anesthetic choice. Although, from a mechanism point of view, it is tempting to hope that the perfect anesthetic exists for mitigating the risk of cancer recurrence given the vast complexity of oncologic disease and patient genetic heterogeneity it is likely that we may never have an answer. It will likely require genetic phenotyping of patients and their disease to personalize the delivery of anesthesia, while the technology is available it is far from being applied clinically (72–74). Nevertheless, given the immense impact that oncologic disease has worldwide and that it is only projected to continue to worsen this remains an area of high potential for improving the lives of many.

AUTHOR CONTRIBUTIONS

JM was the first author contributing literature review, writing manuscript as well as design of figure. VJ-T is the senior author contributing expertise in the field of anesthesiology, editing and advising as well as writing of abstract. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Luo J, Shi Y, Wang X, Zhang R, Chen S, Yu W, et al. A 20-Year Research Trend Analysis of the Influence of Anesthesia on Tumor Prognosis Using Bibliometric Methods. *Front Oncol* (2021) 11:683232. doi: 10.3389/fonc.2021.683232
2. Sekandarzad MW, van Zundert AJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression. *Anesth Analg* (2017) 124(5):1697–708. doi: 10.1213/ANE.0000000000001652
3. Forget P, Aguirre JA, Bencic I, Borgeat A, Cama A, Condron C, et al. How Anesthetic, Analgesic and Other Non-Surgical Techniques During Cancer Surgery Might Affect Postoperative Oncologic Outcomes: A Summary of Current State of Evidence. *Cancers (Basel)* (2019) 11(5):592. doi: 10.3390/cancers11050592
4. Coussens LM, Werb Z. Inflammation and Cancer. *Nature* (2002) 420 (6917):860–7. doi: 10.1038/nature01322
5. Weingart SN, Nelson J, Koethe B, Yaghi O, Dunning S, Feldman A. Association Between Cancer-Specific Adverse Event Triggers and Mortality: A Validation Study. *Cancer Med* (2020) 9(12):4447–59. doi: 10.1002/cam4.3033
6. Chen P, Luo X, Dai G, Jiang Y, Luo Y, Peng S. Dexmedetomidine Promotes the Progression of Hepatocellular Carcinoma Through Hepatic Stellate Cell Activation. *Exp Mol Med* (2020) 52(7):1062–74. doi: 10.1038/s12276-020-0461-6

7. Deng F, Ouyang M, Wang X, Yao X, Chen Y, Tao T, et al. Differential Role of Intravenous Anesthetics in Colorectal Cancer Progression: Implications for Clinical Application. *Oncotarget* (2016) 7(47):77087–95. doi: 10.18632/oncotarget.12800
8. Nguyen J, Luk K, Vang D, Soto W, Vincent L, Robiner S, et al, Luk K, Vang D, Soto W, Vincent L, Robiner S. Morphine Stimulates Cancer Progression and Mast Cell Activation and Impairs Survival in Transgenic Mice With Breast Cancer. *Br J Anaesth* (2014) 113(Suppl 1):i4–13. doi: 10.1093/bja/aeu090
9. Su X, Fan Y, Yang L, Huang J, Qiao F, Yu Fang Y, et al. Dexmedetomidine Expands Monocytic Myeloid-Derived Suppressor Cells and Promotes Tumour Metastasis After Lung Cancer Surgery. *J Transl Med* (2018) 16 (1):347. doi: 10.1186/s12967-018-1727-9
10. Szpunar MJ, Burke KA, Dawes RP, Brown EB, Madden KS. The Antidepressant Desipramine and α2-Adrenergic Receptor Activation Promote Breast Tumor Progression in Association With Altered Collagen Structure. *Cancer Prev Res (Phila)* (2013) 6(12):1262–72. doi: 10.1158/1940-6207.CAPR-13-0079
11. Tian H, Hou L, Xiong Y, Cheng Q, Huang J. Effect of Dexmedetomidine-Mediated Insulin-Like Growth Factor 2 (IGF2) Signal Pathway on Immune Function and Invasion and Migration of Cancer Cells in Rats With Ovarian Cancer. *Med Sci Monit* (2019) 25:4655–64. doi: 10.12659/MSM.915503
12. Wall TP, Crowley PD, Buggy DJ. The Effect of Lidocaine and Bosutinib on 4T1 Murine Breast Cancer Cell Behaviour In Vitro. *Anticancer Res* (2021) 41 (6):2835–40. doi: 10.21873/anticanres.15064
13. Wall TP, Crowley PD, Sherwin A, Foley AG, Buggy DJ. Effects of Lidocaine and Src Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers (Basel)* (2019) 11(10):1414. doi: 10.3390/cancers11101414
14. Zhang P, He H, Bai Y, Liu W, Huang L. Dexmedetomidine Suppresses the Progression of Esophageal Cancer via miR-143-3p/Epidermal Growth Factor Receptor Pathway Substrate 8 Axis. *Anticancer Drugs* (2020) 31(7):693–701. doi: 10.1097/CAD.0000000000000934
15. Ganesh K, Massagué J. Targeting Metastatic Cancer. *Nat Med* (2021) 27 (1):34–44. doi: 10.1038/s41591-020-01195-4
16. Suhail Y, Cain MP, Vanaja K, Kurywchak PA, Levchenko A, Kalluri R, et al. Systems Biology of Cancer Metastasis. *Cell Syst* (2019) 9(2):109–27. doi: 10.1016/j.cels.2019.07.003
17. Al-Quteimat OM, Al-Badaineh MA. Intraperitoneal Chemotherapy: Rationale, Applications, and Limitations. *J Oncol Pharm Pract* (2014) 20 (5):369–80. doi: 10.1177/1078155213506244
18. Ghirardi V, Ronsini C, Trozzi R, Di Ilio C, Di Giorgio A, Cianci S. Hyperthermic Intraperitoneal Chemotherapy in Interval Debulking Surgery for Advanced Epithelial Ovarian Cancer: A Single-Center, Real-Life Experience. *Cancer* (2020) 126(24):5256–62. doi: 10.1002/cncr.33167
19. Revaux A, Carbonnel M, Kanso F, Naoura I, Asmar J, Kadhel P. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer: An Update. *Horm Mol Biol Clin Investig* (2020) 41(3):2019–0028. doi: 10.1515/hmbci-2019-0028
20. Sakhneny L, Khalifa-Malka L, Landsman L. Pancreas Organogenesis: Approaches to Elucidate the Role of Epithelial-Mesenchymal Interactions. *Semin Cell Dev Biol* (2019) 92:89–96. doi: 10.1016/j.semcdb.2018.08.012
21. Sannino G, Marchetto A, Kirchner T, Grünewald TGP. Epithelial-To-Mesenchymal and Mesenchymal-To-Epithelial Transition in Mesenchymal Tumors: A Paradox in Sarcomas? *Cancer Res* (2017) 77(17):4556–61. doi: 10.1158/0008-5472.CAN-17-0032
22. Yang J, Weinberg RA. Epithelial-Mesenchymal Transition: At the Crossroads of Development and Tumor Metastasis. *Dev Cell* (2008) 14(6):818–29. doi: 10.1016/j.devcel.2008.05.009
23. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of Perioperative Anaesthetic and Analgesic Interventions on Oncological Outcomes: A Narrative Review. *Br J Anaesth* (2019) 123(2):135–50. doi: 10.1016/j.bja.2019.04.062
24. Hong B, Lee S, Kim Y, Lee M, Youn AM, Rhim H. Anesthetics and Long-Term Survival After Cancer Surgery-Total Intravenous Versus Volatile Anesthesia: A Retrospective Study. *BMC Anesthesiol* (2019) 19(1):233. doi: 10.1186/s12871-019-0914-4
25. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X
26. Wigmore TJ, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/ALN.0000000000000936
27. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anaesth* (2019) 66(5):546–61. doi: 10.1007/s12630-019-01330-x
28. Lee EK, Ahn HJ, Zo JI, Kim K, Jung DM, Park JH. Paravertebral Block Does Not Reduce Cancer Recurrence, But Is Related to Higher Overall Survival in Lung Cancer Surgery: A Retrospective Cohort Study. *Anesth Analg* (2017) 125 (4):1322–8. doi: 10.1213/ANE.0000000000002342
29. Pérez-González O, Cuéllar-Guzmán LF, Soliz J, Cata JP. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature. *Regional Anesthesia Pain Med* (2017) 42(6):751–6. doi: 10.1097/AAP.0000000000000662
30. Sen Y, Xiyang H, Yu H. Effect of Thoracic Paraspinal Block-Propofol Intravenous General Anesthesia on VEGF and TGF-β in Patients Receiving Radical Resection of Lung Cancer. *Med (Baltimore)* (2019) 98(47):e18088. doi: 10.1097/MD.0000000000018088
31. Bugada D, Lorini LF, Lavand'homme P. Opioid Free Anesthesia: Evidence for Short and Long-Term Outcome. *Minerva Anestesiol* (2021) 87(2):230–7. doi: 10.23736/S0375-9393.20.14515-2
32. Chong PH, Yeo ZZ. Parenteral Lidocaine for Complex Cancer Pain in the Home or Inpatient Hospice Setting: A Review and Synthesis of the Evidence. *J Palliat Med* (2021) 24(8):1154–60. doi: 10.1089/jpm.2020.0622
33. Gabriel RA, Swisher MW, Sztain JF, Furnish TJ, Ilfeld BM, Said ET. State of the Art Opioid-Sparing Strategies for Post-Operative Pain in Adult Surgical Patients. *Expert Opin Pharmacother* (2019) 20(8):949–61. doi: 10.1080/14656566.2019.1583743
34. Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. *Anesth Analg* (2017) 125(5):1749–60. doi: 10.1213/ANE.0000000000002497
35. Kutay Yazici K, Menşure K, Büşra A, Süheyla U. The Effect of Perioperative Lidocaine Infusion on Postoperative Pain and Postsurgical Recovery Parameters in Gynecologic Cancer Surgery. *Clin J Pain* (2021) 37(2):126–32. doi: 10.1097/AJP.0000000000000900
36. Mergeay M, Verster A, Van Aken D, Vercauteren M. Regional Versus General Anesthesia for Spine Surgery. A Comprehensive Review. *Acta Anaesthesiol Belg* (2015) 66(1):1–9.
37. Deng X, Vipani M, Liang G, Gouda D, Wang B, Wei H. Sevoflurane Modulates Breast Cancer Cell Survival via Modulation of Intracellular Calcium Homeostasis. *BMC Anesthesiol* (2020) 20(1):253. doi: 10.1186/s12871-020-01139-y
38. Liu Y, Sun J, Wu T, Lu X, Du Y, Duan H. Effects of Serum From Breast Cancer Surgery Patients Receiving Perioperative Dexmedetomidine on Breast Cancer Cell Malignancy: A Prospective Randomized Controlled Trial. *Cancer Med* (2019) 8(18):7603–12. doi: 10.1002/cam4.2654
39. Ciechanowicz S, Zhao H, Chen Q, Cui J, Mi E, Mi E, et al. Differential Effects of Sevoflurane on the Metastatic Potential and Chemosensitivity of Non-Small-Cell Lung Adenocarcinoma and Renal Cell Carcinoma In Vitro. *Br J Anaesth* (2018) 120(2):368–75. doi: 10.1016/j.bja.2017.11.066
40. Wang L, Wang T, Gu J-Q, Su H-B. Volatile Anesthetic Sevoflurane Suppresses Lung Cancer Cells and miRNA Interference in Lung Cancer Cells. *Oncol Targets Ther* (2018) 11:5689–93. doi: 10.2147/OTT.S171672
41. Enlund M, Enlund A, Berglund A, Bergkvist L. Rationale and Design of the CAN Study: An RCT of Survival After Propofol- or Sevoflurane-Based Anesthesia for Cancer Surgery. *Curr Pharm Des* (2019) 25(28):3028–33. doi: 10.2174/1381612825666190705184218
42. Zhang J, Chang C-L, Lu C-Y, Chen H-M, Wu S-Y. Paravertebral Block in Regional Anesthesia With Propofol Sedation Reduces Locoregional Recurrence in Patients With Breast Cancer Receiving Breast Conservative Surgery Compared With Volatile Inhalational Without Propofol in General Anesthesia. *BioMed Pharmacother* (2021) 142:111991. doi: 10.1016/j.biopha.2021.111991
43. Chen J, Luo F, Lei M, Chen Z. A Study on Cellular Immune Function of Patients Treated With Radical Resection of Pulmonary Carcinoma With Two Different Methods of Anesthesia and Analgesia. *J buon* (2017) 22(6):1416–21.

44. Bimonte S, Barbieri A, Cascella M, Rea D, Palma G, Del Vecchio V, et al. The Effects of Naloxone on Human Breast Cancer Progression: In Vitro and In Vivo Studies on MDA.MB231 Cells. *Onco Targets Ther* (2018) 11:185–91. doi: 10.2147/OTT.S145780
45. Ma M, Wang X, Liu N, Shan F, Feng Y. Low-Dose Naltrexone Inhibits Colorectal Cancer Progression and Promotes Apoptosis by Increasing M1-Type Macrophages and Activating the Bax/Bcl-2/Caspase-3/PARP Pathway. *Int Immunopharmacol* (2020) 83:106388. doi: 10.1016/j.intimp.2020.106388
46. Wu Q, Chen X, Wang J, Sun P, Weng M, Chen W. Nalmefene Attenuates Malignant Potential in Colorectal Cancer Cell via Inhibition of Opioid Receptor. *Acta Biochim Biophys Sin (Shanghai)* (2018) 50(2):156–63. doi: 10.1093/abbs/gmx131
47. Yan T, Zhang GH, Wang BN, Sun L, Hui Zheng H. Effects of Propofol/Remifentanil-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Release of VEGF-C and TGF-β and Prognosis After Breast Cancer Surgery: A Prospective, Randomized and Controlled Study. *BMC Anesthesiol* (2018) 18(1):131. doi: 10.1186/s12871-018-0588-3
48. Franchi S, Moschetti G, Amodeo G, Sacerdote P. Do All Opioid Drugs Share the Same Immunomodulatory Properties? A Review From Animal and Human Studies. *Front Immunol* (2019) 10(2914). doi: 10.3389/fimmu.2019.02914
49. Zhang J, Liu G, Zhang F, Fang H, Zhang D, Liu S, et al. Analysis of Postoperative Cognitive Dysfunction and Influencing Factors of Dexmedetomidine Anesthesia in Elderly Patients With Colorectal Cancer. *Oncol Lett* (2019) 18(3):3058–64. doi: 10.3892/ol.2019.10611
50. Liu M, Yi Y, Zhao M. Effect of Dexmedetomidine Anesthesia on Perioperative Levels of TNF-α and IL-6 in Patients With Ovarian Cancer. *Oncol Lett* (2019) 17(6):5517–22. doi: 10.3892/ol.2019.10247
51. Huyan T, Hu X, Peng H, Zhu Z, Li Q, Zhang W. Perioperative Dexmedetomidine Reduces Delirium in Elderly Patients After Lung Cancer Surgery. *Psychiatr Danub* (2019) 31(1):95–101. doi: 10.31219/osf.io/e9hfw
52. Zhu L, Zhang Y, Zhang Z, Ding X, Gong C, Qian Y. Activation of PI3K/Akt/HIF-1α Signaling is Involved in Lung Protection of Dexmedetomidine in Patients Undergoing Video-Assisted Thoracoscopic Surgery: A Pilot Study. *Drug Des Devel Ther* (2020) 14:5155–66. doi: 10.2147/DDDT.S276005
53. Yi XL, Wang JT, Chu CQ, Li YX, Yin JH, Liu SL. Cardiocerebral Protective Effects of Dexmedetomidine as Anesthetic in Colorectal Cancer Surgery. *Eur Rev Med Pharmacol Sci* (2018) 22(11):3570–6. doi: 10.26355/eurrev_201806_15183
54. Chen HY, Li GH, Tan GC, Liang H, Lai XH, Huang Q, et al. Dexmedetomidine Enhances Hypoxia-Induced Cancer Cell Progression. *Exp Ther Med* (2019) 18(6):4820–8. doi: 10.3892/etm.2019.8136
55. Xia M, Ji NN, Duan ML, Tong JH, Xu JG, Zhang YM, et al. Dexmedetomidine Regulate the Malignancy of Breast Cancer Cells by Activating α2-Adrenoceptor/ERK Signaling Pathway. *Eur Rev Med Pharmacol Sci* (2016) 20(16):3500–6.
56. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, et al. Intraoperative Use of Dexmedetomidine is Associated With Decreased Overall Survival After Lung Cancer Surgery. *J Anaesthesiol Clin Pharmacol* (2017) 33(3):317–23. doi: 10.4103/joacp.JOACP_299_16
57. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120(1):188–96. doi: 10.1016/j.bja.2017.11.004
58. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LHJ, Hahnenkamp K, et al. Continuous Intravenous Perioperative Lidocaine Infusion for Postoperative Pain and Recovery in Adults. *Cochrane Database Syst Rev* (2018) 6(6): Cd009642. doi: 10.1002/14651858.CD009642.pub3
59. Masic D, Liang E, Long C, Sterk EJ, Barbas B, Rech MA. Intravenous Lidocaine for Acute Pain: A Systematic Review. *Pharmacotherapy* (2018) 38 (12):1250–9. doi: 10.1002/phar.2189
60. Khan JS, Hodgson N, Choi S, Reid S, Paul JE, Look Hong NJ, et al. Perioperative Pregabalin and Intraoperative Lidocaine Infusion to Reduce Persistent Neuropathic Pain After Breast Cancer Surgery: A Multicenter, Factorial, Randomized, Controlled Pilot Trial. *J Pain* (2019) 20(8):980–93. doi: 10.1016/j.jpain.2019.02.010
61. Lee JT, Sanderson CR, Xuan W, Agar M. Lidocaine for Cancer Pain in Adults: A Systematic Review and Meta-Analysis. *J Palliat Med* (2019) 22(3):326–34. doi: 10.1089/jpm.2018.0257
62. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, et al. Molecular Mechanisms of Action of Systemic Lidocaine in Acute and Chronic Pain: A Narrative Review. *Br J Anaesth* (2019) 123(3):335–49. doi: 10.1016/j.bja.2019.06.014
63. Galoș EV, Tat T-F, Popa R, Efrimescu C-I, Finnerty D, Buggy DJ, et al. Neutrophil Extracellular Trapping and Angiogenesis Biomarkers After Intravenous or Inhalation Anaesthesia With or Without Intravenous Lidocaine for Breast Cancer Surgery: A Prospective, Randomised Trial. *Br J Anaesth* (2020) 125(5):712–21. doi: 10.1016/j.bja.2020.05.003
64. van Haren F, van den Heuvel S, Radema S, van Erp N, van den Bersselaar L, Vissers K, et al. Intravenous Lidocaine Affects Oxaliplatin Pharmacokinetics in Simultaneous Infusion. *J Oncol Pharm Pract* (2020) 26(8):1850–6. doi: 10.1177/1078155220905011
65. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association Between Intraoperative Intravenous Lidocaine Infusion and Survival in Patients Undergoing Pancreatectomy for Pancreatic Cancer: A Retrospective Study. *Br J Anaesth* (2020) 125(2):141–8. doi: 10.1016/j.bja.2020.03.034
66. Ji W, Zhang X, Sun G, Wang X, Liu J, Bian J, et al. Effect of Perioperative Intravenous Lidocaine on Postoperative Outcomes in Patients Undergoing Resection of Colorectal Cancer: A Protocol for Systematic Review and Meta-Analysis. *BMJ Open* (2021) 11(8):e048803. doi: 10.1136/bmjopen-2021-048803
67. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine, Propofol and Steroids on Pulmonary Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers (Basel)* (2019) 11(5):613. doi: 10.3390/cancers11050613
68. Hou YH, Shi WC, Cai S, Liu H, Zheng Z, Qi FW, et al. Effect of Intravenous Lidocaine on Serum Interleukin-17 After Video-Assisted Thoracic Surgery for Non-Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. *Drug Des Devel Ther* (2021) 15:3379–90. doi: 10.2147/DDDT.S316804
69. Hayden JM, Oras J, Block L, Thörn S-E, Palmqvist C, Salehi S, et al. Intraperitoneal Ropivacaine Reduces Time Interval to Initiation of Chemotherapy After Surgery for Advanced Ovarian Cancer: Randomised Controlled Double-Blind Pilot Study. *Br J Anaesth* (2020) 124(5):562–70. doi: 10.1016/j.bja.2020.01.026
70. Hofstetter G, Concin N, Braicu I, Chekerov R, Sehouli J, Cadron I, et al. The Time Interval From Surgery to Start of Chemotherapy Significantly Impacts Prognosis in Patients With Advanced Serous Ovarian Carcinoma — Analysis of Patient Data in the Prospective OVCAD Study. *Gynecologic Oncol* (2013) 131(1):15–20. doi: 10.1016/j.ygyno.2013.07.086
71. Wall TP, Buggy DJ. Perioperative Intravenous Lidocaine and Metastatic Cancer Recurrence - A Narrative Review. *Front Oncol* (2021) 11:688896. doi: 10.3389/fonc.2021.688896
72. Bach-Rojecky L, Vađunec D, Lozić M, Žunić K, Špoljar GG, Čutura T, et al. Challenges in Anesthesia Personalization: Resolving the Pharmacogenomic Puzzle. *Per Med* (2019) 16(6):511–25. doi: 10.2217/pme-2019-0056
73. Xie S, Ma W, Guo Q, Liu J, Li W, McLeod HL, et al. The Pharmacogenetics of Medications Used in General Anesthesia. *Pharmacogenomics* (2018) 19 (3):285–98. doi: 10.2217/pgs-2017-0168
74. McKinstry-Wu AR, Wasilczuk AZ, Harrison BA, Bedell VM, Sridharan MJ, Breig JJ, et al. Analysis of Stochastic Fluctuations in Responsiveness is a Critical Step Toward Personalized Anesthesia. *Elife* (2019) 8:e50143. doi: 10.7554/eLife.50143

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REVIEW
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Effects of Perioperative Epidural Analgesia on Cancer Recurrence and Survival

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Surgical resection is the main curative avenue for various cancers. Unfortunately, cancer recurrence following surgery is commonly seen, and typically results in refractory disease and death. Currently, there is no consensus whether perioperative epidural analgesia (EA), including intraoperative and postoperative epidural analgesia, is beneficial or harmful on cancer recurrence and survival. Although controversial, mounting evidence from both clinical and animal studies have reported perioperative EA can improve cancer recurrence and survival *via* many aspects, including modulating the immune/inflammation response and reducing the use of anesthetic agents like inhalation anesthetics and opioids, which are independent risk factors for cancer recurrence. However, these results depend on the cancer types, cancer staging, patients age, opioids use, and the duration of follow-up. This review will summarize the effects of perioperative EA on the oncological outcomes of patients after cancer surgery.

Keywords: epidural analgesia, cancer recurrence, cancer survival, cancer surgeries, oncological outcomes

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INTRODUCTION

Cancer has become a major cause of death worldwide, while metastasis and/or recurrence is the major cause of death from cancer (1–3). Surgical resection of primary solid tumors remains a cornerstone of cancer treatment (4). However, the surgical process is associated with immunosuppression, which may generate a high vulnerability for tumor worse progression (4–6). Meanwhile, several drugs, such as volatile anesthetics and opioids during perioperative periods were also suggested to be implicated in immunosuppression and cancer recurrence (7). Regional anesthesia (RA), such as epidural anesthesia, spinal aesthesia, paravertebral block, can provide effective pain relief preoperatively (8). The adjunctive use of RA for general anesthesia is believed to decrease the requirement of opioids and general anesthetics consumption, and attenuate surgical-related stress and immunosuppression (9). Therefore, RA is theoretically suggested to have potential impacts on oncological outcomes in patients underwent cancer surgeries. Among various regional techniques in RA, the most commonly used for cancer surgery is perioperative epidural analgesia (EA), including both intraoperative or postoperative use. Currently, there is no definitive consensus

whether perioperative EA is beneficial to cancer recurrence and survival. Cancer types and staging may be the major contributors to these inconsistent results. In this review, we summarized the current evidences regarding the effects of perioperative EA on recurrence and survival for various cancer types. Study characteristics were summarized in **Table 1**.

EFFECTS OF SURGERY ON CANCER RECURRENCE

Surgical resection is the main curative avenue for various solid cancers (1). Unfortunately, minimal residual disease may be present persistently after treatment, which can cause metastasis and recurrence (49). Meanwhile, the operation and general anesthesia process themself may facilitate the tumor metastasis and recurrence through several ways, such as stress and immune/inflammation responses, and postoperative pain (50–55). Furthermore, tissue damage caused by surgery, especially the local pro-inflammatory and wound-healing responses, were associated with local and distant recurrence (56). Additionally, postoperative pain is suggested as an important contributor to suppress immunity function, thus promoting cancer progression (49, 57). For general anesthesia, inhaled anesthetics and opioids were reported to be related to worse oncological outcomes for cancer surgeries (20). Therefore, the perioperative period represents as a critical timeframe for metastatic progression and cancer recurrence.

EFFECTS OF PERIOPERATIVE EA ON CANCER RECURRENCE

Mounting evidence from both clinical and animal researches indicated that perioperative EA could improve cancer recurrence and survival (17, 28, 31). The underlying mechanism remains elusive, which was mainly attributed to improve immunosuppression *via* attenuating surgical stress and postoperative pain, reducing requirements for opioid and anesthetics, and direct anti-metastasis effects of local anesthetics (58).

Perioperative EA Attenuates Surgical Stress and Pain

During and/or after the surgical resection of tumor, stress responses and pain are commonly existed and interacted, which may cause immunosuppression, thus promoting cancer recurrence (59, 60). Perioperative EA was reported to attenuate the immunosuppression by inhibiting the stress responses and/or alleviating the perioperative pain (58). Meanwhile, perioperative EA can improve the function of immunity *via* preserve and/or increase the numbers of immune cells and reduce the plasma concentrations of immune suppressive soluble factors (61–65).

Perioperative EA Reduces Opioid and Anesthetics Requirements

Opioids were suggested to be an important factor that suppress the immune function (66, 67). For example, morphine and remifentanil suppress NK cell activity and T cell differentiation, and promote lymphocyte apoptosis (68–71). Likewise, fentanyl and sufentanil decrease NK cell activity or leukocyte migration (72–74). In addition to opioids, previous studies reported that volatile anesthetics are also independent risk factors of cancer recurrence (75–78). It is well known that perioperative EA significantly reduced the requirements for perioperative opioids and volatile anesthetics use during the cancer surgery, thus influencing the oncological outcomes (58, 79, 80).

Direct Anti-Metastasis Effects of Local Anesthetics

Metastasis is an important factor for cancer recurrence and is the major cause of death from most malignant cancers. During the process of metastasis, tumor cells undergo several steps known as the metastatic cascade. At the primary site, tumor cells escape from the antitumor immune response, invade the surrounding parenchyma and intravasate into blood and/or lymphatic vessels, which allows them to circulate and spread. At the metastatic site, these circulating tumor cells extravasate from the blood and/or lymphatic vessel, survive and proliferate to form the metastatic tumor (3). Local anesthetics used in RA were suggested to directly inhibit the metastasis process (81, 82). For example, lidocaine has anti-growth and anti-metastatic properties towards lung cancer cells (83). Ropivacaine is demonstrated to reduce the proliferation of breast cancer cells and induce the apoptosis processes (84). Although there is no consensus whether different local anesthetics have different effects on the cancer outcomes *in vivo*, it is suggested that all local anesthetics at high concentrations are toxic to cancer cells *in vitro* with different potencies (bupivacaine > lidocaine > ropivacaine) (85). The underlying mechanism remains elusive, which may involves ion channels (86–89), inflammatory pathways (90, 91), and cancer stem cells (92, 93).

EFFECTS OF PERIOPERATIVE EA ON CERTAIN CANCER TYPES

In clinic, perioperative EA is commonly used for thoracic and abdominal surgeries due to many advantage aspects, such as postoperative pain management, reducing requirements for anesthetics as well as postoperative complications (58, 94, 95). However, the potential benefit of perioperative EA on cancer recurrence and survival is debated in patients undergoing thoracic and abdominal surgeries, which is suggested most likely related to cancer types. Du et al. evaluated the effects of perioperative EA on the long-term oncological outcomes in elderly patients (60 to 90 years old) with major thoracic and abdominal surgeries. The results found that, compared with general anesthesia alone with postoperative intravenous analgesia, combined epidural-general anesthesia with postoperative epidural analgesia did not improve overall or cancer-specific mortality, or the recurrence-free survival after a median follow-up duration of 66 months (96). Similarly, another retrospective study also did not support an association

TABLE 1 | Study characteristics.

Study	Study design	Number of participants	Age (years)*	Cancer type	Surgery approach	Analgesia period and LAs used	Follow-up duration	Oncological outcomes	Association between EA and outcomes
Wu 2020 (10)	Retrospective	2,748	EA group: 69 ± 14; Non-EA group: 68 ± 13	Colon cancer (stage I-III)	NA	Intraoperative and postoperative analgesia (0.25% or 0.5% bupivacaine)	46.1 months	Recurrence-free survival and overall survival	No
Wu 2021 (11)	Retrospective	1,282	EA group: 69 ± 13; Non-EA group: 66 ± 13	Rectal cancer (stage I-III)	NA	Intraoperative and postoperative analgesia (0.25% or 0.5% bupivacaine)	46.1 months	Cancer recurrence, all–cause mortality and cancer –specific mortality	No
Tai 2018 (12)	Retrospective	999	EA group: 65 ± 13; Non-EA group: 66 ± 14	Colorectal cancer (stage IV)	NA	Intraoperative and postoperative analgesia (0.25% or 0.5% bupivacaine)	17.5 months	Progression-free survival and overall survival	No
Day 2012 (13)	Retrospective	280	EA group: 72; Non-EA group: 70	Colorectal cancer	Laparoscopic	Intraoperative and postoperative analgesia (0.15% bupivacaine)	37 months	Overall survival and disease-free survival	No
Gupta 2011 (14)	Retrospective	655	EA group: 71.4 (21-96); Non-EA group: 73.2 (38-92)	Colorectal cancer (stage I-III)	Open	Intraoperative and postoperative analgesia	2.68 years	All-cause mortality	Yes for all-cause mortality of rectal but No for colon cancer
Gottschalk 2010 (15)	Retrospective	669	EA group: 65 (54-74); Non-EA group: 63 (55-72)	Colorectal cancer	NA	Intraoperative and postoperative analgesia	1.8 years	Cancer recurrence	No
Falk 2021 (16)	Prospective	221	EA group: 67.9 (41-80); Non-EA group: 67.2 (39-81)	Colorectal cancer	NA	Intraoperative and postoperative analgesia	5 years	Disease-free survival	No
Vogelaar 2015 (17)	Retrospective	588	EA group: 70 ± 12; Non-EA group: 71 ± 13	Colon cancer (stage I-IV)	NA	Intraoperative and postoperative analgesia	53 months	Survival	Yes
Holler 2013 (18)	Retrospective	749	NA	Colorectal cancer	NA	Intraoperative and postoperative analgesia	5 years	Survival	Yes
Christopherson 2008 (19)	Prospective	177	EA group: 68.6 ± 7.7; Non-EA group: 69.1 ± 7.8	Colon cancer	NA	Intraoperative and postoperative analgesia (0.5% bupivacaine)	10 years	Survival	Yes for patients without metastases before 1.46 years
Cummings 2012 (20)	Retrospective	42,151	EA group: 77.1 (72.2-82.1); Non-EA group: 78.1 (72.8-83.6)	Nonmetastatic colorectal cancer	Open	Intraoperative and postoperative analgesia	4 years	Cancer recurrence and survival	Yes for survival; No for cancer recurrence
Cummings 2014 (21)	Retrospective	2,745	EA group: 76.5 (72.0-81.8); Non-EA group: 76.9 (72.5-82.3)	Nonmetastatic gastric cancer	Open	Intraoperative and postoperative analgesia	4 years	Cancer recurrence and survival	No
Shin 2017 (22)	Retrospective	3,799	EA group: 57.5 ± 11.7; Non-EA group: 59.6 ± 11.6	Gastric cancer	NA	Intraoperative and postoperative analgesia (0.15% ropivacaine)	53.3 months	Cancer recurrence and mortality	No

(Continued)

TABLE 1 | Continued

Study	Study design	Number of participants	Age (years)*	Cancer type	Surgery approach	Analgesia period and LAs used	Follow-up duration	Oncological outcomes	Association between EA and outcomes
Wang 2016 (23)	Retrospective	273	EA group: 67 (59-76); Non-EA group: 70 (63-78)	Gastric cancer	NA	Intraoperative and postoperative analgesia (0.25% levobupivacaine or ropivacaine)	8 years	Survival	Yes for patients < 64 years
Pei 2020 (24)	Retrospective	194	< 70	Gastric cancer	NA	Intraoperative and postoperative analgesia	5 years	Overall survival	Yes
Cummings 2019 (25)	Retrospective	1,921	EA group: 73.4 ± 4.9; Non-EA group: 74.0 ± 5.2	Esophageal cancer	NA	Intraoperative and postoperative analgesia	2.2 years	Survival	Yes
Heinrich 2015 (26)	Retrospective	153	EA group: 61 (53-69); Non-EA group: 65 (57.5-72.5)	Esophageal cancer	NA	Postoperative analgesia (0.2% ropivacaine)	5 years	Cancer recurrence and survival	No
Li 2016 (27)	Retrospective	356	NA	Esophageal cancer	NA	Postoperative analgesia (0.125% ropivacaine)	34.9 months	Cancer recurrence and overall survival	No
Hiller 2014 (28)	Retrospective	140	EA group: 67 ± 10; Non-EA group: 66 ± 11	Gastro-oesophageal cancer	NA	Intraoperative and postoperative analgesia (0.125% bupivacaine)	2 years	Cancer recurrence and survival	Yes
Xu 2021 (29)	Prospective	400	EA group: 60 ± 10; Non-EA group: 61 ± 10	Lung cancer	NA	Intraoperative (0.375% ropivacaine) and postoperative (0.12% ropivacaine) analgesia	32 months	Recurrence-free survival, overall survival and cancer-specific survival	No
Wu 2019 (30)	Retrospective	744	EA group: 64 ± 12; Non-EA group: 64 ± 11	Non-small-cell lung cancer (stage I–III)	NA	Intraoperative and postoperative analgesia (0.25% or 0.5% bupivacaine)	40.3 months	Recurrence-free and overall survival	No
de Oliveira 2011 (31)	Retrospective	182	EA group: 55 ± 12; Non-EA group: 57 ± 12	Ovarian cancer	NA	Intraoperative and postoperative analgesia or postoperative analgesia only	42 months	Cancer recurrence	Yes for intraoperative and postoperative analgesia; No for postoperative analgesia only
Elias 2015 (32)	Retrospective	194	61.0 (54.0-67.0)	Epithelial ovarian cancer (Stage III)	NA	Intraoperative and postoperative analgesia (bupivacaine)	46 months	Disease-free survival	Yes for more than 48 h of EA use
Tseng 2018 (33)	Retrospective	648	EA group: 62 (19-88); Non-EA group: 61 (30-86)	Ovarian Cancer (stage IIIB-IV)	NA	Intraoperative and postoperative analgesia or postoperative analgesia only (0.05% bupivacaine)	7 years.	Progression-free survival and overall survival	Yes
Lacassie 2013 (34)	Retrospective	80	EA group: 59 (48-65); Non-EA group: 60 (50-69)	Ovarian cancer (stage IIIC-IV)	NA	Intraoperative and postoperative analgesia (0.1%-0.5% bupivacaine)	4.9 years	Cancer recurrence and overall survival	No

(Continued)

TABLE 1 | Continued

Study	Study design	Number of participants	Age (years)*	Cancer type	Surgery approach	Analgesia period and LAs used	Follow-up duration	Oncological outcomes	Association between EA and outcomes
Capmas 2012 (35)	Retrospective	94	EA group: 50 ± 12; Non-EA group: 56 ± 9	Ovarian cancer (advance stage)	NA	Postoperative analgesia (0.2% ropivacaine)	50 months	Recurrence-free survival and overall survival	No
Wuethrich 2010 (36)	Retrospective	261	EA group: 63 (57-67); Non-EA group: 64 (59-68)	Prostate cancer	NA	Intraoperative (0.25% bupivacaine) and postoperative (0.1% bupivacaine) analgesia	11.9 years	Biochemical recurrence-free survival, clinical progression-free survival, cancer-specific survival, and overall survival	Yes for clinical progression-free survival; No for biochemical recurrence-free survival, cancer-specific survival, or overall survival.
Wuethrich 2013 (37)	Retrospective	148	EA group: 63.61 (57.61-68.17); Non-EA group: 63.83 (59.12-67.48)	Prostate cancer	NA	Intraoperative (0.25% bupivacaine) and postoperative (0.1% bupivacaine) analgesia	14 years	Biochemical recurrence-free, local and distant recurrence-free, cancer-specific, and overall survival	No
Forget 2011 (38)	Retrospective	111	65 ± 7	Prostate cancer	NA	Intraoperative and postoperative analgesia (bupivacaine)	38 months	Biochemical recurrence-free survival	No
Tsui 2010 (39)	Prospective	99	EA group: 63.0 ± 5.5; Non-EA group: 63.9 ± 6.1	Prostate cancer	NA	Intraoperative analgesia (0.2% ropivacaine)	4.5 years	Disease-free survival	No
Biki 2008 (40)	Retrospective	225	EA group: 63 ± 5; Non-EA group: 62 ± 6	Prostate cancer	Open	Postoperative analgesia	12.8 years	Cancer recurrence	Yes
Chipollini 2018 (41)	Retrospective	430	EA group: 69; Non-EA group: 70	Bladder cancer	NA	Intraoperative and postoperative analgesia (50 mcg sufentanil)	41.4 months	Recurrence-free and cancer-specific survival	Worse outcomes
Christopher Doiron 2016 (42)	Retrospective	1,628	NA	Bladder cancer	NA	NA	5 years	Cancer-specific survival and overall survival	No
Chang 2019 (43)	Retrospective	554	EA group: 61 ± 14; Non-EA group: 61 ± 12	Hepatocellular carcinoma	NA	Intraoperative (0.25% or 0.5% bupivacaine) and postoperative (0.25% or 0.5% bupivacaine) analgesia	64.5 months	Recurrence-free and overall survival	No
Cao 2014 (44)	Retrospective	819	EA group: 48.0 ± 11.6; Non-EA group: 49.5 ± 12.1	Hepatocellular carcinoma.	NA	Postoperative analgesia (0.15% ropivacaine combined with 0.07 mg/kg per day morphine)	4.2 years	Recurrence-free survival and long-term survival	EA increased cancer recurrence but had no effect on

(Continued)

TABLE 1 | Continued

Study	Study design	Number of participants	Age (years)*	Cancer type	Surgery approach	Analgesia period and LAs used	Follow-up duration	Oncological outcomes	Association between EA and outcomes
									recurrence-free survival
Gao 2019a (45)	Retrospective	225	EA group: 54 (47-60); Non-EA group: 54 (48-63)	Colorectal carcinoma liver metastases	NA	Intraoperative analgesia (0.2% ropivacaine)	5 years	Cancer recurrence	Yes
Zimmitti 2016 (46)	Retrospective	510	EA group: 58 (23-87); Non-EA group: 57 (28-86)	Colorectal carcinoma liver metastases	NA	Intraoperative and postoperative analgesia (0.075% bupivacaine)	84 months	Recurrence-free and overall survival	Yes for recurrence-free survival; No for overall survival
Call 2015 (47)	Retrospective	111	NA	Pancreatic adenocarcinoma	NA	NA	437 days	Survival	Yes
Alexander 2021 (48)	Retrospective	98	65 (41-85)	Pancreatic adenocarcinoma	NA	Intraoperative (0.375% ropivacaine) and postoperative (0.2% ropivacaine) analgesia	17.26 months	Cancer recurrence or overall survival	No

Data are present as mean with standard deviation or median with interquartile range; EA, Epidural analgesia; NA., Not applicable.

between postoperative EA use and recurrence-free and overall survival after abdominal cancer surgery (97). One randomized controlled trial (RCT) involving 503 patients also found that postoperative EA use had no effects on cancer-free survival after abdominal cancer surgery (98). The effects of perioperative EA on long-term oncological outcomes were varied for specific cancer surgery.

Effects of Perioperative EA on Colorectal Cancer Surgery

A large number of retrospective studies have evaluated the effects of perioperative EA on oncological outcomes in patients underwent colorectal cancer surgeries, but the results were inconsistent. One study compared the effects of perioperative EA (combined intraoperative and postoperative analgesia) with intravenous opioid analgesia in patients receiving surgery for colon cancer (stage I to III). No association was found between perioperative EA use and cancer recurrence or death with 46.1 months duration of follow-up. However, higher level of preoperative carcinoembryonic antigen, perioperative blood transfusion, advanced cancer stage, and pathological lymphovascular invasion were independent risk factors for cancer recurrence and death in these patients (10). In patients with rectal cancer resection (stage I-III), postoperative EA also did not improve recurrence or mortality with a follow-up duration of 46.1 months when compared to opioids analgesia (11). For patients with stage IV colorectal cancer, one study involving 999 patients showed perioperative EA was not associated with better progression-free or overall survival after surgeries with 17.5 months follow-up (12). In patients underwent laparoscopic colorectal resection for adenocarcinoma, Day et al. showed that postoperative EA had no significant advantage in 5-year overall or disease-free survival than opioids analgesia (13). In contrast, one study revealed that, compared with patient-controlled analgesia, postoperative EA reduces all-cause mortality after open resection of rectal but not colon cancer in patients (14). Furthermore, the results suggested that elder age (>72 years old) and cancer stage (stages 2 and/or 3) were risk factors for death after colon and rectal cancer surgeries. Interestingly, in another study, age was also supposed to be a factor to influence the effects of perioperative EA on oncological outcomes. Gottschalk et al. showed that, although perioperative EA for colorectal cancer surgery did not improve cancer recurrence with a median follow-up time of 1.8 years, a potential benefit was observed in older patients (> 64 years old) (15). Taken together, these findings suggest that the effects of perioperative EA on oncological outcomes after colorectal cancer surgery may be related to the cancer types, stage, patients' age, and surgery approach, which need further well-designed studies to determine.

Few prospective studies investigated the effects of EA on the cancer recurrence and/or mortality after surgery for colorectal cancer. One multicenter RCT found that, compared with intravenous morphine analgesia, perioperative EA did not improve 5 years disease-free survival in patients underwent colorectal cancer surgery, although perioperative EA significantly reduced postoperative pain during the first 24 h after surgery (16).

However, epidural anesthesia use is also reported beneficial for oncological outcomes in patients after colorectal cancer surgery. One retrospective study revealed that perioperative EA was associated with a better five-year overall survival in patients underwent colorectal cancer surgery. Subgroup analysis also showed that EA contributed to a better overall survival in patients of 80 years and older (17). Another retrospective

study also showed that EA improved 5-year survival in patients after colorectal carcinoma surgeries (18).

Christopherson et al. suggested that the potential benefits of perioperative EA depend on cancer staging. They showed that epidural block was associated with enhanced survival in patients without metastases before 1.46 years, but not in patients without metastases after 1.46 years or with metastases (19). Also, Cummings et al. found that perioperative EA improved 5-year survival in patients with nonmetastatic colorectal cancer after open surgery, but did not decrease cancer recurrence (20).

Effects of Perioperative EA on Gastric Cancer Surgery

For gastric cancer surgeries, the results regarding the effects of EA on oncological outcomes were also conflicting. Most evidences suggest that EA use is not associated with better oncological outcomes in patients underwent gastric cancer surgeries. Compared with intravenous analgesia, perioperative EA was not associated with improved recurrence or survival in patients after gastric cancer surgeries (21, 22). Compared with general anesthesia, epidural anesthesia also showed no effects on the long-term survival of patients after gastric cancer surgeries, but the benefit was observed in younger patients (age up to 64) (23). Furthermore, compared with patient-controlled intravenous analgesia, postoperative EA did not provide better short-term outcomes in patients underwent laparoscopic distal gastrectomy for gastric cancer (99). EA was even associated with a longer length of stay for patients underwent open elective gastrectomies for nonmetastatic cancer (100). Currently, only one retrospective study supported an association between EA use and survival after gastric cancer surgery. The results found that the 5-year overall survival rates were higher in patients receiving general anesthesia combined perioperative EA than that receiving general anesthesia alone (24).

Effects of Perioperative EA on Esophageal Cancer

Four studies have evaluated the effects of EA on oncological outcomes after esophageal surgeries (25–28). Heinrich et al. showed that postoperative EA did not improve cancer recurrence, 1-year mortality, or 5-year survival after esophagus cancer surgery, although it significantly decreased postoperative opioid consumption and the duration of ICU hospitalization (26). Li et al. also confirmed the benefits of postoperative EA on the short-term outcomes after esophagectomy for cancer, such as attenuating inflammatory response, reducing the incidence of pneumonia and anastomotic leakage, but did not support an association between postoperative EA use and improved 3-year overall recurrence and survival (27). The other two retrospective studies revealed potential benefits of EA on oncological outcomes of EA, of which one study found that perioperative EA was associated with better cancer recurrence and survival after esophageal surgery with 2-year follow-up (28). The other one showed that perioperative EA was associated with better 90-day survival after esophagectomy. Additionally, compared with transthoracic esophagectomy, the five-year survival rates were higher after transhiatal esophagectomy (25), suggesting that the surgical approach may influence the effects of EA on oncological outcomes. Prospective RCTs are needed to assess whether perioperative EA use can improve the cancer recurrence and/or survival after esophageal cancer surgeries.

Effects of Perioperative EA on Lung Cancer

The current evidences from prospective and retrospective studies do not show a role of perioperative EA use in improving oncological outcomes after lung cancer surgeries. One randomized trial showed that, compared with general anesthesia alone, the combining use with perioperative EA did not improve recurrence-free, overall, or cancer-specific survival in patients after major lung cancer surgery after median follow-up duration of 32 months (29). In patients having non-small-cell lung cancer resection, one retrospective study showed that thoracic epidural analgesia was not associated with better 3-year recurrence-free and overall survival (30). Wu et al. reported that postoperative EA after surgery for non-small cell lung cancer had no association with better 2-year or 5-year recurrence-free survival or overall survival rates. Instead, elder age (≥ 65 years old), male gender, higher body mass index (≥ 25 kg/m^2), ASA 4, preoperative blood transfusions, pneumonectomy, and postoperative radiation implicated in decreased recurrence-free survival and overall survival (30). Therefore, perioperative EA use appears to not be a factor for oncological outcomes after lung cancer surgeries.

Effects of Perioperative EA on Ovarian Cancer

The current evidences are conflicting regarding the effects of epidural anesthesia in patients with ovarian cancer surgeries. One study showed that perioperative EA was associated with an increased time to tumor recurrence in patients after ovarian cancer surgery (31). Elias et al. found that the additional use of perioperative EA in general anesthesia was also associated with a lower rate of recurrence in patients with stage III ovarian cancer (32). Tseng et al. reported that perioperative EA was associated with improved progression-free survival (70.8 months follow-up) and overall survival (68.8 months follow-up) in patients with advanced ovarian cancer surgeries (33). However, two studies reported the negative results. One study found that the addition of perioperative EA in general anesthesia did not increase the time to recurrence or overall survival in patients with advanced ovarian cancer surgeries (34). Postoperative EA also did not improve recurrence-free survival and overall survival in patients with advanced-stage ovarian cancer surgery (35).

Effects of Perioperative EA on Prostate Cancer

The potential impacts of perioperative EA on oncological outcomes in patients with surgeries for prostate cancer are debated. Most evidences point that perioperative EA was not associated with better oncological outcomes in these patients. One study showed that, compared with ketorolac-morphine analgesia, intraoperative and postoperative epidural analgesia

did not improve biochemical recurrence-free survival (11.8 years follow-up), 5-year and 10-year cancer-specific survival, or 5 year and 10-year overall survival after open radical prostatectomy (36). Wuethrich et al. also reported that general anesthesia combined with perioperative EA did not improve cancer progression or survival after retropubic radical prostatectomy for prostate cancer with 14 years follow-up (37). One retrospective analysis revealed that intraoperative EA was not, but sufentanil administration was associated with an increased risk of cancer recurrence after retropubic radical prostatectomies with a median follow-up of 38 months (38). Similarly, Tsui et al. demonstrated that, compared with general anesthesia alone, combined general anesthesia with intraoperative EA did not improve disease-free survival following radical prostatectomy for adenocarcinoma with 4.5 years follow-up (39). Currently, only one retrospective study investigated the potential effects of postoperative EA on the long-term outcomes after prostate cancer surgeries, and the results showed that postoperative EA improved cancer recurrence for open prostatectomy surgery (40). Recently, Robot-assisted radical prostatectomy (RARP) has been widely used for prostate cancer and show some potential benefits than open radical prostatectomy, such as improved peri-operative outcomes and functional outcomes (101, 102). Emerging evidence showed that, compared with general anesthesia alone, combined general anesthesia and perioperative EA provided better outcomes in patients undergoing RARP, such as attenuating the severity of postoperative diaphragmatic dysfunction (103) and improving intraoperative ventilation/oxygenation (104). However, no studies have yet investigated the effects of perioperative EA on the oncological outcomes after RARP. It is interesting to determine this in future studies.

Effects of Perioperative EA on Bladder Cancer

Limited evidence assessed the effects of EA use on the oncological outcomes after bladder cancer surgeries (105). One study evaluated the influence of EA with sufentanil-based epidural analgesia on cancer outcomes in patients receiving radical cystectomy. The results showed that compared with general anesthesia alone, combined general anesthesia with perioperative EA was associated with worse recurrence and disease-free survival for bladder cancer surgeries with 41.4 months follow-up (41), which may be due to the increased opioids use. In another study, Christopher Doiron et al. reported that EA was not associated with cancer-specific survival or overall survival in patients underwent radical cystectomy for bladder cancer (42).

Effects of Perioperative EA on Hepatocellular Carcinoma

Few studies have evaluated the effects of EA on the oncological outcomes after surgical resection for hepatocellular carcinoma. One retrospective analysis showed no association between perioperative EA use and cancer recurrence or overall survival in patients after surgical resection of hepatocellular carcinoma with a median follow-up time of 64.5 months (43). However, compared with postoperative intravenous analgesia with fentanyl, postoperative EA with morphine increased cancer recurrence and survival but had no effects on recurrence-free survival in patients undergoing resection of hepatocellular carcinoma with a median follow-up time of 4.2 years (44).

Two studies have investigated the association between perioperative EA use and oncological outcomes in patients with colorectal carcinoma liver metastases. Unexpectedly, one study reported that, compared with combined general anesthesia-intraoperative EA, general anesthesia alone may provide a better survival outcome for resected colorectal carcinoma liver metastases with 60 months follow-up (45). However, another study showed that, compared to intravenous analgesia, perioperative EA improved five-year recurrence-free, but not overall survival after colorectal carcinoma liver metastases resection (46).

Effects of Perioperative EA on Pancreatic Cancer

Epidural analgesia has been used widely in patients underwent pancreatic cancer surgeries due to several advantages such as improved pain control, improved infectious and pulmonary complications (106), although it may be contraindicated in elderly patients for increased risk of epidural-induced hypotension or malfunction (107). Currently, limited evidence put insights on the relationship between perioperative EA use and oncological outcomes after pancreatic cancer surgeries. One study investigated the effects of perioperative EA on oncologic outcomes in patients after resection of pancreatic cancer. The results indicated that perioperative EA was associated with prolonged survival in patients underwent resection of pancreatic adenocarcinoma with a median follow-up time of 437 days (47). Whereas, Alexander et al. reported no association between EA use and recurrence or overall survival in patients underwent radical resection of pancreatic adenocarcinoma, although subgroup analysis revealed a trend towards a longer overall survival associated with perioperative EA in patients with better differentiation of pancreatic adenocarcinoma (48). The concentration of LAs may also influence the effects of EA on the oncological outcomes in patients after pancreatic surgery. One retrospective cohort study reported that, compared with low concentration (0.15%-0.25%) of ropivacaine, intraoperative EA with high concentration (0.375%-0.5%) of ropivacaine was associated with improved overall survival in patients underwent pancreatectomy (108).

CONCLUSION

Although it is generally recognized that perioperative EA has advantages in modulating the surgical stress, inflammatory, and immunological responses in patients after cancer surgeries, no definitive evidence yet support or refute an association between the use of perioperative EA and improved cancer recurrence and/or survival. The effects of perioperative EA on oncological outcomes likely depend on the cancer types, cancer staging, patients' age, opioids use, and the duration of follow-up. Large

prospective multicenter RCTs are needed to assess the role of EA in long-term oncological outcomes for cancer surgeries.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

1. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic Techniques for Risk of Malignant Tumour Recurrence. *Cochrane Database Syst Rev* (2014) CD008877. doi: 10.1002/14651858.CD008877.pub2
2. Gupta GP, Massagué J. Cancer Metastasis: Building a Framework. *Cell* (2006) 127:679–95. doi: 10.1016/j.cell.2006.11.001
3. Kitamura T, Qian BZ, Pollard JW. Immune Cell Promotion of Metastasis. *Nat Rev Immunol* (2015) 15:73–86. doi: 10.1038/nri3789
4. Le-Wendling L, Nin O, Capdevila X. Cancer Recurrence and Regional Anesthesia: The Theories, the Data, and the Future in Outcomes. *Pain Med* (2016) 17:756–75. doi: 10.1111/pme.12893
5. Cata JP, Bauer M, Sokari T, Ramirez MF, Mason D, Plautz G, et al. 1-2 Effects of Surgery, General Anesthesia, and Perioperative Epidural Analgesia on the Immune Function of Patients With Non-Small Cell Lung Cancer. *J Clin Anesth* (2013) 25:255–62. doi: 10.1016/j.jclinane.2012.12.007
6. Ramirez MF, Ai D, Bauer M, Vauthey JN, Gottumukkala V, Kee S, et al. Innate Immune Function After Breast, Lung, and Colorectal Cancer Surgery. *J Surg Res* (2015) 194:185–93. doi: 10.1016/j.jss.2014.10.030
7. Guerrero Orriach JL, Raigon Ponferrada A, Malo Manso A, Herrera Imbroda B, Escalona Belmonte JJ, Ramirez Aliaga M, et al. Anesthesia in Combination With Propofol Increases Disease-Free Survival in Bladder Cancer Patients Who Undergo Radical Tumor Cystectomy as Compared to Inhalational Anesthetics and Opiate-Based Analgesia. *Oncol* (2020) 98:161–7. doi: 10.1159/000504807
8. Hutton M, Brull R, Macfarlane AJR. 13-9 Regional Anaesthesia and Outcomes. *BJA Educ* (2018) 18:52–6. doi: 10.1016/j.bjae.2017.10.002
9. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC. 13-14 Inhibition of the Stress Response to Breast Cancer Surgery by Regional Anesthesia and Analgesia Does Not Affect Vascular Endothelial Growth Factor and Prostaglandin E2. *Anesth Analg* (2005) 100:244–9. doi: 10.1213/01.Ane.0000143336.37946.7d
10. Wu HL, Tai YH, Mandell MS, Tsou MY, Yang SH, Chen TH, et al. Effect of Epidural Analgesia on Cancer Prognosis After Colon Cancer Resection: A Single-Centre Cohort Study in Taiwan. *BMJ Open* (2020) 10:e036577. doi: 10.1136/bmjopen-2019-036577
11. Wu HL, Tai YH, Lin SP, Yang SH, Tsou MY, Chang KY. Epidural Analgesia Does Not Impact Recurrence or Mortality in Patients After Rectal Cancer Resection. *Sci Rep* (2021) 11:913. doi: 10.1038/s41598-020-79657-5
12. Tai YH, Chang WK, Wu HL, Chan MY, Chen HH, Chang KY. 4-31 The Effect of Epidural Analgesia on Cancer Progression in Patients With Stage IV Colorectal Cancer After Primary Tumor Resection: A Retrospective Cohort Study. *PloS One* (2018) 13:e0200893. doi: 10.1371/journal.pone.0200893
13. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective Analysis of the Effect of Postoperative Analgesia on Survival in Patients After Laparoscopic Resection of Colorectal Cancer. *Br J Anaesth* (2012) 109:185–90. doi: 10.1093/bja/aes106
14. Gupta A, Björnsson A, Fredriksson M, Hallböök O, Eintrei C. Reduction in Mortality After Epidural Anaesthesia and Analgesia in Patients Undergoing Rectal But Not Colonic Cancer Surgery: A Retrospective Analysis of Data From 655 Patients in Central Sweden. *Br J Anaesth* (2011) 107:164–70. doi: 10.1093/bja/aer100
15. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association Between Epidural Analgesia and Cancer Recurrence After Colorectal Cancer Surgery. *Anesthesiol* (2010) 113:27–34. doi: 10.1097/ALN.0b013e3181de6d0d
16. Falk W, Magnuson A, Eintrei C, Henningsson R, Myrelid P, Matthiessen P, et al. Comparison Between Epidural and Intravenous Analgesia Effects on Disease-Free Survival After Colorectal Cancer Surgery: A Randomised Multicentre Controlled Trial. *Br J Anaesth* (2021) 127:65–74. doi: 10.1016/j.bja.2021.04.002
17. Vogelaar FJ, Abegg R, van der Linden JC, Cornelisse HG, van Dorsten FR, Lemmens VE, et al. Epidural Analgesia Associated With Better Survival in Colon Cancer. *Int J Colorectal Dis* (2015) 30:1103–7. doi: 10.1007/s00384-015-2224-8
18. Holler JP, Ahlbrandt J, Burkhardt E, Gruss M, Röhrig R, Knapheide J, et al. Peridural Analgesia may Affect Long-Term Survival in Patients With Colorectal Cancer After Surgery (PACO-RAS-Study): An Analysis of a Cancer Registry. *Ann Surg* (2013) 258:989–93. doi: 10.1097/SLA.0b013e3182915f61
19. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-Term Survival After Colon Cancer Surgery: A Variation Associated With Choice of Anesthesia. *Anesth Analg* (2008) 107:325–32. doi: 10.1213/ane.0b013e3181770f55
20. Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence After Colectomy: A Population-Based Study. *Anesthesiol* (2012) 116:797–806. doi: 10.1097/ALN.0b013e31824674f6
21. Cummings KC3rd, Patel M, Htoo PT, Bakaki PM, Cummings LC, Koroukian S. A Comparison of the Effects of Epidural Analgesia Versus Traditional Pain Management on Outcomes After Gastric Cancer Resection: A Population-Based Study. *Reg Anesth Pain Med* (2014) 39:200–7. doi: 10.1097/aap.0000000000000079
22. Shin S, Kim HI, Kim NY, Lee KY, Kim DW, Yoo YC. Effect of Postoperative Analgesia Technique on the Prognosis of Gastric Cancer: A Retrospective Analysis. *Oncotarget* (2017) 8:104594–604. doi: 10.18632/oncotarget.21979
23. Wang J, Guo W, Wu Q, Zhang R, Fang J. Impact of Combination Epidural and General Anesthesia on the Long-Term Survival of Gastric Cancer Patients: A Retrospective Study. *Med Sci Monit* (2016) 22:2379–85. doi: 10.12659/msm.899543
24. Pei JP, Zhang CD, Liang Y, Zhang C, Wu KZ, Zhao ZM, et al. Effects of Epidural Combined With General Anesthesia Versus General Anesthesia Alone in Gastric Cancer Surgery: A Propensity Score Matching Analysis. *Ann Transl Med* (2020) 8:473. doi: 10.21037/atm.2020.03.127
25. Cummings Iii KC, Kou TD, Chak A, Schluchter MD, Margevicius S, Cooper GS, et al. Surgical Approach and the Impact of Epidural Analgesia on Survival After Esophagectomy for Cancer: A Population-Based Retrospective Cohort Study. *PloS One* (2019) 14:e0211125. doi: 10.1371/journal.pone.0211125
26. Heinrich S, Janitz K, Merkel S, Klein P, Schmidt J. 4-10 Short- and Long Term Effects of Epidural Analgesia on Morbidity and Mortality of Esophageal Cancer Surgery. *Langenbecks Arch Surg* (2015) 400:19–26. doi: 10.1007/s00423-014-1248-9
27. Li W, Li Y, Huang Q, Ye S, Rong T. Short and Long-Term Outcomes of Epidural or Intravenous Analgesia After Esophagectomy: A Propensity-Matched Cohort Study. *PloS One* (2016) 11:e0154380. doi: 10.1371/journal.pone.0154380
28. Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative Epidural Analgesia Reduces Cancer Recurrence After Gastro-Oesophageal Surgery. *Acta Anaesthesiol Scand* (2014) 58:281–90. doi: 10.1111/aas.12255
29. Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anesthesia-Analgesia and Recurrence-Free Survival After Lung Cancer Surgery: A Randomized Trial. *Anesthesiol* (2021) 135:419–32. doi: 10.1097/aln.0000000000003873

30. Wu HL, Tai YH, Chan MY, Tsou MY, Chen HH, Chang KY. Effects of Epidural Analgesia on Cancer Recurrence and Long-Term Mortality in Patients After Non-Small-Cell Lung Cancer Resection: A Propensity Score-Matched Study. *BMJ Open* (2019) 9:e027618. doi: 10.1136/bmjopen-2018-027618
31. de Oliveira GS Jr, Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. Intraoperative Neuraxial Anesthesia But Not Postoperative Neuraxial Analgesia Is Associated With Increased Relapse-Free Survival in Ovarian Cancer Patients After Primary Cytoreductive Surgery. *Reg Anesth Pain Med* (2011) 36:271–7. doi: 10.1097/AAP.0b013e318217aada
32. Elias KM, Kang S, Liu X, Horowitz NS, Berkowitz RS, Frendl G. Anesthetic Selection and Disease-Free Survival Following Optimal Primary Cytoreductive Surgery for Stage III Epithelial Ovarian Cancer. *Ann Surg Oncol* (2015) 22:1341–8. doi: 10.1245/s10434-014-4112-9
33. Tseng JH, Cowan RA, Afonso AM, Zhou Q, Iasonos A, Ali N, et al. 4-59 Perioperative Epidural Use and Survival Outcomes in Patients Undergoing Primary Debulking Surgery for Advanced Ovarian Cancer. *Gynecol Oncol* (2018) 151:287–93. doi: 10.1016/j.ygyno.2018.08.024
34. Lacassie HJ, Cartagena J, Brañes J, Assel M, Echevarría GC. The Relationship Between Neuraxial Anesthesia and Advanced Ovarian Cancer-Related Outcomes in the Chilean Population. *Anesth Analg* (2013) 117:653–60. doi: 10.1213/ANE.0b013e3182a07046
35. Capmas P, Billard V, Gouy S, Lhommé C, Pautier P, Morice P, et al. Impact of Epidural Analgesia on Survival in Patients Undergoing Complete Cytoreductive Surgery for Ovarian Cancer. *Anticancer Res* (2012) 32:1537–42.
36. Wuethrich PY, Hsu Schmitz SF, Kessler TM, Thalmann GN, Studer UE, Stueber F, et al. Potential Influence of the Anesthetic Technique Used During Open Radical Prostatectomy on Prostate Cancer-Related Outcome: A Retrospective Study. *Anesthesiol* (2010) 113:570–6. doi: 10.1097/ALN.0b013e3181e4f6ec
37. Wuethrich PY, Thalmann GN, Studer UE, Burkhard FC. Epidural Analgesia During Open Radical Prostatectomy Does Not Improve Long-Term Cancer-Related Outcome: A Retrospective Study in Patients With Advanced Prostate Cancer. *PloS One* (2013) 8:e72873. doi: 10.1371/journal.pone.0072873
38. Forget P, Tombal B, Scholtès JL, Nzimbala J, Meulders C, Legrand C, et al. Do Intraoperative Analgesics Influence Oncological Outcomes After Radical Prostatectomy for Prostate Cancer? *Eur J Anaesthesiol* (2011) 28:830–5. doi: 10.1097/EJA.0b013e32834b7d9a
39. Tsui BC, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, et al. Epidural Anesthesia and Cancer Recurrence Rates After Radical Prostatectomy. *Can J Anaesth* (2010) 57:107–12. doi: 10.1007/s12630-009-9214-7
40. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence: A Retrospective Analysis. *Anesthesiol* (2008) 109:180–7. doi: 10.1097/ALN.0b013e31817f5b73
41. Chipollini J, Alford B, Boulware DC, Forget P, Gilbert SM, Lockhart JL, et al. Epidural Anesthesia and Cancer Outcomes in Bladder Cancer Patients: Is it the Technique or the Medication? A Matched-Cohort Analysis From a Tertiary Referral Center. *BMC Anesthesiol* (2018) 18:157. doi: 10.1186/s12871-018-0622-5
42. Christopher Doiron R, Jaeger M, Booth CM, Wei X, Robert Siemens D. Is There a Measurable Association of Epidural Use at Cystectomy and Postoperative Outcomes? A Population-Based Study. *Can Urol Assoc J* (2016) 10:321–7. doi: 10.5489/cuaj.3856
43. Chang WK, Lee MY, Tai YH, Kuo YM, Tsou MY, Chang KY. Does Epidural Analgesia Improve the Cancer Outcome in Hepatocellular Carcinoma After Resection Surgery? A Retrospective Analysis. *J Chin Med Assoc* (2019) 82:295–9. doi: 10.1097/jcma.0000000000000054
44. Cao L, Chang Y, Lin W, Zhou J, Tan H, Yuan Y, et al. Long-Term Survival After Resection of Hepatocelluar Carcinoma: A Potential Risk Associated With the Choice of Postoperative Analgesia. *Anesth Analg* (2014) 118:1309–16. doi: 10.1213/ane.0000000000000207
45. Gao H, Meng XY, Wang HQ, Zhu FF, Guo AL, Zhu M, et al. Association Between Anaesthetic Technique and Oncological Outcomes After Colorectal Carcinoma Liver Metastasis Resection. *Int J Med Sci* (2019) 16:337–42. doi: 10.7150/ijms.28016
46. Zimmitti G, Soliz J, Aloia TA, Gottumukkala V, Cata JP, Tzeng CW, et al. Positive Impact of Epidural Analgesia on Oncologic Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. *Ann Surg Oncol* (2016) 23:1003–11. doi: 10.1245/s10434-015-4933-1
47. Call TR, Pace NL, Thorup DB, Maxfield D, Chortkoff B, Christensen J, et al. 16-53 Factors Associated With Improved Survival After Resection of Pancreatic Adenocarcinoma: A Multivariable Model. *Anesthesiol* (2015) 122:317–24. doi: 10.1097/aln.0000000000000489
48. Alexander A, Lehwald-Tywuschik N, Rehders A, Rabenalt S, Verde PE, Eisenberger CF, et al. Peridural Anesthesia and Cancer-Related Survival After Surgery for Pancreatic Cancer-A Retrospective Cohort Study. *Clin Pract* (2021) 11:532–42. doi: 10.3390/clinpract11030070
49. Aguirre-Ghiso JA. 18-1 Models, Mechanisms and Clinical Evidence for Cancer Dormancy. *Nat Rev Cancer* (2007) 7:834–46. doi: 10.1038/nrc2256
50. Bartal I, Melamed R, Greenfeld K, Atzil S, Glasner A, Domankevich V, et al. 21 B 2010 Immune Perturbations in Patients Along the Perioperative Period: Alterations in Cell Surface Markers and Leukocyte Subtypes Before and After Surgery. *Brain Behav Immun* (2010) 24:376–86. doi: 10.1016/j.bbi.2009.02.010
51. Benish M, Bartal I, Goldfarb Y, Levi B, Avraham R, Raz A, et al. 21 B 2008 Perioperative Use of Beta-Blockers and COX-2 Inhibitors may Improve Immune Competence and Reduce the Risk of Tumor Metastasis. *Ann Surg Oncol* (2008) 15:2042–52. doi: 10.1245/s10434-008-9890-5
52. Goldfarb Y, Benish M, Rosenne E, Melamed R, Levi B, Glasner A, et al. 21gold 2009 CpG-C Oligodeoxynucleotides Limit the Deleterious Effects of Beta-Adrenoceptor Stimulation on NK Cytotoxicity and Metastatic Dissemination. *J Immunother* (2009) 32:280–91. doi: 10.1097/CJI.0b013e31819a2982
53. Greenfeld K, Avraham R, Benish M, Goldfarb Y, Rosenne E, Shapira Y, et al. 21 GREEN 2007 Immune Suppression While Awaiting Surgery and Following it: Dissociations Between Plasma Cytokine Levels, Their Induced Production, and NK Cell Cytotoxicity. *Brain Behav Immun* (2007) 21:503–13. doi: 10.1016/j.bbi.2006.12.006
54. Neeman E, Ben-Eliyahu S. 19 N B 2013 Surgery and Stress Promote Cancer Metastasis: New Outlooks on Perioperative Mediating Mechanisms and Immune Involvement. *Brain Behav Immun* (2013) 30 Suppl:S32–40. doi: 10.1016/j.bbi.2012.03.006
55. Shahzad MMK, Arevalo JM, Armaiz-Pena GN, Lu C, Stone RL, Moreno-Smith M, et al. 21shah 2018 Stress Effects on FosB and Interleukin-8 (IL8)-Driven Ovarian Cancer Growth and Metastasis. *J Biol Chem* (2018) 293:10041. doi: 10.1074/jbc.AAC118.004299
56. Pascual M, Alonso S, Parés D, Courtier R, Gil MJ, Grande L, et al. 21 PASCU 2011 Randomized Clinical Trial Comparing Inflammatory and Angiogenic Response After Open Versus Laparoscopic Curative Resection for Colonic Cancer. *Br J Surg* (2011) 98:50–9. doi: 10.1002/bjs.7258
57. Yücel Y, Barlan M, Lenhardt R, Kurz A, Sessler DI. 21 YUC 2005 Perioperative Hypothermia Does Not Enhance the Risk of Cancer Dissemination. *Am J Surg* (2005) 189:651–5. doi: 10.1016/j.amjsurg.2005.03.002
58. Hong JY, Lim KT. Effect of Preemptive Epidural Analgesia on Cytokine Response and Postoperative Pain in Laparoscopic Radical Hysterectomy for Cervical Cancer. *Reg Anesth Pain Med* (2008) 33:44–51. doi: 10.1016/j.rapm.2007.07.010
59. Ben-Eliyahu S. The Promotion of Tumor Metastasis by Surgery and Stress: Immunological Basis and Implications for Psychoneuroimmunology. *Brain Behav Immun* (2003) 17(Suppl 1):S27–36. doi: 10.1016/s0889-1591(02)00063-6
60. Melamed R, Rosenne E, Shakhar K, Schwartz Y, Abudarham N, Ben-Eliyahu S. Marginating Pulmonary-NK Activity and Resistance to Experimental Tumor Metastasis: Suppression by Surgery and the Prophylactic Use of a Beta-Adrenergic Antagonist and a Prostaglandin Synthesis Inhibitor. *Brain Behav Immun* (2005) 19:114–26. doi: 10.1016/j.bbi.2004.07.004
61. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic Technique and the Cytokine and Matrix Metalloproteinase Response to Primary Breast Cancer Surgery. *Reg Anesth Pain Med* (2010) 35:26–31490–5. doi: 10.1097/AAP.0b013e3181ef4d05
62. Li MH, Xu ZZ, Huang SM, Li T, Li XY, Wang DX. 26-47 Effect of Combined Epidural Anaesthesia on Tumor-Infiltrating Lymphocytes in Lung Adenocarcinoma: A Prospective Exploratory Sub-Analysis. *Hepatogastroenterology* (2018) 61:1142–7. doi: 10.1111/aas.13068

63. Liu K, Liming T, Wang J, Yang HH, Ren J. Effect of Combined General/Epidural Anesthesia on Postoperative NK Cell Activity and Cytokine Response in Gastric Cancer Patients Undergoing Radical Resection. *Randomized Controlled Trial* (2014) 61:1142–7.
64. Zhu J, Zhang XR, Yang HJM. Effects of Combined Epidural and General Anesthesia on Intraoperative Hemodynamic Responses, Postoperative Cellular Immunity, and Prognosis in Patients With Gallbladder Cancer: A Randomized Controlled Trial. *Med (Baltimore)* (2017) 96:e6137. doi: 10.1097/MD.0000000000006137
65. Xu YJ, Chen WK, Zhu Y, Wang SL, Miao CH. 26-48 Effect of Thoracic EpiduralAnaesthesia on Serum Vascular Endothelial Growth Factor C and Cytokinesin Patients Undergoing Anaesthesia and Surgery for Colon Cancer. *Br J Anaesth* (2014) 113(Suppl 1):149–55. doi: 10.1093/bja/aeu148
66. Boland JW, Pockley AG. Influence of Opioids on Immune Function in Patients With Cancer Pain: From Bench to Bedside. *Br J Pharmacol* (2018) 175:2726–36. doi: 10.1111/bph.13903
67. Gach K, Wyrębska A, Fichna J, Janecka A. The Role of Morphine in Regulation of Cancer Cell Growth. *Naunyn Schmiedebergs Arch Pharmacol* (2011) 384:221–30. doi: 10.1007/s00210-011-0672-4
68. Das J, Kumar S, Khanna S, Mehta Y. *J.J.o.A.C.P* (2014) 30:2. doi: 10.4103/0970-9185
69. Mei G, Jie S, Jin W, Qian YJI. Morphine, But Not Ketamine, Decreases the Ratio of Th1/Th2 in CD4-Positive Cells Through T-Bet and GATA3. *Inflammation* (2012) 35:1069–77. doi: 10.1007/s10753-011-9413-6
70. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, et al. The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients. *Anesth Analg* (2000) 90:1411–4. doi: 10.1097/00000539-200006000-00028
71. Sacerdote P, Gaspani L, Rossoni G, Panerai AE, Bianchi MJII. Effect of the Opioid Remifentanil on Cellular Immune Response in the Rat. *Int Immunopharmacol* (2001) 1:713–9. doi: 10.1016/S1567-5769(01)00005-4
72. Gong L, Qin Q, Lei Z, Ouyang W, Li YJ. Effects of Fentanyl Anesthesia and Sufentanil Anesthesia on Regulatory T Cells Frequencies. *Int J Clin Exp Pathol* (2014) 7:7708–16.
73. Hofbauer R, Moser D, Salfinger H, Frass M, Kapiotis S. 14-57 Sufentanil Inhibits Migration of Human Leukocytes Through Human Endothelial Cell Monolayers. *Anesth Analg* (1998) 87:1181–5. doi: 10.1097/00000539-199811000-00038
74. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B. 14-55 Effects of Fentanyl on Natural Killer Cell Activity and on Resistance to Tumor Metastasis in Rats. Dose and Timing Study. *Neuroimmunomodulation* (2004) 11:255–60. doi: 10.1159/000078444
75. Ecimovic P, McHugh B, Murray D, Doran P, Buggy DJ. Effects of Sevoflurane on Breast Cancer Cell Function. *Vitro Anticancer Res* (2013) 33:4255–60.
76. Fan L, Wu Y, Wang J, He J, Han X. Sevoflurane Inhibits the Migration and Invasion of Colorectal Cancer Cells Through Regulating ERK/MMP-9 Pathway by Up-Regulating miR-203. *Eur J Pharmacol* (2019) 850:43–52. doi: 10.1016/j.ejphar.2019.01.025
77. Jun IJ, Jo JY, Kim JI, Chin JH, Kim WJ, Kim HR, et al. Impact of Anesthetic Agents on Overall and Recurrence-Free Survival in Patients Undergoing Esophageal Cancer Surgery: A Retrospective Observational Study. *Sci Rep* (2017) 7:14020. doi: 10.1038/s41598-017-14147-9
78. Jun R, Gui-he Z, Xing-xing S, Hui Z, Li-xian X. Isoflurane Enhances Malignancy of Head and Neck Squamous Cell Carcinoma Cell Lines: A Preliminary Study. *Vitro Oral Oncol* (2011) 47:329–33. doi: 10.1016/j.oraloncology.2011.03.002
79. Guay J, Kopp S. Epidural Pain Relief Versus Systemic Opioid-Based Pain Relief for Abdominal Aortic Surgery. *Cochrane Database Syst Rev* (2016) 1: CD005059. doi: 10.1002/14651858.CD005059.pub4
80. Wu CL, Cohen SR, Richman JM, Rowlingson AJ, Courpas GE, Cheung K, et al. Efficacy of Postoperative Patient-Controlled and Continuous Infusion Epidural Analgesia Versus Intravenous Patient-Controlled Analgesia With Opioids: A Meta-Analysis. (2005) 103:1079–88. doi: 10.1097/00000542-200511000-00023
81. Gao J, Hu H, Wang XJ. Clinically Relevant Concentrations of Lidocaine Inhibit Tumor Angiogenesis Through Suppressing VEGF/VEGFR2 Signaling. *C.C.Pharmacol* (2019) 83:1–31. doi: 10.1007/s00280-019-03815-4
82. Yang J, Li G, Bao K, Liu W, Zhang Y, Ting W, et al. 1-32 Ropivacaine Inhibits Tumor Angiogenesis *via* Sodium-Channel-Independent Mitochondrial Dysfunction and Oxidative Stress. *J Bioenerg Biomembr* (2019) 51:231–8. doi: 10.1007/s10863-019-09793-9
83. Sun H, Sun Y. Lidocaine Inhibits Proliferation and Metastasis of Lung Cancer Cell via Regulation of miR-539/EGFR Axis. *Artif Cells Nanomed Biotechnol* (2019) 47:2866–74. doi: 10.1080/21691401.2019.1636807
84. Zhao L, Han S, Hou J, Shi W, Zhao Y, Chen Y. The Local Anesthetic Ropivacaine Suppresses Progression of Breast Cancer by Regulating miR-27b-3p/YAP Axis. *Aging (Albany NY)* (2021) 13:16341–52. doi: 10.18632/aging.203160
85. Liu H, Dilger JP, Lin J. 11 Effects of Local Anesthetics on Cancer Cells. *Pharmacol Ther* (2020) 212:107558. doi: 10.1016/j.pharmthera.2020.107558
86. Baptista-Hon DT, Robertson FM, Robertson GB, Owen SJ, Rogers GW, Lydon EL, et al. 11 BAP 2014 Potent Inhibition by Ropivacaine of Metastatic Colon Cancer SW620 Cell Invasion and NaV1.5 Channel Function. *Br J Anaesth* (2014) 113 Suppl 1:i39–48. doi: 10.1093/bja/aeu104
87. Brisson L, Driffort V, Benoist L, Poet M, Counillon L, Antelmi E, et al. 1-29 NaV1.5 Na^+ Channels Allosterically Regulate the NHE-1 Exchanger and Promote the Activity of Breast Cancer Cell Invadopodia. *J Cell Sci* (2013) 126:4835–42. doi: 10.1242/jcs.123901
88. Djamgoz MBA, Fraser SP, Brackenbury WJ. 11 DJA 2019 *In Vivo* Evidence for Voltage-Gated Sodium Channel Expression in Carcinomas and Potentiation of Metastasis. *Cancers (Basel)* (2019) 11:1675. doi: 10.3390/cancers11111675
89. Jiang Y, Gou H, Zhu J, Tian S, Yu L. 11 JIANG 2016 Lidocaine Inhibits the Invasion and Migration of TRPV6-Expressing Cancer Cells by TRPV6 Downregulation. *Oncol Lett* (2016) 12:1164–70. doi: 10.3892/ol.2016.4709
90. Piegeler T, Schläpfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, et al. 1-34 Clinically Relevant Concentrations of Lidocaine and Ropivacaine Inhibit Tnfα-Induced Invasion of Lung Adenocarcinoma Cells *In Vitro* by Blocking the Activation of Akt and Focal Adhesion Kinase. *Br J Anaesth* (2015) 115:784–91. doi: 10.1093/bja/aev341
91. Tohme S, Simmons RL, Tsung AJCR. 11 TOH 2017 Surgery for Cancer: A Trigger for Metastases. *Cancer Res* (2017) 77:1548. doi: 10.1158/0008-5472.CAN-16-1536
92. Lang A, Horin SB, Picard O, Fudim E, Amariglio N, Chowers YJI. 11 LAN 2010 Lidocaine Inhibits Epithelial Chemokine Secretion *via* Inhibition of Nuclear Factor Kappa B Activation. *Immunobiology* (2010) 215:304–13. doi: 10.1016/j.imbio.2009.05.006
93. Ni J, Xie T, Xiao M, Wei X, Wang LJB, Communications BR. Amide-Linked Local Anesthetics Preferentially Target Leukemia Stem Cell Through Inhibition of Wnt/β-Catenin. *Biochem Biophys Res Commun* (2018) 503:956–62. doi: 10.1016/j.bbrc.2018.06.102
94. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural Analgesia Enhances Functional Exercise Capacity and Health-Related Quality of Life After Colonic Surgery: Results of a Randomized Trial. *Anesthesiol* (2002) 97:540–9. doi: 10.1097/00000542-200209000-00005
95. Feltracco P, Bortolato A, Barbieri S, Michieletto E, Serra E, Ruol A, et al. Perioperative Benefit and Outcome of Thoracic Epidural in Esophageal Surgery: A Clinical Review. *Dis Esophagus* (2018) 31:1–14. doi: 10.1093/dote/dox135
96. Du YT, Li YW, Zhao BJ, Guo XY, Feng Y, Zuo MZ, et al. Long-Term Survival After Combined Epidural-General Anesthesia or General Anesthesia Alone: Follow-Up of a Randomized Trial. *Anesthesiol* (2021) 135:233–45. doi: 10.1097/aln.0000000000003835
97. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major Abdominal Surgery for Cancer: Does Epidural Analgesia Have a Long-Term Effect on Recurrence-Free and Overall Survival? *Ann Fr Anesth Reanim* (2013) 32: e81–88. doi: 10.1016/j.annfar.2013.02.027
98. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI. 4-28 Perioperative Epidural Analgesia for Major Abdominal Surgery for Cancer and Recurrence-Free Survival: Randomised Trial. *BMJ* (2011) 342:d1491. doi: 10.1136/bmj.d1491
99. Kikuchi S, Kuroda S, Nishizaki M, Matsusaki T, Kuwada K, Kimura Y, et al. Comparison of the Effects of Epidural Analgesia and Patient-Controlled Intravenous Analgesia on Postoperative Pain Relief and Recovery After Laparoscopic Gastrectomy for Gastric Cancer. *Surg Laparosc Endosc Percutan Tech* (2019) 29:405–8. doi: 10.1097/sle.0000000000000605

100. Pesco J, Young K, Nealon K, Fluck M, Shabahang M, Blansfield J. Use and Outcomes of Epidural Analgesia in Upper Gastrointestinal Tract Cancer Resections. *J Surg Res* (2021) 257:433–41. doi: 10.1016/j.jss.2020.08.018
101. Kishikawa H, Suzuki N, Suzuki Y, Hamasaki T, Kondo Y, Sakamoto A. Effect of Robot-Assisted Surgery on Anesthetic and Perioperative Management for Minimally Invasive Radical Prostatectomy Under Combined General and Epidural Anesthesia. *J Nippon Med Sch* (2021) 88:121–7. doi: 10.1272/jnms.JNMS.2021_88-304
102. Seo HJ, Lee NR, Son SK, Kim DK, Rha KH, Lee SH. Comparison of Robot-Assisted Radical Prostatectomy and Open Radical Prostatectomy Outcomes: A Systematic Review and Meta-Analysis. *Yonsei Med J* (2016) 57:1165–77. doi: 10.3349/ymj.2016.57.5.1165
103. Oh YJ, Lee JR, Choi YS, Koh SO, Na S. Randomized Controlled Comparison of Combined General and Epidural Anesthesia Versus General Anesthesia on Diaphragmatic Function After Laparoscopic Prostatectomy. *Minerva Anestesiol* (2013) 79:1371–80.
104. Hong JY, Lee SJ, Rha KH, Roh GU, Kwon SY, Kil HK. Effects of Thoracic Epidural Analgesia Combined With General Anesthesia on Intraoperative Ventilation/Oxygenation and Postoperative Pulmonary Complications in Robot-Assisted Laparoscopic Radical Prostatectomy. *J Endourol* (2009) 23:1843–9. doi: 10.1089/end.2009.0059
105. Rahman SN, Cao DJ, Flores VX, Monaghan TF, Weiss JP, McNeil BK, et al. Impact of Neuraxial Analgesia on Outcomes Following Radical Cystectomy: A Systematic Review. *Urol Oncol* (2021) 39:100–8. doi: 10.1016/j.urolonc.2020.10.073
106. Simpson RE, Fennerty ML, Colgate CL, Kilbane EM, Ceppa EP, House MG, et al. Post-Pancreaticoduodenectomy Outcomes and Epidural Analgesia: A 5-Year Single-Institution Experience. *J Am Coll Surg* (2019) 228:453–62. doi: 10.1016/j.jamcollsurg.2018.12.038
107. Axelrod TM, Mendez BM, Abood GJ, Sinacore JM, Aranha GV, Shoup M. Peri-Operative Epidural may Not be the Preferred Form of Analgesia in Select Patients Undergoing Pancreaticoduodenectomy. *J Surg Oncol* (2015) 111:306–10. doi: 10.1002/jso.23815
108. Chen W, Xu Y, Zhang Y, Lou W, Han X. Positive Impact of Intraoperative Epidural Ropivacaine Infusion on Oncologic Outcomes in Pancreatic Cancer Patients Undergoing Pancreatectomy: A Retrospective Cohort Study. *J Cancer* (2021) 12:4513–21. doi: 10.7150/jca.57661

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REVIEW
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Direct Cytotoxic and Indirect, Immune-Mediated Effects of Local Anesthetics Against Cancer

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Local anesthetics are frequently employed during surgery in order to control peri- and postoperative pain. Retrospective studies have revealed an unexpected correlation between increased long-term survival and the use of local anesthetics during oncological surgery. This effect of local anesthetics might rely on direct cytotoxic effects on malignant cells or on indirect, immune-mediated effects. It is tempting to speculate, yet needs to be formally proven, that the combination of local anesthetics with oncological surgery and conventional anticancer therapy would offer an opportunity to control residual cancer cells. This review summarizes findings from fundamental research together with clinical data on the use of local anesthetics as anticancer standalone drugs or their combination with conventional treatments. We suggest that a better comprehension of the anticancer effects of local anesthetics at the preclinical and clinical levels may broadly improve the surgical treatment of cancer.

Keywords: local anesthetics, immunity, cancer, cell death, surgery

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INTRODUCTION

Malignant disease remains the second cause of death worldwide. According to the World Health Organization, cancers were responsible for 10 million deaths in 2020 (1). In most cases, treatment of solid cancers relies on tumor removal by surgical excision combined with conventional therapies such as chemotherapy and radiotherapy (2). However, standard oncological surgery may promote recurrence by facilitating cancer cell dissemination due to the mechanical removal of the tumor accompanied by the stimulation of vascular endothelial growth factor (VEGF) production by the surrounding tissue (3). Moreover, surgery often induces a stress response composed of organismal metabolic changes, local inflammation and pain, thus causing an elevation of circulating

Abbreviations: ACTH, adrenocorticotropic hormone; Ca2+, calcium ion; DNMT, DNA methyltransferase; EGA, epidural-general anesthesia; EGFR, epithelial growth factor receptor; GA, general anesthesia; HB-EGF, heparin-binding epidermal growth factor-like growth factor; IFN, interferon; IL, interleukin; LA, local anesthetic; MMP, matrix metalloproteinase; NK, natural killer; PCA, patient controlled analgesia; PGE2, prostaglandin E2; PVB, paravertebral block; ROS, reactive oxygen species; TGF, tumor growth factor; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

glucocorticoids and compromising antitumor immune responses (4–6). Finally, surgery negatively impacts on natural killer (NK) lymphocytes that spontaneously recognize and kill cancer cells and are known to play a determinant role in controlling tumor metastasis (7). Thus, we need novel adjuvant treatments during oncological surgery to optimally control pain, while limiting inflammation in order to decrease glucocorticoid stress, sustain anticancer immune responses and control residual cancer cells.

Surprisingly, several observational retrospective studies reported an improved overall survival after the use of local anesthetics (LAs) employed alone or in combination with general anesthesia during solid tumor resection. Thus, as compared to general anesthesia alone, the combination of epidural and general anesthesia, which is usually performed to relief major surgery-induced pain, was associated with a better long-term survival after abdominal and gynecological debulking (8–11). An enhancement of clinical progression-free time was also noticed after regional anesthesia after prostate, liver or breast primary tumor removal (12–14). Despite supplemental meta-analyses strengthening these positive outcomes, no guidelines emerged from these studies given their limits and weaknesses (15–18). However, rational hypotheses to explain these observations appeared in the literature, supporting the possibility of novel guidelines in oncological anesthesia.

Here we aim at discussing the main signaling pathways underlying the antitumor effect of local anesthetics. For this, we summarize published fundamental and clinical research while focusing on the mechanisms through which the immune system is activated by local anesthetics. We specifically dwell on their capacity to potentiate conventional antineoplastic therapies, hoping to improve clinical praxis in this area of oncology.

LOCAL ANESTHETICS POSSESS DIRECT ANTITUMORAL ACTIVITIES

Local Anesthetics Counteract Tumor Cell Migration

LAs such as lidocaine, ropivacaine, levobupivacaine, bupivacaine, procaine or chloroprocaine are used in clinical practice for their analgesic properties, which are explained by the blockade of voltage-gated sodium channels necessary for pain nerve conduction (19). Surprisingly, many observational preclinical studies noticed unexpected side effects of LAs on tumor cells. For instance, migration of cancer cells was profoundly impaired after LA exposure, likely due to effects on Ca^{2+} signaling that affect the cytoskeleton. In human triple-negative breast cancer MDA-MB-231 cells, lidocaine (10 μM or 100 μM) inhibited the CXCR4-induced Ca^{2+} release, leading to actin polymerization and impaired cytoskeletal remodeling (20). Lidocaine-inhibited migration and invasion are also mediated by TRPV6 downregulation that reduced Ca^{2+} influx in MDA-MB-231 cells, prostate cancer PC-3 cells and ovarian cancer ES-2 cells (21). Finally, infiltration of lidocaine at surgical concentrations (5-20 mM) reduced cellular migration by inhibiting the shedding of heparin-binding epidermal growth factor-like growth factor from human fibrosarcoma cells and by modulating intracellular Ca^{2+} (22). Ropivacaine was also described to increase E-cadherin protein expression and to downregulate vimentin, which is a major intermediate filament, thus contributing to reduce metastases (23). Note that tetracaine inhibits the formation of tubulin microtentacles that are required to promote reattachment of detached breast tumor cells during metastatic dissemination (24). Taken together, these findings indicate the existence of multiple molecular mechanisms by which LAs inhibit cancer cell dissemination. It is important to point out that, despite the presence of voltage-gated sodium channels on various cancer types such as breast, colon and lung tumor cells, most of the LA-induced anti-metastatic processes may be ascribed to mechanisms that do not require the inhibition of voltage-gated sodium-channels (22, 25–27) **Figure 1**.

In addition, bupivacaine, procaine and ropivacaine are endowed with the capacity to minimize the migration of neoplastic cells by inhibiting mitochondrial function. Indeed, due to their capacity to block signaling pathways operating downstream of RhoA such as the ROCK/MLC, ERK/MAPK/FAK and Rac1/JNK/paxillin/FAK pathways that commonly lead to apoptosis, local anesthetics inhibit the migration of cancer cells (25–28).

A non-negligible role of microRNAs in cancer regulation and cells migration was suggested in different models of solid cancers treated by LAs. Thus, ropivacaine enhances miT-520a-3p expression in gastric cancer cells, thereby inactivating WEE1 and PI3K/AKT signaling and inhibiting cell migration (29). Lidocaine showed an unexpected ability to up-regulate miR-145 and miR-539 expression in gastric carcinoma MKN45 cells and in lung cancer cells, respectively. These microRNAs directly downregulate epithelial growth factor receptor (EGFR), which is a prominent target for anticancer drugs and plays a major role in tumorigenesis and cancer cell invasion (30, 31). In addition, procaine induces similar antiproliferative effects by up-regulating miR-133b (32).

At clinically relevant concentrations, both lidocaine and ropivacaine block cell invasion. LAs interact with the secretion of matrix metalloproteinases (MMP) such as MMP-2 and with tumor necrosis factor (TNF) α-dependent MMP-9 involved in invasion process by inhibiting Src-dependent inflammatory signaling pathways (33, 34). This anti-invasive effect does not result from direct effects on the cytoskeleton but rather from the capacity of LAs to block cancer cell migration secondary to their anti-inflammatory properties. Indeed, Src protein tyrosine kinase plays a key role in the homeostasis of the endothelial barrier. Its activation by phosphorylation is induced in response to inflammation. Furthermore, surgical procedures provoke acute inflammatory process including vasodilatation, edema and loss of endothelial barrier integrity, thereby facilitating transmigration, extravasation and dissemination of tumor cells through lymphatic and vascular circulation **Figure 1**.

Interestingly, some LAs (lidocaine and bupivacaine) elicit an anti-invasive property at concentrations lower than those used in clinical practice (< 1mM) (21, 25). We may hypothesize that low plasma concentrations of LAs from patients receiving local or

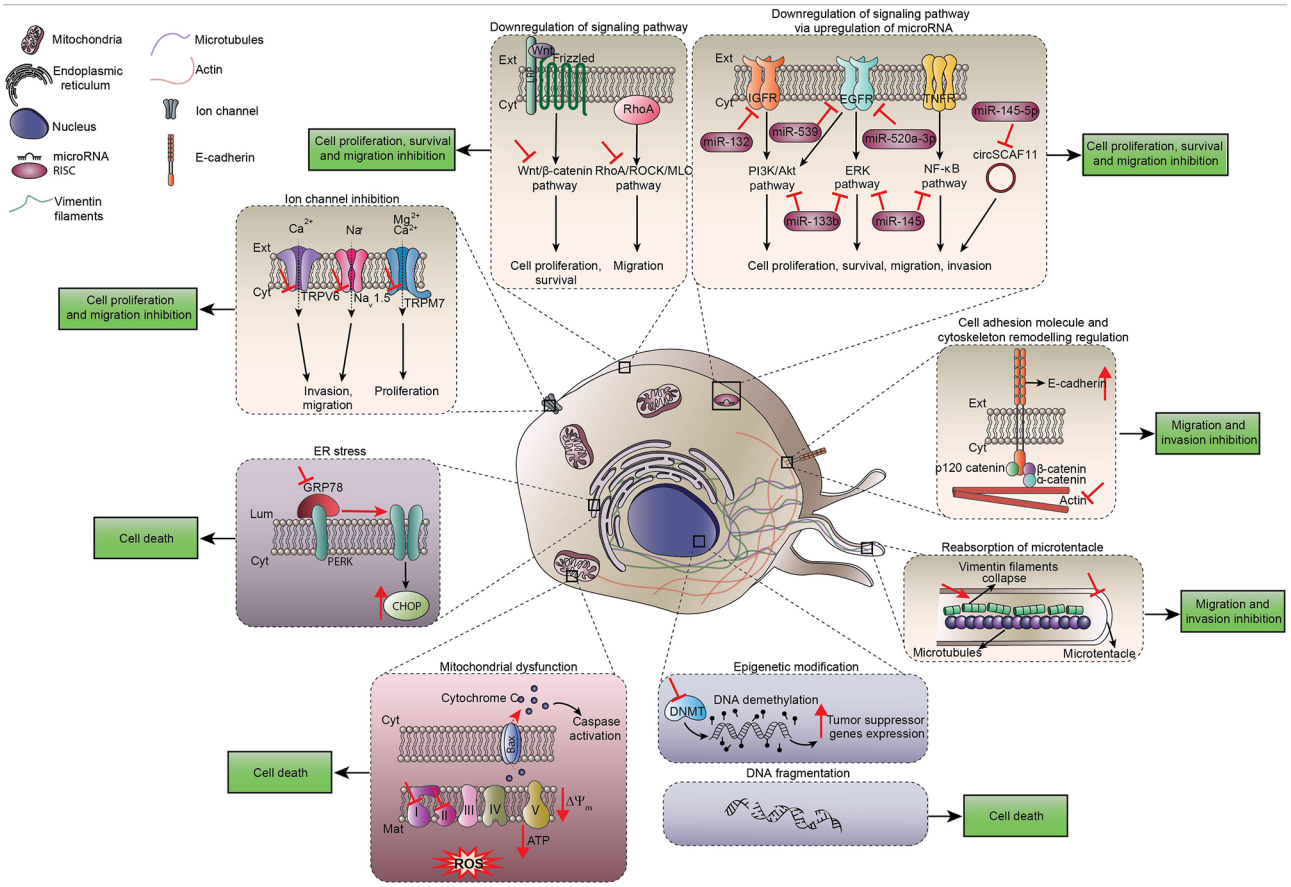

FIGURE 1 | Direct cytotoxic effects of local anesthetics. Scheme summarizing direct effects of local anesthetics on cancer cells including the regulation of signaling pathways that control proliferation, survival and migration of cancer cells. Ca2+, calcium ion; CHOP, C/EBP Homologous protein; Cyt, Cytoplasm; DNMT, DNA methyltransferase; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; Ext, extracellular space; IGFR, insulin growth factor receptor; Mg2+, magnesium ion; Na+, sodium ion; TNFR, tumor necrosis factor receptor; ROS, reactive oxygen species; PERK, protein kinase R-like ER kinase.

regional injection of LAs could suffice to exert systemic effects on residual cancer cells, stopping their migration.

Finally, in models of tumor resection established in immunocompetent mice that have developed syngeneic transplantable EL4 lymphomas or 4T1 breast cancers, lidocaine and bupivacaine used alone or combined with general anesthesia significantly decreased spontaneous metastasis independently of the route of administration (intravenous, spinal block or local infiltration of the inoculation site) (35–38). The mechanisms accounting for these antimetastatic effects remain unclear. However, an LA-induced reduction of circulating MMP-2 levels might contribute to impair tumor cell migration (38).

Local Anesthetics Inhibit Tumor Cell Proliferation

LAs are able to stop tumor cell proliferation as indicated by the decrease in the mitotic marker Ki-67 as well as by a cell cycle arrest (39, 40). Most of the published data showed that this effect is concentration and time dependent (41–43). Many mechanisms may explain this process. LAs directly interfere with the advancement of the cell cycle by reducing cyclins (A2, B1, B2, D, E) and cyclin-dependent kinases expression in various models of human solid cancers (colon, lung, melanoma, thyroid, liver, breast) (28, 34, 39, 44–47). In addition, LAs induce mitochondrial dysfunction causing inhibition of respiratory chain activity and ATP production as well as a shutdown of glycolysis. This LA-induced disruption leads to mitochondrial membrane depolarization, the release of cytochrome c into the cytosol favoring the activation of apoptotic caspases, as well as cell damage mediated by reactive oxygen species (ROS) (48–51). Some LAs affect the DNA methylation status by modulating DNA methyltransferases (DNMT) activation in several types of cancer cell lines. The decrease in global methylation induced by LAs may restore the expression of previously silenced tumor suppressor genes and mediate growth-inhibitory effects on cancer cells (40, 52–58). Furthermore, some experiments suggest the implication of microRNAs in the inhibition of cancer cell proliferation (23, 29, 59). Finally, in a model of human colorectal cancer, bupivacaine and its levorotatory enantiomer levobupivacaine promote the expression of C/EBP

homologous protein (CHOP), which is one of the key effectors of the endoplasmic reticulum stress response (60).

Local Anesthetics Promote Cancer Cell Death

Many preclinical studies suggested the capacity of LAs to induce apoptosis after triggering the activation of tumor suppressor protein p53 (TP53) (61), DNA damage (62), dissipation of the mitochondrial transmembrane potential (48, 51, 63, 64), ROS production (51, 64, 65) or activation of the mitogen-activated protein kinase (MAPK) pathway (64). LAs can provoke mitochondrial rupture and cause the release of pro-apoptotic molecules such as cytochrome c (48, 63, 64) and SMAC (61). In addition, LAs upregulate the pro-apoptotic proteins Bax, Bak (31, 34, 42, 43, 47, 55, 64, 66) and down-regulate their antagonist BCL-2 (34, 42, 63, 64, 66). This ultimately favors the formation of the apoptosome (composed by APAF1, caspase 9 and cytochrome c) (67) and the proteolytic activation of a range of pro-caspases (30, 34, 51, 61–64, 68) including pro-caspase 3 (31, 34, 42, 47, 48, 51, 63, 64, 66, 69–71) and *in fine* the cleavage of poly (ADP-ribose) polymerase 1, marking the apoptotic death of cancer cells (31, 51, 63, 64, 66, 67, 71).

LOCAL ANESTHETICS MAY POSSESS INDIRECT ANTITUMORAL EFFECTS BY SUSTAINING THE IMMUNE SYSTEM

Surgery *per se* induces stress responses involving endocrine and metabolic reactions which generate acute inflammation and interact with the immune system (6). From incision, afferent nerve pathways stimulate catecholamine production and activate the corticotropic axis (6). The increase of plasma cortisol and catecholamine levels modifies the distribution of circulating leukocytes leading to lymphopenia and promotes the synthesis of the pro-tumoral cytokine IL-6, hence potentially enhancing tumor progression. Epinephrine and norepinephrine may act on beta-adrenergic receptors found in several tumor types such as breast, prostate or liver cancer and stimulate cancer cell proliferation and migration (72, 73). The adrenocorticotropic hormone (ACTH) interferes with antibody synthesis and inhibits the production of interferon (IFN) by T cells (74). This glucocorticoid stress is sufficient to profoundly subvert anticancer immunosurveillance in a range of murine models (4). In this context, it appears important to note that regional anesthesia by LAs injected into the epidural space provides a stable pain relief by blocking nociceptive pathways. Moreover, different neuroaxial anesthetic modalities possess the outstanding capacity to minimize glucocorticoid stress during surgery and to counteract the immunodepression induced by general anesthesia. Assessment of cortisol, epinephrine and norepinephrine in the serum and in the urine of patients after laparotomy under spinal anesthesia were significantly decreased during peri- and postoperative period compared to patients under general anesthesia (75–78). Thus, LAs could prevent the neuroendocrine stress responses resulting from oncological surgery and sustain anticancer immunity. This is strongly suggested by a preclinical study of Bar-Yosef et al., in which spinal block using bupivacaine not only controlled pain in rats during laparotomy but also attenuated the post-surgical dissemination of metastases (79) **Figure 2**.

Acute pain generated by surgery also compromises NK cell-mediated immunity, which is in the first line of defense against tumor development (80, 81), and fosters T helper lymphocyte polarization towards a Th2 profile (82). These findings highlight the need for optimal perioperative analgesia and the necessity to strengthen the immune system. Of note, at clinically relevant concentrations lidocaine enhances the cytotoxic effect of NK cells assessed by the release of lytic granules (granzyme B and perforin) (83). In addition, the serum from patients receiving LAs during tumor resection (independently of the route of administration) was particularly competent to kill cancer cells (84, 85), to preserve lymphocyte proliferation and to attenuate apoptosis of peripheral blood lymphocytes. The ratio of Th1/Th2 cells inclined towards a Th1 profile with secretion of IFN-γ (86). Finally, the level of Th17 and regulatory T cells (Tregs) was also significantly lower compared to the control group (87) **Table 1** and **Figure 2**.

Another hypothesis that might explain indirect anticancer effects of LAs is their capacity to blunt surgical inflammation. Despite the employment of minimally surgical procedures, the production of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and the inhibition of IFN-γ responses occur from the incision of the patient's skin (82). Inflammation is marked by major vascular and exudative phenomena (edema, diapedesis and congestion) compromising the endothelial barrier and thus facilitating the formation of new metastases. Secretion of inflammatory cytokines also stimulates MMP-9 and VEGF production in the tumor-surrounding tissue and activates Src kinase that compromises vessel barrier integrity and facilitates cancer cell migration through the extracellular matrix (94). Moreover, the cytokine IL-6 produced in the microenvironment exerts a pro-tumor activity (95). IL-6 directly stimulates the proliferation and survival of cancer cells by stimulating the advancement of the cell cycle, the expression of anti-apoptotic molecules and angiogenesis (72, 96). In addition, IL-6 exerts immunosuppressive effects by inhibiting dendritic cells and lymphocytes, by activating Tregs and *in fine* by promoting tumor immune escape. In clinical practice, high levels of IL-6 predict chemotherapy resistance and poor prognosis in many type of cancers (97). Taken together, these data suggest that the anti-inflammatory effects of LAs may contribute to sustain immune effectors and to reduce tumor progression. Indeed, several randomized controlled trials showed a significant decrease of IL-1, IL-6, IL-8 and MMP-3 and-9 in the serum of patients after LA injection (88, 89, 92). Unfortunately, the impact on clinical outcomes has not yet been investigated **Table 1** and **Figure 2**.

LOCAL ANESTHETICS COULD IMPACT ON ONCOLOGICAL OUTCOMES

Local Anesthetics Potentiate Conventional Anticancer Treatments

Primary tumor resection is often combined with neo-adjuvant or adjuvant anticancer treatments (chemotherapy, radiotherapy or immunotherapy) shortly before or after the surgical procedure.

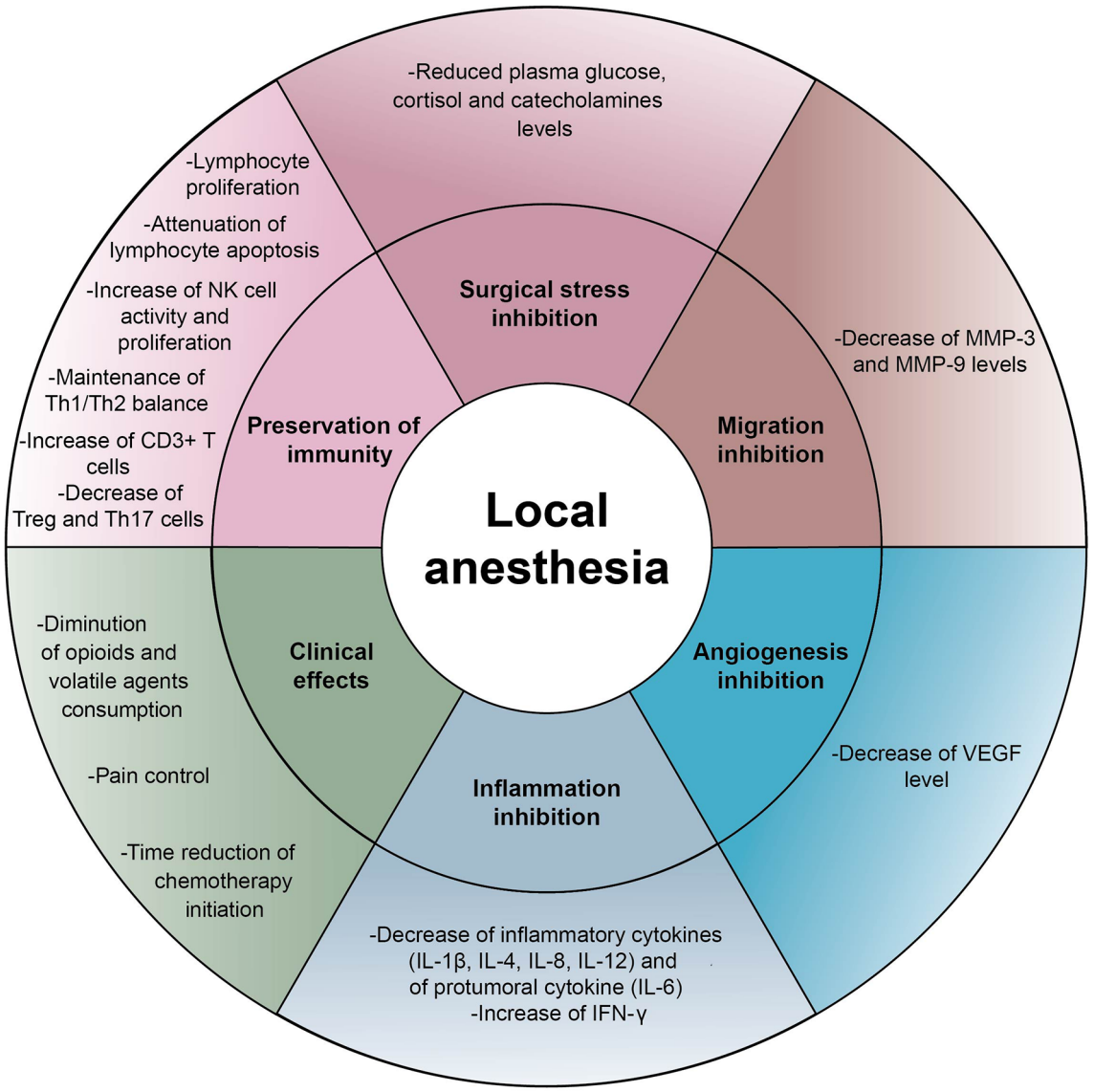

FIGURE 2 | Indirect effects of local anesthetics Schematic representation of indirect effects induced by local anesthetics on cancer cells and immune effectors: inhibition of inflammation, inhibition of cancer cell proliferation and migration, surgical stress control, reduction of neoangiogenesis, preservation of immunity and clinical effects. IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; NK, natural killer cell; VEGF, vascular endothelial growth factor.

Interestingly, LAs can sensitize cancer cells to conventional antitumor therapeutics. Thus, the cytotoxic effects of chemotherapy (with 5-fluorouracil, paclitaxel, cisplatin or carboplatin) or protein kinase inhibitors (such as vemurafenib or erlotinib) were significantly potentiated by LAs (25, 27, 50, 54, 58, 68, 98, 99). Associated with 5-aza-2′-deoxycytidine, lidocaine showed additive demethylating effects in breast cancer cells (57). *In vivo*, the combination of cisplatin and LAs increased life span and cure rate in several mouse models (42, 100, 101), contrasting with the observation that bosutinib reversed the anti-metastatic effect of lidocaine (38). Surprisingly, procaine demonstrated an unexpected protection against cisplatin-induced nephrotoxicity as indicated by reduced blood urea nitrogen and renal tubular degeneration (102).

Local Anesthetics Improve Overall Survival After Cancer Surgery

Many retrospective clinical studies investigated the impact of LAs on oncological prognosis. Thirteen trials suggest a potential benefit of LA injection on recurrence free survival and overall survival after cancer surgery compared to control groups. For instance, in a cohort of 588 patients undergoing primary colon cancer resection, epidural anesthesia improved the five-year survival after adjustement for relevant patient characteristics,

TABLE 1 | Trials assessing local anesthetics on biological markers.

Cancer	Patients	Design	Biological markers outcome	Ref
Breast	N=17	Control group: general anesthesia (sevoflurane)+opioid	PVB decreased IL-1β, MMP-3, MMP-9 and increased IL-10	
	N=15	Studied group: general anesthesia (propofol) + PVB		(88)
Breast	N=20	Studied group: general anesthesia (propofol) + PVB (bupivacaine)	PVB decreased IL-6, increased IL-12, IFN-γ and IL-10/IFN-γ ratio	(89)
	N=20	Control group: general anesthesia (sevoflurane) + fentanyl		
Breast	N=15	Control group: general anesthesia (sevoflurane)	-PVB inhibited surgical stress response (reduced plasma glucose, cortisol and C-reactive protein levels)	(90)
		Postoperative: PCA (morphine)	-No significant difference in VEGF and PGE2 values between groups	
	N=15	Studied group: general anesthesia (sevoflurane) + PVB (bupivacaine)		
Breast	N=20	Control group: general anesthesia (sevoflurane) Postoperative (morphine)	Increased VEGF after surgery in the general anesthesia group TGF-β1 increased after surgery in the propofol-PVB group	(91)
	N=20	Studied group: general anesthesia (propofol) + PVB (levobupivacaine bolus and infusion for 48h)		
Cervical	N=15	Control group: general anesthesia (sevoflurane) + fentanyl	Lidocaine preserved lymphocyte proliferation, attenuated apoptosis of peripheral blood lymphocyte, maintained the balance of Th1/Th2 cells and decreased production of cytokines	(86)
	N=15	Studied group: general anesthesia (sevoflurane) + fentanyl + bolus and infusion of lidocaine		
Colon	N=20	Control group: general anesthesia (desflurane) + epidural (ropivacaine + morphine)	Lidocaine *via* both epidural and IV routes decreased opioid consumption and reduced production of pro-inflammatory cytokines (IL-6, IL-8 and IL-1)	(92)
	N=20	Studied group: general anesthesia+ epidural analgesia (lidocaine bolus and infusion) + Postoperative epidural (ropivacaine + morphine)		
	N=20	Studied group: general anesthesia + epidural analgesia (lidocaine bolus and infusion) + lidocaine IV + Postoperative epidural (ropivacaine + morphine)		
ENT	N=15	Control group: general anesthesia (isoflurane) + morphine	Epidural analgesia decreased the requirement of morphine and stress response (blood glucose and serum cortisol)	(78)
	N=15	Studied group: general anesthesia (isoflurane) + epidural (ropivacaine)		
Liver	N=30	Control group: general anesthesia (sevoflurane) Postoperative: morphine	Epidural shifted Th1/Th2 balance (Th1 dominance) and decreased Th17 and Treg cells	(87)
	N=31	Studied group: general anesthesia (sevoflurane) + epidural (bupivacaine); Postoperative: bupivacaine + morphine		
Ovary	N=30	Control group: general anesthesia (propofol) + fentanyl	Epidural group: higher NK cell cytotoxicity, higher serum concentrations of IL-10 and IFN-γ and lower serum concentrations of IL-1β and IL-8	(85)
	N=31	Studied group: general anesthesia (propofol) + fentanyl + epidural (ropivacaine + lidocaine bolus and infusion)		
Ovary	N=20	Control group: general anesthesia (volatile agents)	Intraperitoneal ropivacaine reduced time of chemotherapy initiation	
	N=20	Studied group: general anesthesia (volatile agents) + intraperitoneal ropivacaine		(93)

ENT, ear nose throat; IL, interleukin; IV, intravenous; MMP, metalloproteinase; NK, natural killer; PCA, patient-controlled analgesia; PGE2, prostaglandin E2; PVB, paravertebral block; TGF, tumor growth factor; VEGF, vascular endothelial growth factor.

tumor type, and type of treatment ([adjusted HR]=1.30 95% CI 1.05-1.59, p=0.01) (8). In the study of Cummings et al. involving 42 151 patients, the use of neuroaxial anesthesia significantly improved overall survival ([adjusted HR] = 0.91, 95% CI 0.87-0.94, p<0.001) (103). After hepatic resection for colorectal metastases, epidural analgesia appeared as an independent predictor of longer recurrence-free survival [HR] = 0.74, 95% CI 0.56-0.95, p=0.036) (104). After gastro-esophageal resection, epidural anesthesia increased the time to recurrence ([HR] = 0.33, 95% CI 0.17-0.63, p < 0.0001), and overall survival ([HR] = 0.42, 95% CI 0.21-0.83, p < 0.0001) at 2 years of follow-up (105). It should be noted that ten retrospective trials failed to confirm these findings. However, the putative anticancer effects of LAs are difficult to demonstate as they are influenced by various independent factors such as- cancer type, comorbidities, the drug used for local anesthesia and its posology (concentration, exposure time, administration route), as well as the combination with other anesthetics (opioids, volatile agents), which may affect immunosurveillance as well **Table 2**.

Irrespective of these limitations, four large meta-analyses all concluded in favor of beneficial effects of epidural anesthesia alone or associated with general anesthesia. With 14 studies including 47 000 patients, Chen et al. demonstrated an improved overall survival of epidural anesthesia compared with general anesthesia alone (HR = 0.84, 95% CI 0.74-0.96, p = 0.013) (15). In the meta-analysis by Pei et al., combined general-epidural anesthesia was associated with decreased recurrence and metastasis rate in the subgroup of prostate cancer patients and in the subgroup with followup less than or equal to 2 years (OR = 0.66, 95% CI 0.46-0.95, p=0.027; OR = 0.70, 95% CI 0.51-0.98, p=0.035; respectively) (16). Sun et al. showed similar results with a significant better overall survival for patients receiving perioperative regional anesthesia ([HR] = 0.84, 95% CI, 0.75-0.94; I^2 =41%) compared to the control group (17). Finally, the meta-analysis by Weng et al. involving 21 studies and 51 620 patients concluded that neuroaxial anesthesia improved both overall survival ([HR] = 0.853, CI= 0.741-0.981, p=0.026) and recurrence-free survival ([HR] = 0.846, CI=0.718-0.998, p=0.047) (18) **Table 3**.

TABLE 2 | Retrospective studies assessing local anesthetics impact on cancer prognosis.

Cancer	Patients	Design	Cancer prognosis outcome	Ref
Breast	N=79	Control group: general anesthesia (sevoflurane) Postoperative: PCA (morphine)	Studied group: lower recurrence- and metastasis-free survival (p=0.012)	(14)
	N=50	Studied group: general anesthesia (sevoflurane) + PVB (bolus and infusion of levobupivacaine for 48h)		
Cervical	N=69	Control group: general anesthesia	Studied group: not associated with lower cancer burden or a reduced risk of tumor recurrence and mortality	(106)
	N=63	Studied group: neuraxial anaesthesia (spinal and epidural analgesia)		
Colon	N=2 299	Control group: general anesthesia + opioid-based analgesia	No association between epidural analgesia and recurrence or death	(107)
	N=449	Studied group: loading dose of lidocaine + general anesthesia and epidural anesthesia (bupivacaine with or without fentanyl for 48-72h)		
Colon	N=668	Control group: general anesthesia	Peridural analgesia:not associated with better oncological outcome	(108)
	N=208	Studied group: epidural anesthesia		
Colon	N=189	Control group: general anesthesia	Epidural analgesia: better 5-year survival (p=0.01)	(8)
	N=399	Studied group: epidural anesthesia		
Colon	N=253	Control group: general anesthesia	Epidural: lower cancer recurrence in patients older than 64 years	(109)
	N=256	Studied group: epidural anesthesia		
Colon	N=32 481	Control group: general anesthesia	Epidural anesthesia: improved survival (p<0.001)	(103)
	N=9 670	Studied group: epidural anesthesia		
Colo-rectal	N=93	Control group: general anesthesia sevoflurane or desflurane + fentanyl and IV morphine for 2 to 5 days	Epidural anesthesia: lower mortality in the sub-group of rectal cancer (p=0.049)	(110)
	N=562	Studied group: general anesthesia sevoflurane or desflurane + epidural (bolus local anesthetic and fentanyl or local anesthetic alone and infusion of local anesthetic with fentanyl or local anesthetic and morphine for 2-5 days)		
Colo-rectal	N=173	Control group: PCA (morphine)	No significant difference in overall survival or disease-free survival at 5 years	(111)
	N=107	Studied group: epidural anesthesia (Bolus and infusion of bupivacaine with fentanyl for 48h)		
	N=144	Studied group: spinal anesthesia (bupivacaine with morphine)		
Colo-rectal	N=307	Control group: general anesthesia (isoflurane or desflurane + fentanyl)	Epidural analgesia: greater long-term survival (p<0.02)	(9)
	N=442	Studied group: general anesthesia (isoflurane or desflurane + fentanyl) + epidural analgesia		
Colo-rectal + liver metastases	N=120	Control group: IV anesthesia	Epidural anesthesia: improved five-year recurrence free survival (p=0.036)	(104)
	N=390	Studied group: epidural anesthesia		
Gastro-oeso-phageal	N=140 (total)	Control group: general anesthesia (sevoflurane or propofol infusion) + IV opioid analgesia Studied group: general anesthesia (sevoflurane or propofol) + epidural anesthesia (bupivacaine bolus + infusion with morphine for 96h)	Epidural was associated with 2-year recurrence and overall survival benefit (p<0.0001)	(105)
ENT	N=160	Control group: general anesthesia + morphine	Epidural anesthesia:increased cancer-free survival (p=0.04) and overall survival (p=0.03)	(112)
	N=111	Studied group: general anesthesia + epidural anesthesia		
Liver	N=244	Control group: general anesthesia (sevoflurane or propofol) + sufentanil + nonsteroidal anti-inflammatory drugs	Local anesthetic increased recurrence free survival (p=0.002) and overall survival (p=0.036)	(12)
	N=245	Studied group: lidocaine+nonsteroidal anti-inflammatory drugs		
Melanoma	N=221	Control group: general anesthesia (isoflurane or propofol) + sufentanil or remifentanil	Spinal anesthesia: a trend of better cumulative survival rate	(113)
	N=52	Studied group: spinal anesthesia (bupivacaine)		
NSCLC	NA	Control group: general anestheisa (isoflurane, sevoflurane or desflurane) + IV opioid analgesia; postoperative PCA (hydromorphone, fentanyl or morphine) Studied group: general anesthesia (isoflurane, sevoflurane or desflurane) + IV opioid analgesia Postoperative: epidural (bupivacaine + fentanyl or bupivacaine + hydromorphone or ropivacaine and fentanyl) Studied group: general anesthesia (isoflurane, sevoflurane, or desflurane) + IV opioid analgesia Postoperative: epidural/PCA: bupivacaine + fentanyl or bupivacaine + hydromorphone or ropivacaine + fentanyl	No difference on recurrence-free survival or overall survival	(114)
Ovary	N=37	Control group: general anesthesia (sevoflurane or isoflurane) + PCA fentanyl	Epidural anesthesia: greater 3- and 5-year overall survival rates (p=0.043)	(10)
	N=106	Studied group: epidural anesthesia (Infusion of bupivacaine or ropivacaine and morphine for 48h)		
Ovary	N=43	Control group: general anesthesia (volatile + fentanyl) Postoperative: ketorolac and PCA (morphine)	Epidural anesthesia: not associated with improved overall survival or time to recurrence	(115)
	N=37	Studied group: general anesthesia +epidural anesthesia (bolus of bupivacaine with or without fentanyl); Postoperative: ketorolac and epidural for 48h		
Pancreas	N=2 239 (total)	Control group: general anesthesia (sevoflurane) + epidural analgesia (ropivacaine) Studied group:lidocaine bolus+ continuous infusion + general anesthesia (sevoflurane) + epidural analgesia (ropivacaine);	Lidocaine group:longer overall survival (p=0.013)	(11)

(Continued)

TABLE 2 | Continued

Cancer	Patients	Design	Cancer prognosis outcome	Ref
Prostate	N=123	Control group: general anesthesia(propofol) + fentanyl Postoperative: PCA (morphine)	Epidural anesthesia: lower risk of recurrence (p=0.012)	(13)
	N=102	Studied group: general anesthesia (propofol) + fentanyl Postoperative: local anesthetic infusion for 48-72h		
Prostate	N=158	Control group: general anesthesia (isoflurane) + fentanyl; Postoperative: ketorolac + paracetamol	Epidural analgesia: improved clinical progression-free survival (p=0.002).	(116)
	N=103	Studied group: general anesthesia (isoflurane) + Epidural (bupivacaine) + fentanyl		
Prostate	N=533	Control group: intravenous analgesia	Epidural analgesia:not associated with a significant effect	(117)
	N=578	Studied group: epidural analgesia		
Visceral	N=63	Control group: general anesthesia (isoflurane + fentanyl); Postoperative: morphine	A trend in favor of epidural anesthesia was observed for recurrence free survival	(118)
	N=69	Epidural group: bupivacaine + general anesthesia (isoflurane); postoperative: bupivacaine + morphine		

IV, intravenous; PCA, patient-controlled analgesia; PVB, paravertebral block.
PCA, patient-controlled analgesia; IV, intravenous.

TABLE 3 | Meta-analyses assessing local anesthetics impact on cancer prognosis.

Cancer	Patients	Design	Cancer prognosis outcome	Ref
Solid tumors	14 studies (47 000 patients)	Control group: general anesthesia Studied group: epidural anesthesia with or without general anesthesia	Epidural anesthesia improved overall survival (p=0.013).	(15)
Solid tumors	10 studies (3254 patients)	Control group: general anesthesia Studied group: combined general-epidural anesthesia	Combined general-epidural anesthesia was associated with decreased recurrence (p=0.027) and metastasis rate (p=0.035) within the subgroup of prostate cancer patients and the subgroup with follow-up less than or equal to 2 years	(16)
Solid tumors	20 studies (NA)	Control group: general anesthesia Studied group: perioperative regional anesthesia	Perioperative regional anesthesia associated with improved overall survival ([HR] = 0.84, 95% CI, 0.75-0.94; I^2 =41%)	(17)
Solid tumors	21 studies (51 620 patients)	Control group: general anesthesia Studied group: neuroaxial anesthesia combined with or without general anesthesia	Neuroaxial anesthesia improved overall survival (p=0.026) and recurrence-free survival (p=0.047)	(18)

Finally, among 11 prospective randomized controlled trials, two studies reported a better disease-free survival after epidural anesthesia (ropivacaine or bupivacaine) associated with intravenous or volatile agents during colon (p=0.012) or bladder tumor resection (p=0.02) compared to general anesthesia alone (119, 120). One study investigated the antitumor activity of patient sera after levobupivacaine infiltration during breast cancer resection. A significant blockade of MDA-MB-231 breast carcinoma cells was observed (p=0.01) (121). A better survival after hepatectomy was also noticed after infiltration of ropivacaine close to the incision site (p=0.029) (122). However, other trials failed to confirm these findings, perhaps due to a lack of power and major confusion bias compromising data analyses (injection of multiple different anesthetic agents, inclusion of cancers at different stages, loss of patients due to deficient followup, heterogenous groups…). **Table 4** Multicenter randomized controlled trials with high quality of methodology are urgently awaited to definitevely conclude on the potential benefit of LAs on oncological outcomes.

Until now, no guidelines and no recommendations in onco-anesthesia are available to guide clinical practice. Indeed, most of the results issued from clinical studies are not convincing enough to elaborate new guidelines due to a lack of power, presence of bias, heterogeneity of groups and the combined use of various anesthetics that exert conflicting effects on tumor cells. However, based on the sheer number of prospective multicenter randomized controlled trials, we may expect the translation of preclinical data into the clinics for the near future. Thus, we anticipate that Phase III clinical trials will confirm that, beyond their useful analgesic properties, local anesthetics exert antitumor effects, meaning that their use will be approved for this additional indication.

DISCUSSION

Oncological surgery generates neuroendocrine stress, inflammation and acute pain responsible for immunosuppression, hence impacting on the antitumor immune response (4, 83). The manipulation of the tumor by the surgeon, vascular invasion and the peri-operative synthesis of VEGF also promote the migration and proliferation of residual cancer cells and thus, future metastatic recurrence (131).

The impact of local anesthetics on cancer and its recurrence after surgery has spurred a wave of interest over the last decade. Two recent reviews covering this field have been published (132, 133).

TABLE 4 | Randomized controlled trials assessing local anesthetics impact on cancer prognosis.

Cancer	Patients	Design	Cancer prognosis outcome	Ref
Bladder	N=150	Control group: general anesthesia (sevoflurane)+fentanyl Postoperative (morphine)	Local anesthesia: longer disease-free survival (p=0.02)	(119)
	N=510	Studied group (propofol) +lidocaine+ epidural (ropivacaine)		
Breast	N=11	Control group: general anesthesia (sevoflurane) + morphine postoperative: PCA (morphine)	Patient serum from studied group reduced MDA-MB-231 breast carcinoma cell proliferation (p=0.01)	(121)
	N=11	Studied group: general anesthesia (propofol) + PVB (bolus and infusion of levobupivacaine)		
Breast	N=30	Control group: general anesthesia (volatile anesthetic)	No difference between groups	
	N=30	Studied group: general anesthesia (volatile anesthetic) + PVB (ropivacaine bolus and infusion)		(123)
Breast	N=1065	Control group: general anesthesia (sevoflurane)	No difference between groups	
	N=1043	Studied group: general anesthesia (propofol) + PVB		(124)
Breast	N=58	Control group: general anesthesia (propofol)	No difference between groups	
	N=56	Studied group: general anesthesia + single injection PVB (ropivacaine)		(125)
	N=59	Studied group: general anesthesia + continuous-PVB (ropivacaine for 72h)		
Colon	N=92	Control group: general anesthesia (isoflurane)+ fentanyl	Epidural improved survival in patients without metastases (p=0.012)	
	N=85	Studied group: general anesthesia (isoflurane) + fentanyl + epidural group (bupivacaine)		(120)
Colon Rectum	N=30	Control group: general anesthesia (propofol+ remifentanyl); postoperative: PCA fentanyl	No difference for postoperative NK cell cytotoxicity and IL-2, recurrence or metastasis	(126)
	N=30	Studied group: general anesthesia (propofol and remifentanyl) + surgical wound infiltration of ropivacaine		
Liver	N=20	Control group: tramadol injections	Ropivacaine increased postoperative survival (p=0.029)	
	N=20	Studied group: local incision analgesia (ropivacaine bolus + infiltration)		(122)
	N=20	Studied group: PCA (fentanyl)		
Lung	N=200	Control group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanyl); postoperative: PCA morphine	No difference between groups for recurrence-free and overall survival	(127)
	N=200	Studied group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanyl)+ epidural anesthesia (ropivacaine)		
Prostate	N=50	Control group: general anesthesia; postoperative: morphine	No difference between groups	
	N=49	Studied group: general anesthesia + ropivacaine bolus and infusion with fentanyl		(128)
Solid tumors	N=216	Control group: general anesthesia; postoperative: opioid-based analgesia	No difference between groups	
	N=230	Studied group: general anesthesia + epidural group (bupivacaine or ropivacaine); postoperative: continous bupivacaine or ropivacaine + fentanyl or pethidine		(129)
Solid tumors	N=822	Control group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanyl/ fentanyl); postoperative: PCA morphine	No difference between groups for overall survival	(130)
	N=772	Studied group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanyl/ fentanyl)+ epidural anesthesia (ropivacaine)		

PCA, patient-controlled analgesia; NK, natural killer; PVB, paravertebral block.

In the present article we attempted to synthesize the current preclinical and clinical state of the art, while evoking the capacity of local anesthetics to stimulate anticancer immune responses, thereby potentiating the efficacy conventional anticancer therapies. Particular emphasis has been laid on the difference direct effects impacting on cancer cells and indirect, immune-mediated effects controlling residual tumor cells that mediate local relapse or distant metastasis.

LAs possess analgesic and anti-inflammatory properties that indirectly improve cancer immunosurveillance. In addition, LAs have direct molecular effects on mitochondrial metabolism, generate oxidative stress, trigger apoptosis pathways in cancer cells and activate NK cells (34, 64). Preclinical studies found that treatment of cancer cells with clinically relevant concentrations of LAs inhibits their proliferation and migration or induces cell death (39). These direct antitumor effects described in many cancer cell lines are time- and concentration-dependent. In murine models, LAs showed a remarkable ability to decrease the incidence of metastases after surgery (35, 38). In humans, several clinical studies noticed that LAs used for extradural block attenuated the immunosuppressive endocrine effects generated by surgery (75). In addition, an array of retrospective trials and meta-analyses concluded that LAs used alone or in combination with general anesthesia preserved NK cell activity and improved overall survival and recurrence-free survival (18).

Several putative mechanisms may explain the antitumor properties of LAs. First, LAs reduce the immunosuppressive effects of surgery by reducing glucocorticoid stress and by dampening inflammation (88). Second, LAs stimulate the proliferation and the activity of NK cells that play an important role in the innate immune defense against cancer (83). Third, LAs have direct toxicity on cancer cells and may induce apoptosis before residual cancer cells migrate into adjacent tissues or reach the lumen of lymphatic or vascular capillaries. Finally, LAs reduce the consumption of major protumor molecules such as opioids and volatile agents during cancer surgery (78, 92). Preclinical data sustaining these findings are rather convincing as they have been reproduced in many cancer types. However, these promising data now need translation into the clinics. The outcome of ongoing

randomized multicenter prospective trials dealing with the potential anticancer effects of LAs are urgently awaited. Indeed, the confirmation that LAs improve patient outcome would have a major impact on clinical practice, in particular in the context of oncological surgery.

AUTHOR CONTRIBUTIONS

AW provided the list of trials and designed the figures. OK helped for the design of figures. GK and LB wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Ferlay J EM, Lam F, Colombet M, Mery L, Pineros M, et al. *Global Cancer Observatory: Cancer Today* (2020). Lyon: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today (Accessed February 2021). 2020.
2. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global Cancer Surgery: Delivering Safe, Affordable, and Timely Cancer Surgery. *Lancet Oncol* (2015) 16(11):1193–224. doi: 10.1016/S1470-2045(15)00223-5
3. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging Biological Principles of Metastasis. *Cell* (2017) 168(4):670–91. doi: 10.1016/j.cell.2016.11.037
4. Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, et al. Stress-Glucocorticoid-TSC22D3 Axis Compromises Therapy-Induced Antitumor Immunity. *Nat Med* (2019) 25(9):1428–41. doi: 10.1038/s41591-019-0566-4
5. Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, et al. Increased Surgical Stress Promotes Tumor Metastasis. *Surgery* (2003) 133(5):547–55. doi: 10.1067/msy.2003.141
6. Salmon P, Kaufman L. Preoperative Anxiety and Endocrine Response to Surgery. *Lancet* (1990) 335(8701):1340. doi: 10.1016/0140-6736(90)91215-V
7. Ramirez MF, Ai D, Bauer M, Vauthey JN, Gottumukkala V, Kee S, et al. Innate Immune Function After Breast, Lung, and Colorectal Cancer Surgery. *J Surg Res* (2015) 194(1):185–93. doi: 10.1016/j.jss.2014.10.030
8. Vogelaar FJ, Abegg R, van der Linden JC, Cornelisse HG, van Dorsten FR, Lemmens VE, et al. Epidural Analgesia Associated With Better Survival in Colon Cancer. *Int J Colorectal Dis* (2015) 30(8):1103–7. doi: 10.1007/s00384-015-2224-8
9. Holler JP, Ahlbrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, et al. Peridural Analgesia may Affect Long-Term Survival in Patients With Colorectal Cancer After Surgery (PACO-RAS-Study): An Analysis of a Cancer Registry. *Ann Surg* (2013) 258(6):989–93. doi: 10.1097/SLA.0b013e3182915f61
10. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic Technique may Affect Prognosis for Ovarian Serous Adenocarcinoma: A Retrospective Analysis. *Br J Anaesthesia* (2011) 106(6):814–22. doi: 10.1093/bja/aer055
11. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association Between Intraoperative Intravenous Lidocaine Infusion and Survival in Patients Undergoing Pancreatectomy for Pancreatic Cancer: A Retrospective Study. *Br J Anaesthesia* (2020) 125(2):141–8. doi: 10.1016/j.bja.2020.03.034
12. Wang X, Xie W, Gan S, Wang T, Chen X, Su D, et al. Effects of General Anesthesia Versus Local Anesthesia in Primary Hepatocellular Carcinoma Patients Presenting for Thermal Ablation Surgery: A Multiple Center Retrospective Cohort Study With Propensity Score Matching. *Ann Trans Med* (2020) 8(6):277. doi: 10.21037/atm.2020.03.88
13. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence: A Retrospective Analysis. *Anesthesiology* (2008) 109(2):180–7. doi: 10.1097/ALN.0b013e31817f5b73
14. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008
15. Chen WK, Miao CH. The Effect of Anesthetic Technique on Survival in Human Cancers: A Meta-Analysis of Retrospective and Prospective Studies. *PloS One* (2013) 8(2):e56540. doi: 10.1371/journal.pone.0056540
16. Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, et al. Comparison of Combined General-Epidural Anesthesia With General Anesthesia Effects on Survival and Cancer Recurrence: A Meta-Analysis of Retrospective and Prospective Studies. *PloS One* (2014) 9(12):e114667. doi: 10.1371/journal.pone.0114667
17. Sun Y, Li T, Gan TJ. The Effects of Perioperative Regional Anesthesia and Analgesia on Cancer Recurrence and Survival After Oncology Surgery: A Systematic Review and Meta-Analysis. *Regional Anesthesia Pain Med* (2015) 40(5):589–98. doi: 10.1097/AAP.0000000000000273
18. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The Effect of Neuraxial Anesthesia on Cancer Recurrence and Survival After Cancer Surgery: An Updated Meta-Analysis. *Oncotarget* (2016) 7(12):15262–73. doi: 10.18632/oncotarget.7683
19. Strichartz GR. The Inhibition of Sodium Currents in Myelinated Nerve by Quaternary Derivatives of Lidocaine. *J Gen Physiol* (1973) 62(1):37–57. doi: 10.1085/jgp.62.1.37
20. D'Agostino G, Saporito A, Cecchinato V, Silvestri Y, Borgeat A, Anselmi L, et al. Lidocaine Inhibits Cytoskeletal Remodelling and Human Breast Cancer Cell Migration. *Br J Anaesthesia* (2018) 121(4):962–8. doi: 10.1016/j.bja.2018.07.015
21. Jiang Y, Gou H, Zhu J, Tian S, Yu L. Lidocaine Inhibits the Invasion and Migration of TRPV6-Expressing Cancer Cells by TRPV6 Downregulation. *Oncol Lett* (2016) 12(2):1164–70. doi: 10.3892/ol.2016.4709
22. Mammoto T, Higashiyama S, Mukai M, Mammoto A, Ayaki M, Mashimo T, et al. Infiltration Anesthetic Lidocaine Inhibits Cancer Cell Invasion by Modulating Ectodomain Shedding of Heparin-Binding Epidermal Growth

Factor-Like Growth Factor (HB-EGF). *J Cell Physiol* (2002) 192(3):351–8. doi: 10.1002/jcp.10145
23. Yin D, Liu L, Shi Z, Zhang L, Yang Y. Ropivacaine Inhibits Cell Proliferation, Migration and Invasion, Whereas Induces Oxidative Stress and Cell Apoptosis by Circscaf11/miR-145-5p Axis in Glioma. *Cancer Manage Res* (2020) 12:11145–55. doi: 10.2147/CMAR.S274975
24. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. Local Anesthetics Inhibit Kinesin Motility and Microtentacle Protrusions in Human Epithelial and Breast Tumor Cells. *Breast Cancer Res Treat* (2011) 129(3):691–701. doi: 10.1007/s10549-010-1239-7
25. Dan J, Gong X, Li D, Zhu G, Wang L, Li F. Inhibition of Gastric Cancer by Local Anesthetic Bupivacaine Through Multiple Mechanisms Independent of Sodium Channel Blockade. *Biomed Pharmacother Biomed Pharmacother* (2018) 103:823–8. doi: 10.1016/j.biopha.2018.04.106
26. Zhang Y, Peng X, Zheng Q. Ropivacaine Inhibits the Migration of Esophageal Cancer Cells *via* Sodium-Channel-Independent But Prenylation-Dependent Inhibition of Rac1/JNK/Paxillin/FAK. *Biochem Biophys Res Commun* (2018) 501(4):1074–9. doi: 10.1016/j.bbrc.2018.05.110
27. Zheng Q, Peng X, Zhang Y. Cytotoxicity of Amide-Linked Local Anesthetics on Melanoma Cells *via* Inhibition of Ras and RhoA Signaling Independent of Sodium Channel Blockade. *BMC Anesthesiol* (2020) 20(1):43. doi: 10.1186/s12871-020-00957-4
28. Li C, Gao S, Li X, Li C, Ma L. Procaine Inhibits the Proliferation and Migration of Colon Cancer Cells Through Inactivation of the ERK/MAPK/FAK Pathways by Regulation of RhoA. *Oncol Res* (2018) 26(2):209–17. doi: 10.3727/096504017X14944585873622
29. Zhang N, Xing X, Gu F, Zhou G, Liu X, Li B. Ropivacaine Inhibits the Growth, Migration and Invasion of Gastric Cancer Through Attenuation of WEE1 and PI3K/AKT Signaling *via* miR-520a-3p. *OncoTargets Ther* (2020) 13:5309–21. doi: 10.2147/OTT.S244550
30. Sui H, Lou A, Li Z, Yang J. Lidocaine Inhibits Growth, Migration and Invasion of Gastric Carcinoma Cells by Up-Regulation of miR-145. *BMC Cancer* (2019) 19(1):233. doi: 10.1186/s12885-019-5431-9
31. Sun H, Sun Y. Lidocaine Inhibits Proliferation and Metastasis of Lung Cancer Cell *via* Regulation of miR-539/EGFR Axis. *Artif Cells Nanomed Biotechnol* (2019) 47(1):2866–74. doi: 10.1080/21691401.2019.1636807
32. Ying B, Huang H, Li H, Song M, Wu S, Ying H. Procaine Inhibits Proliferation and Migration and Promotes Cell Apoptosis in Osteosarcoma Cells by Upregulation of MicroRNA-133b. *Oncol Res* (2017) 25(9):1463–70. doi: 10.3727/096504017X14878518291077
33. Piegeler T, Schlapfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, et al. Clinically Relevant Concentrations of Lidocaine and Ropivacaine Inhibit TNFalpha-Induced Invasion of Lung Adenocarcinoma Cells *In Vitro* by Blocking the Activation of Akt and Focal Adhesion Kinase. *Br J Anaesthesia* (2015) 115(5):784–91. doi: 10.1093/bja/aev341
34. Qin A, Liu Q, Wang J. Ropivacaine Inhibits Proliferation, Invasion, Migration and Promotes Apoptosis of Papillary Thyroid Cancer Cells *via* Regulating ITGA2 Expression. *Drug Dev Res* (2020) 81(6):700–7. doi: 10.1002/ddr.21671
35. Wada H, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, et al. Combined Spinal and General Anesthesia Attenuates Liver Metastasis by Preserving TH1/TH2 Cytokine Balance. *Anesthesiology* (2007) 106(3):499–506. doi: 10.1097/00000542-200703000-00014
36. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Ketamine-Xylazine Anaesthesia for Breast Tumour Resection in a Murine Model. *Br J Anaesthesia* (2018) 121(1):76–85. doi: 10.1016/j.bja.2017.12.043
37. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine, Propofol and Steroids on Pulmonary Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers* (2019) 11(5):1–12. doi: 10.3390/cancers11050613
38. Wall TP, Crowley PD, Sherwin A, Foley AG, Buggy DJ. Effects of Lidocaine and Src Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers* (2019) 11(10):1–10. doi: 10.3390/cancers11101414
39. Chen J, Jiao Z, Wang A, Zhong W. Lidocaine Inhibits Melanoma Cell Proliferation by Regulating ERK Phosphorylation. *J Cell Biochem* (2019) 120 (4):6402–8. doi: 10.1002/jcb.27927
40. Tada M, Imazeki F, Fukai K, Sakamoto A, Arai M, Mikata R, et al. Procaine Inhibits the Proliferation and DNA Methylation in Human Hepatoma Cells. *Hepatol Int* (2007) 1(3):355–64. doi: 10.1007/s12072-007-9014-5
41. Sakaguchi M, Kuroda Y, Hirose M. The Antiproliferative Effect of Lidocaine on Human Tongue Cancer Cells With Inhibition of the Activity of Epidermal Growth Factor Receptor. *Anesthesia Analgesia* (2006) 102 (4):1103–7. doi: 10.1213/01.ane.0000198330.84341.35
42. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells *In Vitro* and in a Xenograft Model *In Vivo*. *Anesthesiology* (2017) 126(5):868–81. doi: 10.1097/ALN.0000000000001528
43. Ye L, Zhang Y, Chen YJ, Liu Q. Anti-Tumor Effects of Lidocaine on Human Gastric Cancer Cells *In Vitro*. *Bratislavske Lekarske Listy* (2019) 120(3):212–7. doi: 10.4149/BLL_2019_036
44. Zhang L, Hu R, Cheng Y, Wu X, Xi S, Sun Y, et al. Lidocaine Inhibits the Proliferation of Lung Cancer by Regulating the Expression of GOLT1A. *Cell Prolif* (2017) 50(5):1–8. doi: 10.1111/cpr.12364
45. Le Gac G, Angenard G, Clement B, Laviolle B, Coulouarn C, Beloeil H. Local Anesthetics Inhibit the Growth of Human Hepatocellular Carcinoma Cells. *Anesth Analg* (2017) 125(5):1600–9. doi: 10.1213/ANE.0000000000002429
46. Castelli V, Piroli A, Marinangeli F, d'Angelo M, Benedetti E, Ippoliti R, et al. Local Anesthetics Counteract Cell Proliferation and Migration of Human Triple-Negative Breast Cancer and Melanoma Cells. *J Cell Physiol* (2020) 235 (4):3474–84. doi: 10.1002/jcp.29236
47. Kwakye AK, Kampo S, Lv J, Ramzan MN, Richard SA, Falagan AA, et al. Levobupivacaine Inhibits Proliferation and Promotes Apoptosis of Breast Cancer Cells by Suppressing the PI3K/Akt/mTOR Signalling Pathway. *BMC Res Notes* (2020) 13(1):386. doi: 10.1186/s13104-020-05191-2
48. Arita K, Utsumi T, Kato A, Kanno T, Kobuchi H, Inoue B, et al. Mechanism of Dibucaine-Induced Apoptosis in Promyelocytic Leukemia Cells (HL-60). *Biochem Pharmacol* (2000) 60(7):905–15. doi: 10.1016/S0006-2952(00)00406-8
49. Jose C, Hebert-Chatelain E, Dias Amoedo N, Roche E, Obre E, Lacombe D, et al. Redox Mechanism of Levobupivacaine Cytostatic Effect on Human Prostate Cancer Cells. *Redox Biol* (2018) 18:33–42. doi: 10.1016/j.redox.2018.05.014
50. Gong X, Dan J, Li F, Wang L. Suppression of Mitochondrial Respiration With Local Anesthetic Ropivacaine Targets Breast Cancer Cells. *J Thorac Dis* (2018) 10(5):2804–12. doi: 10.21037/jtd.2018.05.21
51. Okamoto A, Tanaka M, Sumi C, Oku K, Kusunoki M, Nishi K, et al. The Antioxidant N-Acetyl Cysteine Suppresses Lidocaine-Induced Intracellular Reactive Oxygen Species Production and Cell Death in Neuronal SH-SY5Y Cells. *BMC Anesthesiol* (2016) 16(1):104. doi: 10.1186/s12871-016-0273-3
52. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine Time- and Dose-Dependently Demethylates Deoxyribonucleic Acid in Breast Cancer Cell Lines *In Vitro*. *Br J Anaesthesia* (2012) 109(2):200–7. doi: 10.1093/bja/aes128
53. Villar-Garea A, Fraga MF, Espada J, Esteller M. Procaine is a DNA-Demethylating Agent With Growth-Inhibitory Effects in Human Cancer Cells. *Cancer Res* (2003) 63(16):4984–9.
54. Sabit H, Samy MB, Said OA, El-Zawahri MM. Procaine Induces Epigenetic Changes in HCT116 Colon Cancer Cells. *Genet Res Int* (2016) 2016:8348450. doi: 10.1155/2016/8348450
55. Li YC, Wang Y, Li DD, Zhang Y, Zhao TC, Li CF. Procaine is a Specific DNA Methylation Inhibitor With Anti-Tumor Effect for Human Gastric Cancer. *J Cell Biochem* (2018) 119(2):2440–9. doi: 10.1002/jcb.26407
56. Gao Z, Xu Z, Hung MS, Lin YC, Wang T, Gong M, et al. Procaine and Procainamide Inhibit the Wnt Canonical Pathway by Promoter Demethylation of WIF-1 in Lung Cancer Cells. *Oncol Rep* (2009) 22 (6):1479–84. doi: 10.3892/or_00000590
57. Lirk P, Hollmann MW, Fleischer M, Weber NC, Fiegl H. Lidocaine and Ropivacaine, But Not Bupivacaine, Demethylate Deoxyribonucleic Acid in Breast Cancer Cells. *Vitro Br J Anaesthesia* (2014) 113(Suppl 1):i32–8. doi: 10.1093/bja/aeu201
58. Chen D, Yan Y, Xie J, Pan J, Chen Y, Li Q, et al. Amide-Type Local Anesthetics may Suppress Tumor Cell Proliferation and Sensitize Human Hepatocellular Carcinoma Cells to Cisplatin *via* Upregulation of RASSF1A Expression and Demethylation. *J Cancer* (2020) 11(24):7312–9. doi: 10.7150/jca.46630

59. Xia W, Wang L, Yu D, Mu X, Zhou X. Lidocaine Inhibits the Progression of Retinoblastoma *In Vitro* and *In Vivo* by Modulating the Mir520a3p/EGFR Axis. *Mol Med Rep* (2019) 20(2):1333–42. doi: 10.3892/mmr.2019.10363
60. Li T, Chen L, Zhao H, Wu L, Masters J, Han C, et al. Both Bupivacaine and Levobupivacaine Inhibit Colon Cancer Cell Growth But Not Melanoma Cells *In Vitro*. *J Anesthesia* (2019) 33(1):17–25. doi: 10.1007/s00540-018-2577-6
61. Tat T, Jurj A, Selicean C, Pasca S, Ionescu D. Antiproliferative Effects of Propofol and Lidocaine on the Colon Adenocarcinoma Microenvironment. *J BUON Off J Balkan Union Oncol* (2019) 24(1):106–15.
62. Chang YC, Liu CL, Chen MJ, Hsu YW, Chen SN, Lin CH, et al. Local Anesthetics Induce Apoptosis in Human Breast Tumor Cells. *Anesthesia Analgesia* (2014) 118(1):116–24. doi: 10.1213/ANE.0b013e3182a94479
63. Chang YC, Hsu YC, Liu CL, Huang SY, Hu MC, Cheng SP. Local Anesthetics Induce Apoptosis in Human Thyroid Cancer Cells Through the Mitogen-Activated Protein Kinase Pathway. *PloS One* (2014) 9(2): e89563. doi: 10.1371/journal.pone.0089563
64. Wang HW, Wang LY, Jiang L, Tian SM, Zhong TD, Fang XM. Amide-Linked Local Anesthetics Induce Apoptosis in Human Non-Small Cell Lung Cancer. *J Thorac Dis* (2016) 8(10):2748–57. doi: 10.21037/jtd.2016.09.66
65. Lu J, Xu SY, Zhang QG, Xu R, Lei HY. Bupivacaine Induces Apoptosis via Mitochondria and P38 MAPK Dependent Pathways. *Eur J Pharmacol* (2011) 657(1-3):51–8. doi: 10.1016/j.ejphar.2011.01.055
66. Mirshahidi S, Shields TG, de Necochea-Campion R, Yuan X, Janjua A, Williams NL, et al. Bupivacaine and Lidocaine Induce Apoptosis in Osteosarcoma Tumor Cells. *Clin Orthopaedics Related Res* (2021) 479 (1):180–94. doi: 10.1097/CORR.0000000000001510
67. Wang W, Zhu M, Xu Z, Li W, Dong X, Chen Y, et al. Ropivacaine Promotes Apoptosis of Hepatocellular Carcinoma Cells Through Damaging Mitochondria and Activating Caspase-3 Activity. *Biol Res* (2019) 52(1):36. doi: 10.1186/s40659-019-0242-7
68. Zhang X, Pang W, Liu H, Wang J. Lidocine Potentiates the Cytotoxicity of 5-Fluorouracil to Choriocarcinoma Cells by Downregulating ABC Transport Proteins Expression. *J Cell Biochem* (2019) 120(10):16533–42. doi: 10.1002/jcb.28913
69. Liang Y, Ji J, Lin Y, He Y, Liu J. The Ganglioside GM-1 Inhibits Bupivacaine-Induced Neurotoxicity in Mouse Neuroblastoma Neuro2a Cells. *Cell Biochem Funct* (2016) 34(6):455–62. doi: 10.1002/cbf.3208
70. Xuan W, Zhao H, Hankin J, Chen L, Yao S, Ma D. Local Anesthetic Bupivacaine Induced Ovarian and Prostate Cancer Apoptotic Cell Death and Underlying Mechanisms *In Vitro*. *Sci Rep* (2016) 6:26277. doi: 10.1038/srep26277
71. Zhang H, Lin J, Hu T, Ren Z, Wang W, He Q. Effect of miR-132 on Bupivacaine-Induced Neurotoxicity in Human Neuroblastoma Cell Line. *J Pharmacol Sci* (2019) 139(3):186–92. doi: 10.1016/j.jphs.2019.01.014
72. Bernabe DG, Tamae AC, Biasoli ER, Oliveira SH. Stress Hormones Increase Cell Proliferation and Regulates Interleukin-6 Secretion in Human Oral Squamous Cell Carcinoma Cells. *Brain Behav Immun* (2011) 25(3):574–83. doi: 10.1016/j.bbi.2010.12.012
73. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, et al. Norepinephrine Upregulates VEGF, IL-8, and IL-6 Expression in Human Melanoma Tumor Cell Lines: Implications for Stress-Related Enhancement of Tumor Progression. *Brain Behav Immun* (2009) 23 (2):267–75. doi: 10.1016/j.bbi.2008.10.005
74. Baker GH, Irani MS, Byrom NA, Nagvekar NM, Wood RJ, Hobbs JR, et al. Stress, Cortisol Concentrations, and Lymphocyte Subpopulations. *Br Med J* (1985) 290(6479):1393. doi: 10.1136/bmj.290.6479.1393
75. Carli F, Webster J, Pearson M, Pearson J, Bartlett S, Bannister P, et al. Protein Metabolism After Abdominal Surgery: Effect of 24-H Extradural Block With Local Anaesthetic. *Br J Anaesthesia* (1991) 67(6):729–34. doi: 10.1093/bja/67.6.729
76. Liu S, Carpenter RL, Neal JM. Epidural Anesthesia and Analgesia. Their Role in Postoperative Outcome. *Anesthesiology* (1995) 82(6):1474–506. doi: 10.1097/00000542-199506000-00019
77. Whelan P, Morris PJ. Immunological Responsiveness After Transurethral Resection of the Prostate: General Versus Spinal Anaesthetic. *Clin Exp Immunol* (1982) 48(3):611–8.
78. Kochhar A, Banday J, Ahmad Z, Panjiar P, Vajifdar H. Cervical Epidural Analgesia Combined With General Anesthesia for Head and Neck Cancer Surgery: A Randomized Study. *J Anaesthesiol Clin Pharmacol* (2020) 36 (2):182–6. doi: 10.4103/joacp.JOACP_72_19
79. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the Tumor-Promoting Effect of Surgery by Spinal Blockade in Rats. *Anesthesiology* (2001) 94(6):1066–73. doi: 10.1097/00000542-200106000-00022
80. Sacerdote P, Manfredi B, Bianchi M, Panerai AE. Intermittent But Not Continuous Inescapable Footshock Stress Affects Immune Responses and Immunocyte Beta-Endorphin Concentrations in the Rat. *Brain Behav Immun* (1994) 8(3):251–60. doi: 10.1006/brbi.1994.1023
81. Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G. Evidence That Stress and Surgical Interventions Promote Tumor Development by Suppressing Natural Killer Cell Activity. *Int J Cancer* (1999) 80(6):880–8. doi: 10.1002/(SICI)1097-0215(19990315)80:6<880::AID-IJC14>3.0.CO;2-Y
82. Lin E, Calvano SE, Lowry SF. Inflammatory Cytokines and Cell Response in Surgery. *Surgery* (2000) 127(2):117–26. doi: 10.1067/msy.2000.101584
83. Ramirez MF, Tran P, Cata JP. The Effect of Clinically Therapeutic Plasma Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. *Regional Anesthesia Pain Med* (2015) 40(1):43–8. doi: 10.1097/AAP.0000000000000191
84. Jaura AI, Flood G, Gallagher HC, Buggy DJ. Differential Effects of Serum From Patients Administered Distinct Anaesthetic Techniques on Apoptosis in Breast Cancer Cells In Vitro: A Pilot Study. *Br J Anaesthesia* (2014) 113 Suppl 1:i63–7. doi: 10.1093/bja/aet581
85. Dong H, Zhang Y, Xi H. The Effects of Epidural Anaesthesia and Analgesia on Natural Killer Cell Cytotoxicity and Cytokine Response in Patients With Epithelial Ovarian Cancer Undergoing Radical Resection. *J Int Med Res* (2012) 40(5):1822–9. doi: 10.1177/030006051204000520
86. Wang HL, Yan HD, Liu YY, Sun BZ, Huang R, Wang XS, et al. Intraoperative Intravenous Lidocaine Exerts a Protective Effect on Cell-Mediated Immunity in Patients Undergoing Radical Hysterectomy. *Mol Med Rep* (2015) 12(5):7039–44. doi: 10.3892/mmr.2015.4235
87. Zhou D, Gu FM, Gao Q, Li QL, Zhou J, Miao CH. Effects of Anesthetic Methods on Preserving Anti-Tumor T-Helper Polarization Following Hepatectomy. *World J Gastroenterol* (2012) 18(24):3089–98. doi: 10.3748/wjg.v18.i24.3089
88. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic Technique and the Cytokine and Matrix Metalloproteinase Response to Primary Breast Cancer Surgery. *Regional Anesthesia Pain Med* (2010) 35(6):490–5. doi: 10.1097/AAP.0b013e3181ef4d05
89. Sultan SS. Paravertebral Block can Attenuate Cytokine Response When it Replaces General Anesthesia for Cancer Breast Surgeries. *Saudi J Anaesthesia* (2013) 7(4):373–7. doi: 10.4103/1658-354X.121043
90. O'Riain SC, Buggy DJ, Kerin MJ, Watson RWG, Moriarty DC. Inhibition of the Stress Response to Breast Cancer Surgery by Regional Anesthesia and Analgesia Does Not Affect Vascular Endothelial Growth Factor and Prostaglandin E2. *Anesthesia Analgesia* (2005) 100(1):244–9. doi: 10.1213/01.ANE.0000143336.37946.7D
91. Looney M, Doran P, Buggy DJ. Effect of Anesthetic Technique on Serum Vascular Endothelial Growth Factor C and Transforming Growth Factor Beta in Women Undergoing Anesthesia and Surgery for Breast Cancer. *Anesthesiology* (2010) 113(5):1118–25. doi: 10.1097/ALN.0b013e3181f79a69
92. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, et al. Comparison of the Effects of Thoracic Epidural Analgesia and I.V. Infusion With Lidocaine on Cytokine Response, Postoperative Pain and Bowel Function in Patients Undergoing Colonic Surgery. *Br J Anaesthesia* (2006) 97(5):640–6. doi: 10.1093/bja/ael217
93. Hayden JM, Oras J, Block L, Thorn SE, Palmqvist C, Salehi S, et al. Intraperitoneal Ropivacaine Reduces Time Interval to Initiation of Chemotherapy After Surgery for Advanced Ovarian Cancer: Randomised Controlled Double-Blind Pilot Study. *Br J Anaesthesia* (2020) 124(5):562–70. doi: 10.1016/j.bja.2020.01.026
94. Zhao T, Xia WH, Zheng MQ, Lu CQ, Han X, Sun YJ. Surgical Excision Promotes Tumor Growth and Metastasis by Promoting Expression of MMP-9 and VEGF in a Breast Cancer Model. *Exp Oncol* (2008) 30(1):60–4.

95. Maccio A, Madeddu C. Inflammation and Ovarian Cancer. *Cytokine* (2012) 58(2):133–47. doi: 10.1016/j.cyto.2012.01.015
96. Wang Y, Yang J, Gao Y, Du Y, Bao L, Niu W, et al. Regulatory Effect of E2, IL-6 and IL-8 on the Growth of Epithelial Ovarian Cancer Cells. *Cell Mol Immunol* (2005) 2(5):365–72.
97. Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL. IL-6 and Ovarian Cancer: Inflammatory Cytokines in Promotion of Metastasis. *Cancer Manage Res* (2018) 10:6685–93. doi: 10.2147/CMAR.S179189
98. Li K, Yang J, Han X. Lidocaine Sensitizes the Cytotoxicity of Cisplatin in Breast Cancer Cells *via* Up-Regulation of RARbeta2 and RASSF1A Demethylation. *Int J Mol Sci* (2014) 15(12):23519–36. doi: 10.3390/ijms151223519
99. Zhu G, Zhang L, Dan J, Zhu Q. Differential Effects and Mechanisms of Local Anesthetics on Esophageal Carcinoma Cell Migration, Growth, Survival and Chemosensitivity. *BMC Anesthesiol* (2020) 20(1):126. doi: 10.1186/s12871-020-01039-1
100. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. *Anticancer Res* (2018) 38(10):5599–606. doi: 10.21873/anticanres.12894
101. Viale M, Vannozzi MO, Mandys V, Esposito M. Time-Dependent Influence of Procaine Hydrochloride on Cisplatin Antitumor Activity in P388 Tumor Bearing Mice. *Anticancer Res* (2001) 21(1A):485–7.
102. Esposito M, Fulco RA, Collecchi P, Zicca A, Cadoni A, Merlo F, et al. Improved Therapeutic Index of Cisplatin by Procaine Hydrochloride. *J Natl Cancer Inst* (1990) 82(8):677–84. doi: 10.1093/jnci/82.8.677
103. Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence After Colectomy: A Population-Based Study. *Anesthesiology* (2012) 116(4):797–806. doi: 10.1097/ALN.0b013e31824674f6
104. Zimmitti G, Soliz J, Aloia TA, Gottumukkala V, Cata JP, Tzeng CW, et al. Positive Impact of Epidural Analgesia on Oncologic Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. *Ann Surg Oncol* (2016) 23(3):1003–11. doi: 10.1245/s10434-015-4933-1
105. Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative Epidural Analgesia Reduces Cancer Recurrence After Gastro-Oesophageal Surgery. *Acta Anaesthesiol Scandinavica* (2014) 58(3):281–90. doi: 10.1111/aas.12255
106. Ismail H, Ho KM, Narayan K, Kondalsamy-Chennakesavan S. Effect of Neuraxial Anaesthesia on Tumour Progression in Cervical Cancer Patients Treated With Brachytherapy: A Retrospective Cohort Study. *Br J Anaesthesia* (2010) 105(2):145–9. doi: 10.1093/bja/aeq156
107. Wu HL, Tai YH, Mandell MS, Tsou MY, Yang SH, Chen TH, et al. Effect of Epidural Analgesia on Cancer Prognosis After Colon Cancer Resection: A Single-Centre Cohort Study in Taiwan. *BMJ Open* (2020) 10(10):e036577. doi: 10.1136/bmjopen-2019-036577
108. Wurster EF, Pianka F, Warschkow R, Antony P, Brenner T, Weigand MA, et al. Peridural Analgesia Does Not Impact Survival in Patients After Colon Cancer Resection: A Retrospective Propensity Score-Adjusted Analysis. *Int J Colorectal Dis* (2019) 34(7):1283–93. doi: 10.1007/s00384-019-03315-0
109. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association Between Epidural Analgesia and Cancer Recurrence After Colorectal Cancer Surgery. *Anesthesiology* (2010) 113(1):27–34. doi: 10.1097/ALN.0b013e3181de6d0d
110. Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in Mortality After Epidural Anaesthesia and Analgesia in Patients Undergoing Rectal But Not Colonic Cancer Surgery: A Retrospective Analysis of Data From 655 Patients in Central Sweden. *Br J Anaesthesia* (2011) 107(2):164–70. doi: 10.1093/bja/aer100
111. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective Analysis of the Effect of Postoperative Analgesia on Survival in Patients After Laparoscopic Resection of Colorectal Cancer. *Br J Anaesthesia* (2012) 109 (2):185–90. doi: 10.1093/bja/aes106
112. Merquiol F, Montelimard AS, Nourissat A, Molliex S, Zufferey PJ. Cervical Epidural Anesthesia is Associated With Increased Cancer-Free Survival in Laryngeal and Hypopharyngeal Cancer Surgery: A Retrospective Propensity-Matched Analysis. *Regional Anesthesia Pain Med* (2013) 38(5):398–402. doi: 10.1097/AAP.0b013e31829cc3fb
113. Gottschalk A, Brodner G, Van Aken HK, Ellger B, Althaus S, Schulze HJ. Can Regional Anaesthesia for Lymph-Node Dissection Improve the Prognosis in Malignant Melanoma? *Br J Anaesthesia* (2012) 109(2):253–9. doi: 10.1093/bja/aes176
114. Cata JP, Gottumukkala V, Thakar D, Keerty D, Gebhardt R, Liu DD. Effects of Postoperative Epidural Analgesia on Recurrence-Free and Overall Survival in Patients With Nonsmall Cell Lung Cancer. *J Clin Anesthesia* (2014) 26 (1):3–17. doi: 10.1016/j.jclinane.2013.06.007
115. Lacassie HJ, Cartagena J, Branes J, Assel M, Echevarria GC. The Relationship Between Neuraxial Anesthesia and Advanced Ovarian Cancer-Related Outcomes in the Chilean Population. *Anesthesia Analgesia* (2013) 117 (3):653–60. doi: 10.1213/ANE.0b013e3182a07046
116. Wuethrich PY, Hsu Schmitz SF, Kessler TM, Thalmann GN, Studer UE, Stueber F, et al. Potential Influence of the Anesthetic Technique Used During Open Radical Prostatectomy on Prostate Cancer-Related Outcome: A Retrospective Study. *Anesthesiology* (2010) 113(3):570–6. doi: 10.1097/ALN.0b013e3181e4f6ec
117. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, et al. Do Intraoperative Analgesics Influence Oncological Outcomes After Radical Prostatectomy for Prostate Cancer? *Eur J Anaesthesiol* (2011) 28(12):830–5. doi: 10.1097/EJA.0b013e32834b7d9a
118. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major Abdominal Surgery for Cancer: Does Epidural Analgesia Have a Long-Term Effect on Recurrence-Free and Overall Survival? *Annales Francaises D'anesthesie Reanimation* (2013) 32(5):e81–8. doi: 10.1016/j.annfar.2013.02.027
119. Guerrero Orriach JL, Raigon Ponferrada A, Malo Manso A, Herrera Imbroda B, Escalona Belmonte JJ, Ramirez Aliaga M, et al. Anesthesia in Combination With Propofol Increases Disease-Free Survival in Bladder Cancer Patients Who Undergo Radical Tumor Cystectomy as Compared to Inhalational Anesthetics and Opiate-Based Analgesia. *Oncology* (2020) 98(3):161–7. doi: 10.1159/000504807
120. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-Term Survival After Colon Cancer Surgery: A Variation Associated With Choice of Anesthesia. *Anesth Analg* (2008) 107(1):325–32. doi: 10.1213/ane.0b013e3181770f55
121. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of Anaesthetic Technique on Oestrogen Receptor-Negative Breast Cancer Cell Function *In Vitro*. *Br J Anaesthesia* (2009) 103(5):685–90. doi: 10.1093/bja/aep261
122. Wu YF, Li XP, Yu YB, Chen L, Jiang CB, Li DY, et al. Postoperative Local Incision Analgesia for Acute Pain Treatment in Patients With Hepatocellular Carcinoma. *Rev Da Associacao Med Brasileira* (2018) 64(2):175–80. doi: 10.1590/1806-9282.64.02.175
123. Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NPS, et al. Post-Mastectomy Cancer Recurrence With and Without a Continuous Paravertebral Block in the Immediate Postoperative Period: A Prospective Multi-Year Follow-Up Pilot Study of a Randomized, Triple-Masked, Placebo-Controlled Investigation. *J Anesthesia* (2017) 31(3):374–9. doi: 10.1007/s00540-017-2345-z
124. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X
125. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival Analysis of Patients With Breast Cancer Undergoing a Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: A 5-Year Follow-Up of a Randomized Controlled Trial. *Anticancer Res* (2017) 37 (10):5813–20.
126. Kim SY, Kim NK, Baik SH, Min BS, Hur H, Lee J, et al. Effects of Postoperative Pain Management on Immune Function After Laparoscopic Resection of Colorectal Cancer: A Randomized Study. *Medicine* (2016) 95 (19):e3602. doi: 10.1097/MD.0000000000003602
127. Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anesthesia-Analgesia and Recurrence-Free Survival After Lung Cancer Surgery: A Randomized Trial. *Anesthesiology* (2021) 135(3):419–32. doi: 10.1097/ALN.0000000000003873
128. Tsui BC, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, et al. Epidural Anesthesia and Cancer Recurrence Rates After Radical Prostatectomy. *Can J Anaesthesia J Canadien D'anesthesie* (2010) 57 (2):107–12. doi: 10.1007/s12630-009-9214-7

129. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI, et al. Perioperative Epidural Analgesia for Major Abdominal Surgery for Cancer and Recurrence-Free Survival: Randomised Trial. *Bmj* (2011) 342:d1491. doi: 10.1136/bmj.d1491
130. Du YT, Li YW, Zhao BJ, Guo XY, Feng Y, Zuo MZ, et al. Long-Term Survival After Combined Epidural-General Anesthesia or General Anesthesia Alone: Follow-Up of a Randomized Trial. *Anesthesiology* (2021) 135(2):233–45. doi: 10.1097/ALN.0000000000003835
131. Svendsen MN, Werther K, Nielsen HJ, Kristjansen PE. VEGF and Tumour Angiogenesis. Impact of Surgery, Wound Healing, Inflammation and Blood Transfusion. *Scand J Gastroenterol* (2002) 37(4):373–9.
132. Liu H, Dilger JP, Lin J. Effects of Local Anesthetics on Cancer Cells. *Pharmacol Ther* (2020) 212:107558. doi: 10.1016/j.pharmthera.2020.107558
133. Muller SD, Ziegler JSH, Piegeler T. Local Anesthetics and Recurrence After Cancer Surgery-What's New? A Narrative Review. *J Clin Med* (2021) 10 (4):1–14. doi: 10.3390/jcm10040719

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REVIEW
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Effects of Propofol *Versus* Sevoflurane on Postoperative Breast Cancer Prognosis: A Narrative Review

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Perioperative interventions produce substantial biologic perturbations which are associated with the risk of recurrence after cancer surgery. The changes of tumor microenvironment caused by anesthetic drugs received increasing attention. Till now, it's still unclear whether or not anesthetic drugs may exert positive or negative impact on cancer outcomes after surgery. Breast cancer is the most common tumor and the leading cause of cancer deaths in women. Propofol and sevoflurane are respectively the most commonly used intravenous and inhaled anesthetics. Debates regarding which of the two most commonly used anesthetics may relatively contribute to the recurrence and metastasis vulnerability of breast cancer postoperatively remain. This review aimed to provide a comprehensive view about the effect of propofol versus sevoflurane on the prognosis of breast cancer obtained from pre-clinical studies and clinical studies. Laboratory and animal studies have demonstrated that sevoflurane may enhance the recurrence and metastasis of breast cancer, while propofol is more likely to reduce the activity of breast cancer cells by attenuating the suppression of the immune system, promoting tumor cells apoptosis, and through other direct anti-tumor effects. However, retrospective clinical studies have shown contradictory results about the effects of propofol and sevoflurane on long-term survival in breast cancer patients. Furthermore, recent prospective studies did not identify significant differences between propofol and sevoflurane in breast cancer metastasis and recurrence. Therefore, more preclinical studies and randomized controlled studies are needed to guide the choice of anesthetics for breast cancer patients.

Keywords: propofol, sevoflurane, breast cancer, metastasis, recurrence, long-term prognosis

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INTRODUCTION

Breast cancer is the most commonly diagnosed malignant tumor and the leading cause of cancer-related death among females. It was estimated that there were more than 2 million new cases and 0.63 million cancer related deaths worldwide in the single year of 2018 (1). Surgical removal of the tumor is the foremost treatment strategy for breast cancer (2). However, the scattered

micro-metastases and tumor cells after surgery inevitably formed residual disease. Due to the residual disease, a considerable percentage (ranging from 10 to 41%) of surgical cancer patients will suffer from the recurrence of cancer at five years postoperatively depending on different tumor grades and tumor-node-metastasis staging (3). Whether tumor recurs or metastasizes depends on the balance between the immune capacity of the host and the progression of residual disease. The mortality of breast cancer was attributable to the recurrence and distant organ metastasis and the five-year survival rate was ranging from 69.5% to 93.8% (4, 5). The high recurrence rate after surgery questions whether or not there are any perioperative measures that may shift the balance towards host defense to reduce the risk of disease recurrence.

There have been increasing concerns that perioperative substantial biologic perturbations will increase the risk of recurrence after cancer surgery (6). On the one hand, tissue trauma and perioperative stress responses are associated with increases in proinflammatory cytokines, inflammatory factors (7) and stress hormones (8). These might promote the growth of residual tumor cells and increase the vulnerability to cancer recurrence by inducing transient suppression of cell-mediated immunity (9) and by releasing proangiogenic factors such as vascular endothelial growth factor (VEGF) (10). On the other hand, the changes of tumor microenvironment caused by anesthetic drugs is also an area of particular concern (11). Till now, it's still unclear whether anesthetic drugs may exert positive or negative effect on cancer outcomes (12). Propofol and sevoflurane are respectively the most commonly used intravenous and inhaled anesthetics. These two anesthetics have different effects on tumor cells and immune function (13). Which one contributes to the postoperative recurrence and metastasis vulnerability has received increasing attentions (14–16).

This review aimed to compare the effects of propofol versus sevoflurane on immune system, breast cancer cells and patient long-term outcomes observed from pre-clinical studies and clinical studies. We searched PubMed database with search terms ("propofol" or "sevoflurane") and ("breast cancer" or "breast tumor") on Sept. 30, 2021 to obtain the literatures in this review, and only the articles written in English were included.

IMMUNE PATHOGENESIS OF TUMORIGENESIS

The innate and adaptive immune system are vital to the body's surveillance against cancer. The complex processes of cancer cell invasion and metastasis are involved in the "elimination" phase, "equilibrium" state and "escape" phase. During the "elimination" phase, the natural killer (NK) cells, $CD4^+$Th1, $CD8^+$CTL (cytotoxic T lymphocyte), and cytokines including tumor necrosis factor-α (TNF-α), interferon-α, interferon-β, interferon-γ and interleukin-12(IL-12) are the primary factors to recognize and eliminate cancer cells (17). If the cancer cells have escaped elimination and entered into "equilibrium" state, the adaptive immune response began to play a key role in preventing cancer cells from further growth. When the cancer cells enter into the final "escape" phase, the immune control of the host is usually insufficient to inhibit the growth of tumor cells, leading to apparent growth ultimately.

In addition to the host's anti-tumor immunity, tumor cells also produce mediators that fight against host immunity in order to promote their own growth. The cytokines such as VEGF and transforming growth factor-β (TGF-β) which are produced by tumor cells can induce immunosuppressive effects (18, 19). Some inflammatory factors and proinflammatory cytokines including interleukin-6 (IL-6), IL-1β, and prostaglandin E2 (PGE-2) also promote tumor growth. The effects of sevoflurane and propofol on postoperative inflammatory cytokine release were compared in patients undergoing other major surgeries (20, 21), but not in those undergoing breast cancer surgeries so far. Furthermore, regulator T cells, tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs) recruited by cancer cells also favor tumor progression (22). Propofol attenuated the decrease in CD39 and CD73 in circulating CD4+ T cells compared to sevoflurane-based anesthesia in patients undergoing open heart surgeries (23), while similar comparative studies have not been reported in breast cancer patients despite that circulating regulatory T cells has been recently reported to be significantly increased in breast cancer patients which may impact on the stage and histological type of breast cancer (24). The possible mechanisms of propofol and sevoflurane on anticancer immunity, breast cancer cell proliferation, migration and apoptosis are summarized in **Figures 1** and **2**.

EFFECTS OF SEVOFLURANE AND PROPOFOL ON CANCER IMMUNE SYSTEM

Sevoflurane is the most popular volatile anesthetics due to the advantages of fast induction, small respiratory tract stimulation, fast absorption and clearance, less circulation disturbance. Propofol, a kind of alkyl acid short acting anesthetics, is the most commonly used intravenous anesthetic. Laboratory researches have shown that propofol-based intravenous anesthesia and sevoflurane-based inhalation anesthesia may have different effects on breast cancer immune microenvironment.

NK cells, $CD8^+$ CTL and $CD4^+$ Th1 cells are the important weapons to fight against cancer cells (22). By contrary, MDSCs, tumor-associated macrophages and $CD4^+$ Th2 cells promote tumor formation and growth by inhibiting the anti-cancer immune response. Ample evidences support that propofol can enhance anti-tumor immunity by increasing the activity of anti-tumor immune cells. NK cells, a subpopulation of large granular lymphocytes, play an important role in anti-tumor immunity due to direct recognition and lysis of cancer cells (25, 26). Reduction in NK cell numbers and activities make the host prone to promote tumor formation or tumor metastasis (27, 28). Melamed et al. compared the effects of different anesthetics on NK cell activity and tumor metastasis. They found that ketamine, thiopental and halothane but not propofol significantly reduced NK cell activity

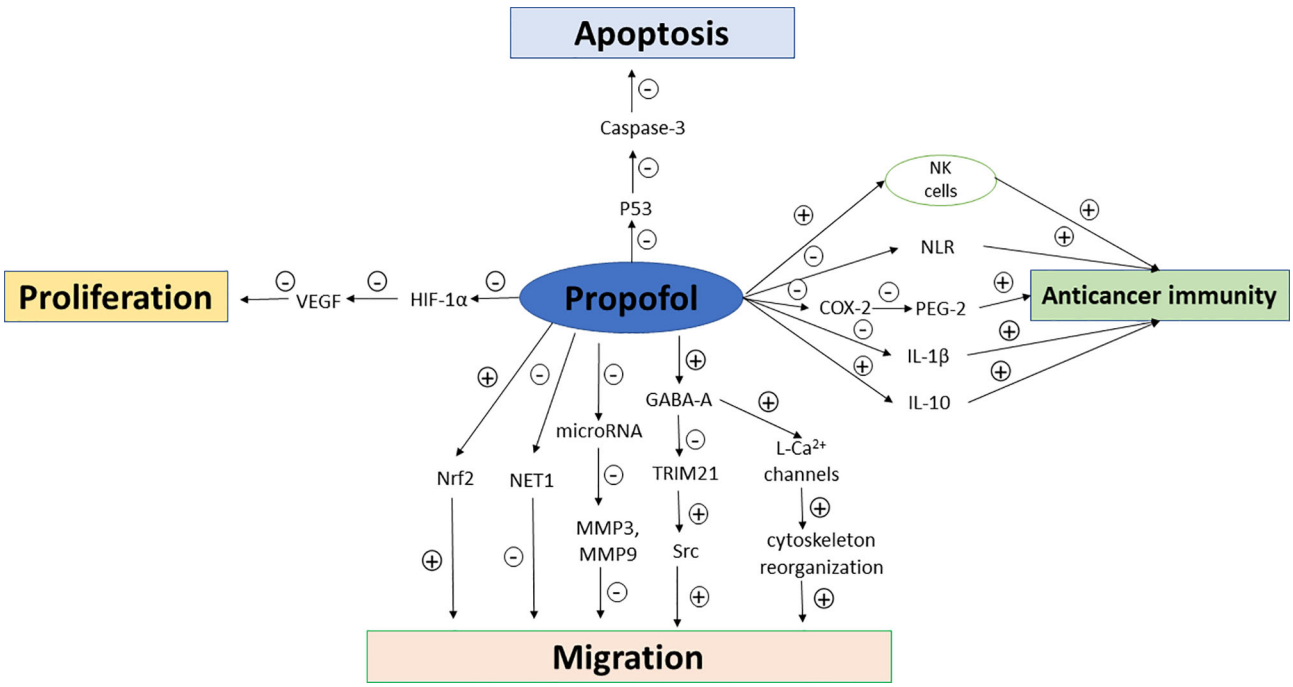

FIGURE 1 | Mechanisms of propofol on anticancer immunity, breast cancer cell proliferation, migration and apoptosis. NK cells, natural killer cells; NLR, neutrophil–lymphocyte ratio; COX-2, cyclooxygenase-2; VEGF, vascular endothelial growth factor; PEG-2, prostaglandin E2; GABA, gamma aminobutyric acid; MMP, Matrix metalloproteinases; HIF-1α, hypoxia inducible factor-1α; TRIM21, tripartite motif 21; Src, non-receptor tyrosine kinase; Nrf2, nuclear factor E2-related factor-2.

and promoted MADB106 breast cancer cell metastases (29). Inada and colleagues demonstrated that propofol increased the production of interferon-gamma (IFN-γ) *via* activating NK cells subsequent to the suppression of thioglycollate-elicited murine peritoneal macrophages (30). And, this team further found that the aforementioned effect of propofol was achieved through inhibiting cyclo-oxygenase activity in human monocytic cell line THP-1 (31). A pilot study from Ireland collected the serum from patients who received propofol-paravertebral block (PPA) or sevoflurane-opioid anesthetic techniques, and co-cultured the serum with breast cancer cells (32). This study showed that the cytotoxicity of NK cells and breast cancer cells apoptosis increased in the serum from patients who received PPA anesthesia technique. The same research team investigated the effect of PPA *vs.* sevoflurane-opioid analgesia on immune cell infiltration in breast cancer tissue, and they also found increased levels of NK cells and T helper cell infiltration into breast cancer tissue in the PPA group (33). A prospective randomized study assigned breast cancer patients to receive propofol anesthesia with ketorolac analgesia and sevoflurane anesthesia with fentanyl analgesia, and the results showed that NK cell cytotoxicity was increased in propofol with ketorolac group, but decreased in the sevoflurane with fentanyl group (34). On the other hand, an *in vitro* study showed that there was no difference in NK cell count, cytotoxic T lymphocyte counts and breast cancer cell apoptosis rate between propofol and sevoflurane groups (35).

Both increased inflammation and reduced cell-mediated immunity contribute to an increase in neutrophil–lymphocyte ratio (NLR) (36). Increased NLR and platelet–lymphocyte ratio (PLR) are related to increased risk of breast cancer recurrence and metastasis (37, 38). Eochagáin et al. performed a subgroup analysis of a randomized study, they found that propofol-paravertebral anesthesia during breast cancer surgery was associated with less increase of NLR when compared with sevoflurane-opioid anesthesia (39). Cluster of differentiation (CD) enzymes on regulatory T cells have immunosuppressive effects. CD39 and CD73 on regulatory T cells have been confirmed to play important roles in promoting cancer recurrence and metastasis due to the impairment of the activities of NK cells and CTL (40, 41). A randomized trail compared the differences between propofol and sevoflurane in CD39 and CD73 expression on regulatory T cells. This study found that there was no difference in the expression of CD39 and CD73 between propofol and sevoflurane anesthesia groups at 1 and 24 hours postoperatively (42). MDSCs play a key role in immune suppression, tumor angiogenesis and tumor metastases in cancer patients (43). MDSC consists of polymorphonuclear MDSC (PMN-MDSC) and monocytic MDSC (M-MDSC). PMN-MDSC are morphologically and phenotypically similar to neutrophils while M-MDSC are similar to monocytes morphologically (44). Yan et al. compared the MDSC expression in breast cancer patients who received sevoflurane-based anesthesia or propofol-based anesthesia. They found that there was no significant difference in MDSC expression between these two groups, whereas MDSC expression and the subtype of MDSC were correlated to tumor stages (45). Most studies have

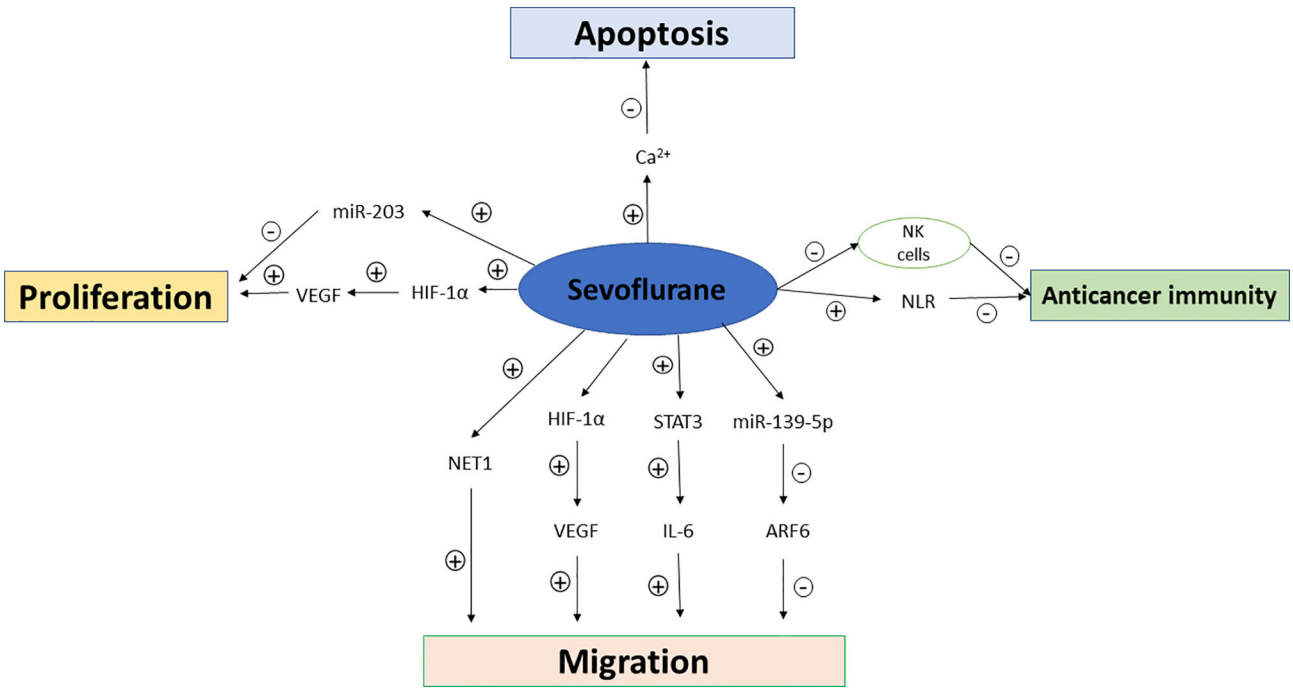

FIGURE 2 | Mechanisms of sevoflurane on anticancer immunity, breast cancer cell proliferation, migration and apoptosis. NK cells, natural killer cells; NLR, neutrophil–lymphocyte ratio; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia inducible factor-1α; NET1, Neuroepithelial Cell Transforming Gene; STAT3, signal transducer and activator of transcription 3; ARF6, ADP-ribosylation factor 6.

shown that propofol anesthesia increased NK cells cytotoxicity, NLR and PLR as compared with sevoflurane. However, a few studies showed no difference in in between propofol and sevoflurane anesthesia regarding the impacts on T lymphocyte cytotoxicity and MDSC expression.

EFFECTS OF SEVOFLURANE AND PROPOFOL ON FUNCTIONS OF BREAST CANCER CELLS

Breast cancer cells have about 21 diverse histological subtypes. According to different presences of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), the diverse subtypes are stratified into four major molecular subtypes namely triple negative breast cancer cell, HER2 overexpressing breast cancer cell, Luminal A breast cancer cell and Luminal B breast cancer cell. Triple negative breast cancer cell is ER-/PR-/HER2-; HER2 overexpressing breast cancer cell is ER-/PR-/HER2+; Luminal B breast cancer cell is ER+ and/or PR+/HER2+; Luminal A breast cancer cell is ER+ and/or PR+/HER2-. In recent years, the potential impact of different general anesthetics on tumor prognosis has garnered particular attention. Different breast cancer cell lines were cultured *in vitro* to investigate the effect of anesthetics on breast cancer cell proliferation, migration and apoptosis (46).

An *in vitro* study investigated the effect of sevoflurane on breast cancer cell proliferation, migration and invasion (47). In this study, MDA-MB-231 ER– and MCF7 ER+ breast cancer cells were incubated with sevoflurane at different concentrations. It was found that sevoflurane increased the proliferation and migration in both breast cancer cell lines, however, the increased invasion was only observed in ER+ cells. In another *in vitro* study, the authors co-cultured MDA-MB-231 ER- cell with the serum from patients who received either PPA or sevoflurane-opioid anesthetic techniques. The authors found that the proliferation of cancer cells was reduced in PPA group compared with sevoflurane-opioid group, while there was no significant difference in migration between two groups (48). Apoptosis of tumor cells is also an important factor that affects breast cancer recurrence and metastasis. A study showed that the apoptosis rate of MDA-MB-231 ER– cells was higher in cells exposed to human serum from patients who received PPA than in cells exposed to human serum from patients who received sevoflurane-opioid anesthesia (49).

Activation of specific gene during the perioperative period may accelerate tumor recurrence and metastasis. Neuroepithelial Cell Transforming Gene 1(NET1) has been identified to have the property of promoting tumor cells migration (50), and has been used as potential prognostic marker for patients (51). An *in vitro* study showed that sevoflurane treatments increased the NET1 gene expression in metastatic canine tubular adenocarcinoma cells at the concentration of 4mM (52). Patricija et al.

demonstrated that propofol reduced both MCE7 ER+ and MDA-MB-231 ER-breast cancer cell migration by the down-regulation of NET1 expression (53). In addition, hypoxia inducible factor-1α (HIF-1α) is a key regulator in hypoxia inducing tumor growth. HIF-1αinduces the secretion of angiogenic factors such as VEGF and angiogenic 2 (54, 55). Therefore, up-regulated expression of HIF-1α has been shown to augment tumor angiogenesis, promote tumor cell proliferation (56) and has been associated with poor prognosis. A recent study also demonstrated that HIF-1α signaling selectively enhanced breast cancer cell proliferation in the brain (57). HIF-1 also plays an important role in breast cancer cell metastasis by regulating multiple key steps of metastasis, such as epithelial-mesenchymal transition, metastatic niche formation, invasion, and extravasation (58). An experimental study showed that 2 mM sevoflurane exposure 72h increased the viability, proliferation and aggressive of triple negative breast cancer and increased HIF-1 expression (59). There are few researches investigating the effect of propofol on HIF-1αin breast cancer cells. However, propofol has been identified to inhibit HIF-1αactivation induced by hypoxia in prostate cancer which may shed light to the mechanism of propofol in breast cancer (60).

EFFECTS OF SEVOFLURANE AND PROPOFOL ON MICROENVIRONMENTS OF BREAST CANCER CELLS

Matrix metalloproteinases (MMPs) provide a favorable microenvironment for tumorigenesis by digesting extracellular matrix components. MMPs also release pro-cancer factors from the extracellular matrix to promote tumor cell migration (61). The levels of MMPs were higher in cancer patients (62, 63). Patients undergoing primary breast cancer surgery who received propofol/paravertebral anesthesia had less elevated MMP-3 and MMP-9 as compared with those who received sevoflurane based anesthesia during primary breast cancer surgery (64). At the same time, propofol has been demonstrated to significantly decrease IL-1β, but significantly increase IL-10 postoperatively as compared with sevoflurane (64). Conversely, sevoflurane has been reported to lead to more lung metastasis with higher level of serum IL-6 *via* activating STAT3 and infiltrating CD11b+ cells as compared to propofol (65). General anesthetics may also influence tumor cells by changing angiogenic factor. VEGF and TGF-β are secreted by tumor cells to help themselves grow and metastasize (66, 67). A prospective randomized study allocated breast cancer patients to sevoflurane group and propofol group respectively, and this study showed that serum VEGF concentrations were significantly higher after surgery in the sevoflurane group than in the propofol group, however, the serum VEGF concentrations kept unchanged in propofol group, and the concentrations of TGF-β did not significantly differ between sevoflurane and propofol groups both before and after surgery (68).

Ca^{2+}, a kind of second messenger, plays a key role in numerous cellular processes including cell proliferation and apoptosis (69). Abnormal Ca^{2+} signaling pathways and Ca^{2+} transport proteins are associated with breast tumor tumorigenesis (70). A study investigated the effects of sevoflurane versus propofol on three kinds of breast cells and Ca^{2+} homeostasis. This study showed that sevoflurane at the concentration of 2% for 6 hours duration increased the survival of both ER- and ER+ breast cancer cells *in vitro* and chelation of cytosolic Ca^{2+} significantly decreased the survival of breast cancer cells (71). Therefore, it can be inferred that breast cancer cells need more cytoplasmic Ca^{2+} for survival, and sevoflurane may increase breast cancer cells survival *via* modulating intracellular Ca^{2+} homeostasis. Indeed, in a mouse model of breast cancer (72), regulation of the microRNA-129-1-3p-mediated calcium signaling pathway has been shown to restrain the growth of breast cancer cells. MicroRNAs are noncoding RNA molecules which participate in post-transcriptional gene regulation. There are more than 1500 miRNA molecules in human body, and miRNAs play critical roles in various cell biology (73, 74). Variations of miRNA expression may affect cancer cell activity and lead to tumor recurrence and metastasis (75, 76). Studies have reported that sevoflurane suppresses breast cancer cell proliferation by upregulating miR-203 (77). Sevoflurane suppressed the invasion, migration, and epithelial-mesenchymal transition of breast cancer cells through downregulating the abundance of ARF6 by upregulating miR-139-5p (78). Propofol has also been reported to affect miRNA and reduce matrix metalloproteinase expression to change anti-cancer microenvironment (79).

It should be noted that there are also studies which showed that propofol had pro-tumor effects in breast cancer. Garib et al. observed that the percentage of MDA-MB-468 cells migration, the velocity and distance of migration were increased in a dose-dependent manner when the breast cancer cells were incubated with various concentrations of propofol (80). They further confirmed that propofol increased breast cancer cell migration through activating gamma aminobutyric acid A (GABA-A) receptor (81), and the process was mediated by increased intracellular calcium *via* L-type calcium channels and the actin cytoskeleton reorganization (81). In another *in vitro* study, MDA-MB-231 cells were treated with propofol at 2-10 ug/ml for 1-12 hours (82). The authors also found that propofol increased breast cancer cells proliferation and migration in a dose- and time-dependent manner. The authors further found that the increased proliferation may be mediated through downregulation of p53 protein, while the promotion of migration may be mediated *via* the activation of the Nrf2 pathway (82). A recent study also demonstrated that propofol promoted tumor metastasis by activating GABA-A receptor, downregulating TRIM21 expression, and upregulating Src (a protein associated with cell adhesion) expression (83). It should be noted that there may be several factors resulting in the inconsistent effects of propofol on breast cancer cells. First of all, different breast cancer cells with different biological characteristics may contribute to the discrepancy. Secondly, the concentration and duration of propofol exposure were variant in different researches.

LONG-TERM PROGNOSIS OF PATIENTS

The effects of anesthetics on tumor immune microenvironment and tumor cells have been documented in well-designed laboratory and animal studies. However, the results of pre-clinical studies should be interpreted with caution. The clinical studies in human are also needed to investigate the association between anesthetics and long-term cancer outcome.

RETROSPECTIVE STUDIES

The currently available retrospective studies comparing propofol with inhalation anesthetics on long-term prognosis of breast cancer surgery were summarized in **Table 1**. The first one was published in 2014 by Enlund and colleagues (84). The data in this study was from a single hospital of Sweden between January 1998 to 31 March 2010. This study reviewed 1837 breast cancer patients with 620 patients in propofol group and 1217 patients in sevoflurane group. The 1-year survival rate were 99% in propofol group and 96% in sevoflurane group respectively, and the difference was 3% ($p<0.001$). However, the difference of 5-year survival rate between these two groups was 2% (84% in propofol group *versus* 82% in sevoflurane group) with no statistical significance. Then, a retrospective study from Korea compared the recurrence-free survival and overall survival between propofol and sevoflurane groups in patients after modified radical mastectomy (85). This study included 325 cases with 173 patients in propofol group and 152 patients in sevoflurane group. The 5-year survival rate was comparable between the two groups. However, there was a lower cancer recurrence rate in propofol group ($p=0.037$), and the hazard ratio of recurrence was 0.55. A larger sample size retrospective cohort study from the United Kingdom enrolled 11395 patients undergoing mixed cancer surgery. After propensity score matching, authors found that the mortality rate was 24% in inhalation anesthetics group, which was higher than the mortality rate of 13.6% in propofol group (86). However, this study included multiple tumor surgeries and they did not analyze breast cancer individually. Four systematic reviews and meta-analyses also showed that propofol-based intravenous anesthesia was associated with improved overall survival and recurrence-free survival than volatile anesthesia in all cancer types (91–94). Another two studies from Korea also demonstrated that the effects of total intravenous anesthesia on 5-year overall survival and recurrence-free survival of breast cancer was comparable to that of volatile inhaled anesthesia (87, 88). Similar results were also demonstrated in another 3 retrospective cohort studies from Taiwan (95), Korea (5) and Japan (90). However, a research from Sweden had different results when different statistical adjustment methods were used (89). The overall 5-year survival rate of breast cancer in propofol group was statistically significantly higher

TABLE 1 | Retrospective clinical studies comparing effects of propofol versus sevoflurane on long-term prognosis of breast cancer.

Country	Cancer	Anesthetic Technique	Number of patients	Evaluations	Outcomes
Swden, 2014 (84)	Breast cancer	Propofol vs. sevoflurane	1837(620 vs. 1217)	1-year and 5-year survival rate	1 year-survival rate: propofol was superior to sevoflurane; 5-year survival rate: no difference
Korea, 2016 (85)	Breast cancer	Propofol vs. sevoflurane	325 (173 vs. 152)	5 year-recurrence-free survival and overall survival	5 year-recurrence-free survival: propofol was superior to sevoflurane; 5 year-overall survival: no difference
UK, 2015 (86)	Mixed cancer	Total intravenous anesthesia (TIVA) vs. volatile inhalational anesthesia (INHA)	7030 (3714 vs. 3316) (2607 in each group after PS matching)	1-yr survival rate and overall mortality rate	TIVA was superior to INHA
Korea, 2017 (87)	Breast cancer	Propofol vs. inhalation anesthetics (sevoflurane, desflurane, isoflurane and enflurane)	2645(56 vs. 2589)	70-monthes recurrence-free survival rate and overall survival rate	Propofol is comparable with volatile agents
Korea, 2019 (88)	Mixed cancer	total intravenous anesthesia (TIVA) vs. volatile inhaled anesthesia (VIA)	729 in each group after PS matching	5-year survival rate	No difference
Korea, 2019 (5)	Breast cancer	IV anesthesia and inhalation anesthesia	7678(3085 vs. 2246); 1766 in each group after PS matching	5-yr recurrence-free survival rates and overall survival	No difference
Sweden, 2020 (89)	Breast cancer	Propofol vs. sevoflurane	6035 (3296 vs. 3209)	1-year survival 5-year survival	Inconsistent conclusions: propofol had higher survival rate without adjusting confounders; No difference in survival by using PS matching; propofol had higher survival rates when adding centers in the PS matching
Japan, 2020 (90)	breast cancer	Propofol vs. sevoflurane	1026(814 vs. 212)	1–year recurrence –free survival	No difference

than that in the sevoflurane group when statistical adjustments were not applied. However, the 1-year and 5-year survival rates were similar when assessed using propensity score matching. Interestingly, the overall survival in propofol group was again significantly higher after adding study centers in the propensity score matching (89).

Despite of large sample size, the inherent defect of retrospective clinical study may contribute to the paradoxical conclusions so far reached. Retrospective studies did not randomize patients to ensure comparable baseline data across groups. In other words, the confounding factors and selection bias are difficult to be controlled in retrospective studies. Furthermore, it is hard to adjust the imbalance between groups in small sample size retrospective studies, for example only 325 patients were included in one study (85). The results from national register-based studies are more accurate due to larger sample size, better precision and the possibility to adjust for more confounders. However, the two recently reported register-based studies from Japan and Denmark compared the difference between propofol and inhalation anesthetics in digestive system neoplasm but not in breast cancer (96, 97). Extremely uneven distribution of population between study groups may also lead to inaccurate results. In a study reported by Kim and colleagues, only 56 patients were included in the propofol group while 2326 patients in inhalation anesthetics group (87). There was only one study that considered the confounding effects of breast cancer subtypes (5), and others ignored the fact that different tumor subtypes may have different responses to anesthetics.

RANDOMIZED CONTROLLED STUDIES

In order to avoid the shortcomings of retrospective studies and to obtain a more precise causal relationship between general anesthetics and breast cancer outcomes, prospective randomized controlled trials (RCTs) are badly needed. **Table 2** summarized the current RCTs comparing the effects of propofol and sevoflurane on long-term prognosis of breast cancer. A small sample prospective randomized study, conducted in Korea, randomly assigned fifty patients scheduled to receive breast cancer surgery to propofol group and sevoflurane group (34). In this study, the authors evaluated 2 years-recurrence or metastasis. Due to small population, no metastasis was found and only one patient in sevoflurane group had recurrence. Another prospective, randomized and controlled study was conducted in China, which compared the effect of propofol versus sevoflurane on recurrence- free survival rates in 80 breast cancer patients. In this study, the 2-year recurrence- free survival rates had no significant difference between the two groups with 95% in propofol group and 78% in sevoflurane group (p=0.221) (68). Although there was 17% absolute difference, there was no significant difference between these two groups due to relative small sample size. On the basis of their retrospective studies, Enlund et al. designed a RCT to explore the effect of propofol- or sevoflurane- based anesthesia on breast and colorectal cancer (100). The results of 5-year follow up are expected in late 2022. A largest international multi-center RCT to date allocated 2132 breast cancer patients respectively to paravertebral blocks combined propofol group and sevoflurane group. This study showed identical recurrences rate of 10% in either of the two groups, with 3 years median follow-up time (98). However, it is hard to separate the effects of propofol vs. sevoflurane and paravertebral block vs. opioids in the study. Therefore, this study did not conclude propofol or loco-regional anesthesia may impact on cancer outcomes (101). A recent interesting RCT explored the effects of different anesthetics on circulating tumor cells after breast cancer surgery (99). Circulating tumor cells are crucial for tumor metastasis and recurrence (102, 103), and has been confirmed as a promising indicator for prognosis (104). In this study, authors used this indicator to overcome the difficulty of long term follow-up. This study enrolled 210 breast cancer patients in total with 107 patients allocated to sevoflurane anesthesia and 103 patients allocated to propofol anesthesia. The authors found that the median circulating tumor cell counts were similar at 48 hours and 72 hours after surgery between the two groups (99). This study did not compare long-term outcomes of patients, but alternatively examined the effects of propofol and sevoflurane

TABLE 2 | Randomized controlled trials comparing effects of propofol versus sevoflurane on long-term prognosis of breast cancer.

Country	Cancer	Anesthetic Technique	Number of patients	Evaluations	Outcomes
Korea, 2017 (34)	Breast Cancer	propofol-remifentanil anesthesia and sevoflurane-remifentanil anesthesia	24 patients in each group	NK cell cytotoxicity (NKCC) and 2-year recurrence or metastasis	Propofol anesthesia preserved NKCC; There was no difference in 2-year recurrence or metastasis
China, 2018 (68)	Breast cancer	propofol-remifentanil anesthesia and sevoflurane-remifentanil anesthesia	40 patients in each group	The serum concentrations of VEGF-C and TGF-β before and 24 h after surgery; 2-year recurrence- free survival rate	Sevoflurane increased serum VEGF-C concentrations surgery; There was no difference in 2-year recurrence- free survival rate
International Multi-center, 2019 (98)	Breast cancer	paravertebral blocks combined propofol and sevoflurane with opioid	1043 in paravertebral blocks combined propofol group,1065 in sevoflurane with opioid group	recurrences rate with 36 months median follow-up; Incisional pain at 6 months and 12 months after surgery	The recurrences rate and incisional pain were all comparable between these two groups
Switzerland, 2020 (99)	Primary Breast Cancer	Propofol and sevoflurane anesthesia	103 in propofol and 107 in sevoflurane group	Circulating tumor cell counts at three time points postoperatively (0, 48, and 72 h)	there was no difference between these two groups with respect to circulating tumor cell counts

on circulating tumor cell counts, and suggested that these two anesthetics may have similar effect on long-term outcomes of patients with primary breast cancer.

Other anesthetic drugs and anesthetic techniques are also of concern in breast cancer surgery. Due to the analgesic properties, opioids are widely used during breast cancer surgery. Some laboratory studies showed that opioids inhibit cell-mediated immunity (105), reduce lymphocyte and macrophage proliferation (106), and drive breast cancer metastasis (107). However, the association between opioid-based anesthesia and breast cancer recurrence is inconclusive till now (108). Interestingly, a recent retrospective study with 1143 triple-negative breast cancer (TNBC) cases demonstrated that intraoperative opioids improved the recurrence-free survival of TNBC (109). Local anesthetics have been shown to have the modulatory effects on the immune and inflammatory response, and have antitumor effects, it was hypothesized that regional anesthesia may improve the prognosis of breast cancer. However, there is no high quality clinical evidence to verify these beneficial effects (110). Two studies compared thoracic paravertebral blockade (PVB) with ropivacaine and sham block, in which no difference in breast cancer recurrence rates was found (111, 112).

CONCLUSION

Overall, pre-clinical studies and retrospective clinical studies comparing the potential benefits of intravenous propofol over inhalational anesthetics for breast cancer lack consistency. A few current randomized controlled studies suggest that the two anesthetics have similar effects on breast cancer recurrence and metastasis. However, a definite conclusion regarding which anesthetic may have more favorable long-term effects on breast cancer recurrence and metastasis cannot be reached largely due to the lack of multicenter or multi-countries large sample clinical trials.

FUTURE RESEARCH DIRECTIONS

So far, the effect of different anesthetics or anesthesia techniques on the prognosis of postoperative breast cancer has not been determined. Further investigations should be implemented to explore the mechanisms of anesthetics on breast cancer cells and immune microenvironment. Meanwhile, large sample, multi-center prospective clinical study involving different subtype of breast cancer, different tumor staging should also be conducted. Only a clear understanding of the relationship between anesthetics and breast cancer can improve the prognosis of patients from the perspective of anesthesiologists.

AUTHOR CONTRIBUTIONS

YL and PF had the original idea of the manuscript. PF, JZ, and YL reviewed the literature and drafted the article. ZX and XL revised manuscript and provided suggestions for improvement. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68 (6):394–424. doi: 10.3322/caac.21492
2. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer Treatment and Survivorship Statistics, 2014. *CA Cancer J Clin* (2014) 64(4):252–71. doi: 10.3322/caac.21235
3. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence After Stopping Endocrine Therapy at 5 Years. *N Engl J Med* (2017) 377(19):1836–46. doi: 10.1056/NEJMoa 1701830
4. Chen CS, Liu TC, Lin HC, Lien YC. Does High Surgeon and Hospital Surgical Volume Raise the Five-Year Survival Rate for Breast Cancer? A Population-Based Study. *Breast Cancer Res Treat* (2008) 110(2):349–56. doi: 10.1007/s10549-007-9715-4
5. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, et al. Total Intravenous Anesthesia Versus Inhalation Anesthesia for Breast Cancer Surgery: A Retrospective Cohort Study. *Anesthesiology* (2019) 130(1):31–40. doi: 10.1097/ALN.0000000000002491
6. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative Events Influence Cancer Recurrence Risk After Surgery. *Nat Rev Clin Oncol* (2018) 15(4):205–18. doi: 10.1038/nrclinonc.2017.194
7. Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, et al. Increased Surgical Stress Promotes Tumor Metastasis. *Surgery* (2003) 133 (5):547–55. doi: 10.1067/msy.2003.141
8. Ben-Eliyahu S, Goldfarb Y. Surgery as a Risk Factor for Breast Cancer Recurrence and Metastasis: Mediating Mechanisms and Clinical Prophylactic Approaches. *Breast Dis* (2006) 26:99–114. doi: 10.3233/bd-2007-26109
9. Smyth MJ, Godfrey DI, Trapani JA. A Fresh Look at Tumor Immunosurveillance and Immunotherapy. *Nat Immunol* (2001) 2(4):293–9. doi: 10.1038/86297
10. Duff S, Connolly C, Buggy DJ. Adrenergic, Inflammatory, and Immune Function in the Setting of Oncological Surgery: Their Effects on Cancer Progression and the Role of the Anesthetic Technique in Their Modulation. *Int Anesthesiol Clin* (2016) 54(4):48–57. doi: 10.1097/AIA.0000000 000000120
11. Shapiro J, Jersky J, Katzav S, Feldman M, Segal S. Anesthetic Drugs Accelerate the Progression of Postoperative Metastases of Mouse Tumors. *J Clin Invest* (1981) 68(3):678–85. doi: 10.1172/jci110303

12. Enlund M. Is It Definitely Clear That Long-Term Survival After Breast Cancer Surgery Is Not Affected by Anaesthetics? *Cancers (Basel)* (2021) 13 (14):3390. doi: 10.3390/cancers13143390
13. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression. *Anesth Analg* (2017) 124(5):1697–708. doi: 10.1213/ane.0000000000001652
14. Dubowitz JA, Sloan EK, Riedel BJ. Implicating Anaesthesia and the Perioperative Period in Cancer Recurrence and Metastasis. *Clin Exp Metastasis* (2017) 35(4):347–58. doi: 10.1007/s10585-017-9862-x
15. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic Techniques for Risk of Malignant Tumour Recurrence. *Cochrane Database Syst Rev* (2014) 11):CD008877. doi: 10.1002/14651858.CD008877.pub2
16. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer Recurrence After Surgery: Direct and Indirect Effects of Anesthetic Agents. *Int J Cancer* (2012) 130(6):1237–50. doi: 10.1002/ijc.26448
17. Schreiber RD, Old LJ, Smyth MJ. Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion. *Science* (2011) 331(6024):1565–70. doi: 10.1126/science.1203486
18. Jaszai J, Schmidt MHH. Trends and Challenges in Tumor Anti-Angiogenic Therapies. *Cells* (2019) 8(9):1102. doi: 10.3390/cells8091102
19. Derynck R, Turley SJ, Akhurst RJ. TGFbeta Biology in Cancer Progression and Immunotherapy. *Nat Rev Clin Oncol* (2021) 18(1):9–34. doi: 10.1038/s41571-020-0403-1
20. Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X. Postoperative Cognitive Dysfunction After Inhalational Anesthesia in Elderly Patients Undergoing Major Surgery: The Influence of Anesthetic Technique, Cerebral Injury and Systemic Inflammation. *BMC Anesthesiol* (2015) 15:154. doi: 10.1186/s12871-015-0130-9
21. Potocnik I, Novak Jankovic V, Sostaric M, Jerin A, Stupnik T, Skitek M, et al. Antiinflammatory Effect of Sevoflurane in Open Lung Surgery With One-Lung Ventilation. *Croat Med J* (2014) 55(6):628–37. doi: 10.3325/cmj.2014.55.628
22. Kurosawa S. Anesthesia in Patients With Cancer Disorders. *Curr Opin Anaesthesiol* (2012) 25(3):376–84. doi: 10.1097/ACO.0b013e328352b4a8
23. Oh CS, Kim K, Kang WS, Woo NS, Kang PS, Kim JS, et al. Comparison of the Expression of Cluster of Differentiation (CD)39 and CD73 Between Propofol- and Sevoflurane-Based Anaesthesia During Open Heart Surgery. *Sci Rep* (2018) 8(1):10197. doi: 10.1038/s41598-018-28505-8
24. Miao X, Guo Q, Pan Z, Xu X, Shao X, Wang X. The Characteristics and Novel Clinical Implications of CD4+CXCR5+Foxp3+ Follicular Regulatory T Cells in Breast Cancer. *Ann Transl Med* (2021) 9(16):1332. doi: 10.21037/atm-21-3848
25. Snyder GL, Greenberg S. Effect of Anaesthetic Technique and Other Perioperative Factors on Cancer Recurrence. *Br J Anaesth* (2010) 105 (2):106–15. doi: 10.1093/bja/aeq164
26. Chiossone L, Dumas PY, Vienne M, Vivier E. Natural Killer Cells and Other Innate Lymphoid Cells in Cancer. *Nat Rev Immunol* (2018) 18(11):671–88. doi: 10.1038/s41577-018-0061-z
27. Ash SA, Buggy DJ. Does Regional Anaesthesia and Analgesia or Opioid Analgesia Influence Recurrence After Primary Cancer Surgery? An Update of Available Evidence. *Best Pract Res Clin Anaesthesiol* (2013) 27(4):441–56. doi: 10.1016/j.bpa.2013.10.005
28. Huntington ND, Cursons J, Rautela J. The Cancer-Natural Killer Cell Immunity Cycle. *Nat Rev Cancer* (2020) 20(8):437–54. doi: 10.1038/s41568-020-0272-z
29. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, But Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth Analg* (2003) 97(5):1331–9. doi: 10.1213/01.ane.0000082995.44040.07
30. Inada T, Kubo K, Shingu K. Promotion of Interferon-Gamma Production by Natural Killer Cells *via* Suppression of Murine Peritoneal Macrophage Prostaglandin E(2) Production Using Intravenous Anesthetic Propofol. *Int Immunopharmacol* (2010) 10(10):1200–8. doi: 10.1016/j.intimp.2010.06.027
31. Inada T, Kubo K, Kambara T, Shingu K. Propofol Inhibits Cyclo-Oxygenase Activity in Human Monocytic THP-1 Cells. *Can J Anaesth* (2009) 56 (3):222–9. doi: 10.1007/s12630-008-9035-0
32. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of Anaesthetic Technique on the Natural Killer Cell Anti-Tumour Activity of Serum From Women Undergoing Breast Cancer Surgery: A Pilot Study. *Br J Anaesth* (2014) 113 Suppl 1:i56–62. doi: 10.1093/bja/aeu200
33. Desmond F, McCormack J, Mulligan N, Stokes M, Buggy DJ. Effect of Anaesthetic Technique on Immune Cell Infiltration in Breast Cancer: A Follow-Up Pilot Analysis of a Prospective, Randomised, Investigator-Masked Study. *Anticancer Res* (2015) 35(3):1311–9.
34. Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *Int J Med Sci* (2017) 14(10):970–6. doi: 10.7150/ijms.20064
35. Lim JA, Oh CS, Yoon TG, Lee JY, Lee SH, Yoo YB, et al. The Effect of Propofol and Sevoflurane on Cancer Cell, Natural Killer Cell, and Cytotoxic T Lymphocyte Function in Patients Undergoing Breast Cancer Surgery: An *In Vitro* Analysis. *BMC Cancer* (2018) 18(1):159. doi: 10.1186/s12885-018-4064-8
36. Lee SK, Choi MY, Bae SY, Lee JH, Lee HC, Kil WH, et al. Immediate Postoperative Inflammation is an Important Prognostic Factor in Breast Cancer. *Oncology* (2015) 88(6):337–44. doi: 10.1159/000368985
37. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, et al. Utility of Pre-Treatment Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio as Prognostic Factors in Breast Cancer. *Br J Cancer* (2015) 113 (1):150–8. doi: 10.1038/bjc.2015.183
38. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The Elevated Preoperative Platelet-to-Lymphocyte Ratio Predicts Poor Prognosis in Breast Cancer Patients. *Br J Cancer* (2014) 110 (10):2524–30. doi: 10.1038/bjc.2014.163
39. Ni Eochagain A, Burns D, Riedel B, Sessler DI, Buggy DJ. The Effect of Anaesthetic Technique During Primary Breast Cancer Surgery on Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Return to Intended Oncological Therapy. *Anaesthesia* (2018) 73(5):603–11. doi: 10.1111/anae.14207
40. Mandapathil M, Szczepanski MJ, Szajnik M, Ren J, Lenzner DE, Jackson EK, et al. Increased Ectonucleotidase Expression and Activity in Regulatory T Cells of Patients With Head and Neck Cancer. *Clin Cancer Res* (2009) 15 (20):6348–57. doi: 10.1158/1078-0432.CCR-09-1143
41. Antonioli L, Pacher P, Vizi ES, Hasko G. CD39 and CD73 in Immunity and Inflammation. *Trends Mol Med* (2013) 19(6):355–67. doi: 10.1016/j.molmed.2013.03.005
42. Oh CS, Lee J, Yoon TG, Seo EH, Park HJ, Piao L, et al. Effect of Equipotent Doses of Propofol Versus Sevoflurane Anesthesia on Regulatory T Cells After Breast Cancer Surgery. *Anesthesiology* (2018) 129(5):921–31. doi: 10.1097/ALN.0000000000002382
43. Gabrilovich DI. Myeloid-Derived Suppressor Cells. *Cancer Immunol Res* (2017) 5(1):3–8. doi: 10.1158/2326-6066.CIR-16-0297
44. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. *Trends Immunol* (2016) 37(3):208–20. doi: 10.1016/j.it.2016.01.004
45. Yan T, Zhang GH, Cheng YZ, Wu LX, Liu XY, Sun YL, et al. Effects of Anesthetic Technique and Surgery on Myeloid-Derived Suppressor Cells and Prognosis in Women Who Underwent Breast Cancer Surgery: A Prospective Study. *Cancer Manag Res* (2019) 11:115513–22. doi: 10.2147/CMAR.S183519
46. Li R, Liu H, Dilger JP, Lin J. Effect of Propofol on Breast Cancer Cell, the Immune System, and Patient Outcome. *BMC Anesthesiol* (2018) 18(1):77. doi: 10.1186/s12871-018-0543-3
47. Ecimovic P, McHugh B, Murray D, Doran P, Buggy DJ. Effects of Sevoflurane on Breast Cancer Cell Function *In Vitro*. *Anticancer Res* (2013) 33(10):4255–60.
48. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of Anaesthetic Technique on Oestrogen Receptor-Negative Breast Cancer Cell Function *In Vitro*. *Br J Anaesth* (2009) 103(5):685–90. doi: 10.1093/bja/aep261
49. Jaura AI, Flood G, Gallagher HC, Buggy DJ. Differential Effects of Serum From Patients Administered Distinct Anaesthetic Techniques on Apoptosis in Breast Cancer Cells *In Vitro*: A Pilot Study. *Br J Anaesth* (2014) 113 Suppl 1:i63–7. doi: 10.1093/bja/aet581
50. Lahiff C, Cotter E, Casey R, Doran P, Pidgeon G, Reynolds J, et al. Expression of Neuroepithelial Transforming Gene 1 is Enhanced in Oesophageal Cancer

and Mediates an Invasive Tumour Cell Phenotype. *J Exp Clin Cancer Res* (2013) 32(1):55. doi: 10.1186/1756-9966-32-55
51. Fang L, Zhu J, Ma Y, Hong C, Xiao S, Jin L. Neuroepithelial Transforming Gene 1 Functions as a Potential Prognostic Marker for Patients With non-Small Cell Lung Cancer. *Mol Med Rep* (2015) 12(5):7439–46. doi: 10.3892/mmr.2015.4385
52. Argano M, De Maria R, Vogl C, Rodlsberger K, Buracco P, Larenza Menzies MP. Canine Mammary Tumour Cells Exposure to Sevoflurane: Effects on Cell Proliferation and Neuroepithelial Transforming Gene 1 Expression. *Vet Anaesth Analg* (2019) 46(3):369–74. doi: 10.1016/j.vaa.2018.12.006
53. Ecimovic P, Murray D, Doran P, Buggy DJ. Propofol and Bupivacaine in Breast Cancer Cell Function *In Vitro* - Role of the NET1 Gene. *Anticancer Res* (2014) 34(3):1321–31.
54. Ban HS, Uno M, Nakamura H. Suppression of Hypoxia-Induced HIF-1alpha Accumulation by VEGFR Inhibitors: Different Profiles of AAL993 Versus SU5416 and KRN633. *Cancer Lett* (2010) 296(1):17–26. doi: 10.1016/j.canlet.2010.03.010
55. Eisinger-Mathason TS, Simon MC. HIF-1alpha Partners With FoxA2, a Neuroendocrine-Specific Transcription Factor, to Promote Tumorigenesis. *Cancer Cell* (2010) 18(1):3–4. doi: 10.1016/j.ccr.2010.06.007
56. Terraneo L, Bianciardi P, Caretti A, Ronchi R, Samaja M. Chronic Systemic Hypoxia Promotes LNCaP Prostate Cancer Growth *In Vivo*. *Prostate* (2010) 70(11):1243–54. doi: 10.1002/pros.21160
57. Ebright RY, Zachariah MA, Micalizzi DS, Wittner BS, Niederhoffer KL, Nieman LT, et al. HIF1A Signaling Selectively Supports Proliferation of Breast Cancer in the Brain. *Nat Commun* (2020) 11(1):6311. doi: 10.1038/s41467-020-20144-w
58. Liu Z-j, Semenza GL, Zhang H-f. Hypoxia-Inducible Factor 1 and Breast Cancer Metastasis. *J Zhejiang Univ Sci B* (2015) 16(1):32–43. doi: 10.1631/jzus.B1400221
59. Tiron CE, Patrascanu E, Postu PA, Vacarean Trandafir IC, Tiron A, Grigoras I. Sevoflurane Modulates AKT Isoforms in Triple Negative Breast Cancer Cells. An Experimental Study. *Curr Issues Mol Biol* (2021) 43(1):264–75. doi: 10.3390/cimb43010022
60. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, et al. Prostate Cancer Cell Malignancy *via* Modulation of HIF-1alpha Pathway With Isoflurane and Propofol Alone and in Combination. *Br J Cancer* (2014) 111(7):1338–49. doi: 10.1038/bjc.2014.426
61. Kessenbrock K, Plaks V, Werb Z. Matrix Metalloproteinases: Regulators of the Tumor Microenvironment. *Cell* (2010) 141(1):52–67. doi: 10.1016/j.cell.2010.03.015
62. Hadler-Olsen E, Winberg JO, Uhlin-Hansen L. Matrix Metalloproteinases in Cancer: Their Value as Diagnostic and Prognostic Markers and Therapeutic Targets. *Tumour Biol* (2013) 34(4):2041–51. doi: 10.1007/s13277-013-0842-8
63. Liang J, Chen M, Hughes D, Chumanevich AA, Altilia S, Kaza V, et al. CDK8 Selectively Promotes the Growth of Colon Cancer Metastases in the Liver by Regulating Gene Expression of TIMP3 and Matrix Metalloproteinases. *Cancer Res* (2018) 78(23):6594–606. doi: 10.1158/0008-5472.CAN-18-1583
64. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic Technique and the Cytokine and Matrix Metalloproteinase Response to Primary Breast Cancer Surgery. *Reg Anesth Pain Med* (2010) 35(6):490–5. doi: 10.1097/AAP.0b013e3181ef4d05
65. Li R, Huang Y, Lin J. Distinct Effects of General Anesthetics on Lung Metastasis Mediated by IL-6/JAK/STAT3 Pathway in Mouse Models. *Nat Commun* (2020) 11(1):642. doi: 10.1038/s41467-019-14065-6
66. Gisterek I, Matkowski R, Lacko A, Sedlaczek P, Szewczyk K, Biecek P, et al. Serum Vascular Endothelial Growth Factors a, C and D in Human Breast Tumors. *Pathol Oncol Res* (2010) 16(3):337–44. doi: 10.1007/s12253-009-9211-8
67. Skobe M, Hawighorst T, Jackson DG, Prevo R, Janes L, Velasco P, et al. Induction of Tumor Lymphangiogenesis by VEGF-C Promotes Breast Cancer Metastasis. *Nat Med* (2001) 7(2):192–8. doi: 10.1038/84643
68. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of Propofol/Remifentanil-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Release of VEGF-C and TGF-Beta and Prognosis After Breast Cancer Surgery: A Prospective, Randomized and Controlled Study. *BMC Anesthesiol* (2018) 18(1):131. doi: 10.1186/s12871-018-0588-3
69. Wu TT, Peters AA, Tan PT, Roberts-Thomson SJ, Monteith GR. Consequences of Activating the Calcium-Permeable Ion Channel TRPV1 in Breast Cancer Cells With Regulated TRPV1 Expression. *Cell Calcium* (2014) 56(2):59–67. doi: 10.1016/j.ceca.2014.04.006
70. So CL, Saunus JM, Roberts-Thomson SJ, Monteith GR. Calcium Signalling and Breast Cancer. *Semin Cell Dev Biol* (2019) 94:74–83. doi: 10.1016/j.semcdb.2018.11.001
71. Deng X, Vipani M, Liang G, Gouda D, Wang B, Wei H. Sevoflurane Modulates Breast Cancer Cell Survival via Modulation of Intracellular Calcium Homeostasis. *BMC Anesthesiol* (2020) 20(1):253. doi: 10.1186/s12871-020-01139-y
72. Li Q, Xu D, Gu Z, Li T, Huang P, Ren L. Rutin Restrains the Growth and Metastasis of Mouse Breast Cancer Cells by Regulating the microRNA-129-1-3p-Mediated Calcium Signaling Pathway. *J Biochem Mol Toxicol* (2021) 35(7):e22794. doi: 10.1002/jbt.22794
73. Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs Modulate Hematopoietic Lineage Differentiation. *Science* (2004) 303(5654):83–6. doi: 10.1126/science.1091903
74. Yi R, Poy MN, Stoffel M, Fuchs E. A Skin microRNA Promotes Differentiation by Repressing 'Stemness'. *Nature* (2008) 452(7184):225–9. doi: 10.1038/nature06642
75. Ishikawa M, Iwasaki M, Sakamoto A, Ma D. Anesthetics may Modulate Cancer Surgical Outcome: A Possible Role of miRNAs Regulation. *BMC Anesthesiol* (2021) 21(1):71. doi: 10.1186/s12871-021-01294-w
76. Calin GA, Croce CM. MicroRNA Signatures in Human Cancers. *Nat Rev Cancer* (2006) 6(11):857–66. doi: 10.1038/nrc1997
77. Liu J, Yang L, Guo X, Jin G, Wang Q, Lv D, et al. Sevoflurane Suppresses Proliferation by Upregulating microRNA-203 in Breast Cancer Cells. *Mol Med Rep* (2018) 18(1):455–60. doi: 10.3892/mmr.2018.8949
78. Wu T, Sun L, Wang C, Yu P, Cheng L, Chen Y. Sevoflurane Suppresses the Migration, Invasion, and Epithelial-Mesenchymal Transition of Breast Cancer Cells Through the miR-139-5p/ARF6 Axis. *J Surg Res* (2021) 258:314–23. doi: 10.1016/j.jss.2020.08.051
79. Li Q, Zhang L, Han Y, Jiang Z, Wang Q. Propofol Reduces MMPs Expression by Inhibiting NF-kappaB Activity in Human MDA-MB-231 Cells. *BioMed Pharmacother* (2012) 66(1):52–6. doi: 10.1016/j.biopha.2011.10.006
80. Garib V, Niggemann B, Zänker KS, Brandt L, Kubens BS. Influence of non-Volatile Anesthetics on the Migration Behavior of the Human Breast Cancer Cell Line MDA-MB-468. *Acta Anaesthesiol Scand* (2002) 46(7):836–44. doi: 10.1034/j.1399-6576.2002.460714.x
81. Garib V, Lang K, Niggemann B, Zänker KS, Brandt L, Dittmar T. Propofol-Induced Calcium Signalling and Actin Reorganization Within Breast Carcinoma Cells. *Eur J Anaesthesiol* (2005) 22(8):609–15. doi: 10.1017/s026502150500102x
82. Meng C, Song L, Wang J, Li D, Liu Y, Cui X. Propofol Induces Proliferation Partially *via* Downregulation of P53 Protein and Promotes Migration *via* Activation of the Nrf2 Pathway in Human Breast Cancer Cell Line MDA-MB-231. *Oncol Rep* (2017) 37(2):841–8. doi: 10.3892/or.2016.5332
83. Liu Q, Sheng Z, Cheng C, Zheng H, Lanuti M, Liu R, et al. Anesthetic Propofol Promotes Tumor Metastasis in Lungs *via* GABAA R-Dependent TRIM21 Modulation of Src Expression. *Adv Sci (Weinh)* (2021) 8(18):e2102079. doi: 10.1002/advs.202102079
84. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The Choice of Anaesthetic–Sevoflurane or Propofol–and Outcome From Cancer Surgery: A Retrospective Analysis. *Ups J Med Sci* (2014) 119(3):251–61. doi: 10.3109/03009734.2014.922649
85. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of Propofol-Based Total Intravenous Anesthesia on Recurrence and Overall Survival in Patients After Modified Radical Mastectomy: A Retrospective Study. *Korean J Anesthesiol* (2016) 69(2):126–32. doi: 10.4097/kjae.2016.69.2.126
86. Wigmore TJ, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/ALN.0000000000000936
87. Myoung H, Kim DWK, Kim JH, Young Lee K, Park S, Chul Yoo Y. Does the Type of Anesthesia Really Affect the Recurrence-Free Survival After Breast Cancer Surgery? *Oncotarget* (2017) 8(52):90477–87. doi: 10.18632/oncotarget.21014

88. Hong B, Lee S, Kim Y, Lee M, Youn AM, Rhim H, et al. Anesthetics and Long-Term Survival After Cancer Surgery—Total Intravenous Versus Volatile Anesthesia: A Retrospective Study. *BMC Anesthesiol* (2019) 19(1) 19(1):233. doi: 10.1186/s12871-019-0914-4
89. Enlund M, Berglund A, Ahlstrand R, Wallden J, Lundberg J, Warnberg F, et al. Survival After Primary Breast Cancer Surgery Following Propofol or Sevoflurane General Anesthesia-A Retrospective, Multicenter, Database Analysis of 6305 Swedish Patients. *Acta Anaesthesiol Scand* (2020) 64 (8):1048–54. doi: 10.1111/aas.13644
90. Shiono S, Shibata SC, Kabata D, Shintani A, Ikeda T, Fujino Y. Comparison of 1-Year Recurrence-Free Survival Between Sevoflurane and Propofol Use for General Anesthesia Management in Primary Breast Cancer Surgery. *J Anesth* (2020) 34(5):694–701. doi: 10.1007/s00540-020-02806-7
91. Chang CY, Wu MY, Chien YJ, Su IM, Wang SC, Kao MC. Anesthesia and Long-Term Oncological Outcomes: A Systematic Review and Meta-Analysis. *Anesth Analg* (2021) 132(3):623–34. doi: 10.1213/ANE.0000000000005237
92. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel BGlobal Onco-Anesthesia Research Collaboration G. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anaesth* (2019) 66(5):546–61. doi: 10.1007/s12630-019-01330-x
93. Soltanizadeh S, Degett TH, Gogenur I. Outcomes of Cancer Surgery After Inhalational and Intravenous Anesthesia: A Systematic Review. *J Clin Anesth* (2017) 42:19–25. doi: 10.1016/j.jclinane.2017.08.001
94. Jin Z, Li R, Liu J, Lin J. Long-Term Prognosis After Cancer Surgery With Inhalational Anesthesia and Total Intravenous Anesthesia: A Systematic Review and Meta-Analysis. *Int J Physiol Pathophysiol Pharmacol* (2019) 11 (3):83–94.
95. Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, et al. Propofol-Based Total Intravenous Anesthesia Did Not Improve Survival Compared to Desflurane Anesthesia in Breast Cancer Surgery. *PLoS One* (2019) 14(11): e0224728. doi: 10.1371/journal.pone.0224728
96. Makito K, Matsui H, Fushimi K, Yasunaga H. Volatile Versus Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery. *Anesthesiology* (2020) 133(4):764–73. doi: 10.1097/ALN.0000000000003440
97. Hasselager RP, Hallas J, Gogenur I. Inhalation or Total Intravenous Anaesthesia and Recurrence After Colorectal Cancer Surgery: A Propensity Score Matched Danish Registry-Based Study. *Br J Anaesth* (2021) 126(5):921–30. doi: 10.1016/j.bja.2020.11.019
98. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/s0140-6736(19)32313-x
99. Hovaguimian F, Braun J, Z'Graggen BR, Schlapfer M, Dumrese C, Ewald C, et al. Anesthesia and Circulating Tumor Cells in Primary Breast Cancer Patients: A Randomized Controlled Trial. *Anesthesiology* (2020) 133(3):548–58. doi: 10.1097/ALN.0000000000003409
100. Enlund M, Enlund A, Berglund A, Bergkvist L. Rationale and Design of the CAN Study: An RCT of Survival After Propofol- or Sevoflurane-Based Anesthesia for Cancer Surgery. *Curr Pharm Des* (2019) 25(28):3028–33. doi: 10.2174/1381612825666190705184218
101. Cata JP, Forget P. Paravertebral Block With Propofol Anaesthesia Does Not Improve Survival Compared With Sevoflurane Anaesthesia for Breast Cancer Surgery: Independent Discussion of a Randomised Controlled Trial. *Br J Anaesth* (2020) 124(1):19–24. doi: 10.1016/j.bja.2019.09.039
102. Nguyen DX, Bos PD, Massague J. Metastasis: From Dissemination to Organ-Specific Colonization. *Nat Rev Cancer* (2009) 9(4):274–84. doi: 10.1038/nrc2622
103. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, et al. Tumor Self-Seeding by Circulating Cancer Cells. *Cell* (2009) 139(7):1315–26. doi: 10.1016/j.cell.2009.11.025
104. Cabel L, Proudhon C, Gortais H, Loirat D, Coussy F, Pierga JY, et al. Circulating Tumor Cells: Clinical Validity and Utility. *Int J Clin Oncol* (2017) 22(3):421–30. doi: 10.1007/s10147-017-1105-2
105. Wang J, Barke RA, Ma J, Charboneau R, Roy S. Opiate Abuse, Innate Immunity, and Bacterial Infectious Diseases. *Arch Immunol Ther Exp (Warsz)* (2008) 56(5):299–309. doi: 10.1007/s00005-008-0035-0
106. Gach K, Wyrebska A, Fichna J, Janecka A. The Role of Morphine in Regulation of Cancer Cell Growth. *Naunyn Schmiedebergs Arch Pharmacol* (2011) 384(3):221–30. doi: 10.1007/s00210-011-0672-4
107. Tripolt S, Neubauer HA, Knab VM, Elmer DP, Aberger F, Moriggl R, et al. Opioids Drive Breast Cancer Metastasis Through the Delta-Opioid Receptor and Oncogenic STAT3. *Neoplasia* (2021) 23(2):270–9. doi: 10.1016/j.neo.2020.12.011
108. Cronin-Fenton D. Opioids and Breast Cancer Recurrence. *Curr Opin Support Palliat Care* (2019) 13(2):88–93. doi: 10.1097/SPC.0000000000000426
109. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative Opioids are Associated With Improved Recurrence-Free Survival in Triple-Negative Breast Cancer. *Br J Anaesth* (2021) 126 (2):367–76. doi: 10.1016/j.bja.2020.10.021
110. Perez-Gonzalez O, Cuellar-Guzman LF, Soliz J, Cata JP. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature. *Reg Anesth Pain Med* (2017) 42(6):751–6. doi: 10.1097/AAP.0000000000000662
111. Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NPS, et al. Post-Mastectomy Cancer Recurrence With and Without a Continuous Paravertebral Block in the Immediate Postoperative Period: A Prospective Multi-Year Follow-Up Pilot Study of a Randomized, Triple-Masked, Placebo-Controlled Investigation. *J Anesth* (2017) 31(3):374–9. doi: 10.1007/s00540-017-2345-z
112. Kairaluoma P, Mattson J, Heikkilä P, Pere P, Leidenius M. Perioperative Paravertebral Regional Anaesthesia and Breast Cancer Recurrence. *Anticancer Res* (2016) 36(1):415–8.

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Antitumorigenic Effect of Tramadol and Synergistic Effect With Doxorubicin in Human Breast Cancer Cells

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Background: Breast cancer in women is one of the leading causes of cancer mortality worldwide, and curative therapy is the main focus of clinical treatment. Anesthetic-analgesic techniques might alter stress responses and immunity and thereby influence outcomes in cancer patients. This study investigated the effect of tramadol on breast cancer progression and metastasis.

Methods: The effects of tramadol on two different subtypes of human breast adenocarcinoma cell lines, MDA-MB-231 and MCF-7, were studied with regard to cell growth, migration, colony formation and invasion and normoxic or hypoxic microenvironment for the expression of hypoxia-inducible factor-1α, reactive oxygen species, epithelial-mesenchymal transition related and cyclin-related proteins. The co-administration of tramadol and doxorubicin was studied to determine whether the effective doxorubicin dose might be reduced in combination with tramadol.

Results: The results showed that tramadol inhibited cell growth at concentrations more than 0.5 and more than 1.0 mg/mL in MDA-MB-231 and MCF-7 cells, respectively. Additionally, cell migration, colony formation and invasion were inhibited in a dose-dependent manner by tramadol in both cell lines. The combination of tramadol and doxorubicin induced synergistic effects in MDA-MD-231 cells and, with specific dosage combinations in MCF-7 cells.

Conclusions: Tramadol may regulate epithelial-mesenchymal transition and possess cytotoxic effects in breast cancer cells. Tramadol inhibits the progression of breast cancer cells and might be a candidate for combination therapy, especially for triple-negative breast cancer, and is a promising treatment strategy for breast cancer.

Keywords: breast cancer, doxorubicin, epithelial–mesenchymal transition, HIF-1α, tramadol

INTRODUCTION

Breast cancer in women, which contributed to 11.7% of the global cancer incidence and 6.9% of global cancer mortality in 2020 (GLOBOCAN report), has surpassed lung cancer as the commonest malignancy and is one of the top five causes of cancer mortality. (1) Surgical resection is one of the major treatment options for breast cancer, and perioperative surgical and anesthetic interventions may alter the stress responses and immunity and could even modulate the tumor microenvironment of patients. (2) The mechanisms through which anesthetic-analgesic techniques influence breast cancer outcomes have increasingly garnered attention although the results of research have been inconsistent. (3–11)

Tramadol is a centrally acting analgesic that is widely accepted in the treatment of moderate postoperative pain. (12) Piñero and colleagues (13) reported that β-adrenoceptor agonists and α_2-adrenoceptor antagonists can effectively suppress breast cancer cell proliferation and tumor growth *via* the inhibition of extracellular signal-regulated kinase 1/2 (ERK 1/2) phosphorylation in an animal model. Tramadol inactivates α_2-adrenoceptor signaling and inhibits the proliferation, migration and invasion of breast cancer cells. (14) Kim and co-workers (8) reported that postoperative tramadol use mitigated the risk of cancer recurrence and improved survival in patients with breast cancer. Also, *in vitro* attenuation of the 5-hydroxytryptamine $(HT)_{2B}$ receptor activity and transient receptor potential vanilloid-1 (TRPV1) inhibited tumor growth and promoted apoptosis.

With regard to cancer survival and metastasis, epithelial-mesenchymal transition (EMT) plays a crucial role in the dissemination of cancer cells. (15) EMT is a cellular process wherein epithelial cancer cells are converted to motile mesenchymal cancer cells that trigger metastatic capability. Furthermore, hypoxia provokes EMT, which increases motility, tumorigenesis and, eventually, distant metastasis. (16) The hypoxic microenvironment plays an important role in breast cancer progression and metastasis. (16, 17) However, the anti-tumorigenic effect of tramadol and EMT on breast cancer has not been elucidated.

This study was conducted with an aim to ascertain the effects of tramadol on cell growth, migration and invasion as well as on EMT in relation to breast cancer recurrence and metastasis. The primary objective was to identify the relationship between tramadol and breast cancer through the evaluation of EMT-associated biomarkers [hypoxia-inducible factor 1 alpha (HIF-1α)] and to examine whether tramadol treatment, in a normoxic or hypoxic microenvironment, affects the expression of HIF-1α, stress-induced reactive oxygen species and EMT- and cyclin-related proteins in the human breast adenocarcinoma cell lines MDA-MB-231 and MCF-7. The secondary objective of this study was to evaluate the feasibility of repurposing combination therapy with tramadol and doxorubicin for breast cancer.

MATERIALS AND METHODS

Cell Culture and Reagents

We used two molecular subtypes of human breast adenocarcinoma [MDA-MB-231 derived from triple-negative breast cancer (TNBC) cells] and MCF-7 (luminal breast cancer cells) to evaluate the effects of tramadol treatment. The MDA-MB-231 (ATCC®HTB-26™) and MCF-7 (BCRC-60436) human breast adenocarcinoma cell lines were purchased from the American Type Culture Collection (Manassas, VA, USA) and Bioresource Collection and Research Center (Hsinchu, Taiwan), respectively. All cells were cultured in minimum essential medium (MEM) with 2 mM L-glutamine and Earle's Balanced Salts that contained 1.5 g/L sodium bicarbonate, 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin (Thermo Fisher Scientific, Waltham, MA, USA). Doxorubicin, propidium iodide (PI), thiazolyl blue tetrazolium bromide (MTT), and tramadol were procured from Sigma Aldrich (St. Louis, MO, USA).

Analysis of Cell Metabolic Activity

The MDA-MB-341 and MCF-7 cells (5×10^3/well) were seeded in 96-well plates, overnight under 5% CO_2 at 37°C, and subsequently exposed to different dosages of tramadol or doxorubicin for 24 h. Thereafter, 10 μL MTT solution [dissolved in phosphate-buffered saline (PBS) to obtain a concentration of 5 mg/mL] per well was added, and the cells were incubated for at 37°C for at least 1 h. After gently removing the MTT medium, plates were washed twice with PBS and 100 μL dimethyl sulfoxide (DMSO) was added to dissolve MTT crystals, and the absorbances at 570 and 650 nm were measured using an enzyme-linked immunosorbent assay plate reader (Multiskan EX, Thermo Fisher Scientific). CalcuSyn (Biosoft, Cambridge, UK) was used to calculate the combination index (CI) to generate an isobologram (CI <1 and >1 indicates a synergistic and an antagonistic combination effect, respectively). (18)

Cell-Cycle Profiles

Cells were fixed in 70% ice-cold ethanol and stored at −20°C overnight, then centrifuged (1,000 rpm for 5 min), washed twice with ice-cold PBS supplemented with 1% FBS and stained with PI solution (5 μg/mL PI in PBS, 0.5% Triton X-100, and 0.5 μg/mL RNase A) for 30 min at 37°C in the dark. For each test condition, we collected 10,000 cells for flow cytometry (BD FACSCalibur™) and Cell Quest Pro software (BD Biosciences, Franklin Lakes, NJ, USA).

Wound-Healing Assay

Cells (3×10^5 cells/well) were seeded in a 24-well plate and incubated for 24 h under 5% CO_2 at 37°C to form a confluent monolayer. Next, a sterile 200-μL pipette tip was used to vertically draw a cross in each well, and the cells in each well were treated with different tramadol concentrations. After wounding (0 h) and at 16 h post-wounding, the scratch closure was monitored and imaged using a LeadView 2800AC-FL microscope (Leader Scientific Co. Ltd., Taiwan) that was equipped with a 40× objective; the change in the wound area was measured using ImageJ (NIH, Bethesda, MD).

Colony-Formation Assay

Cells (2×10^3/well) were seeded into six-well plates for 24 h, incubated with different tramadol concentrations for 2 weeks

and the colonies that formed were fixed with methanol and stained with 0.005% crystal violet. Colonies that were larger than 0.05 mm were numbered using ImageJ software (NIH, Bethesda, MD).

Invasion Assay

The invasion assay was performed in Transwell chambers coated with Matrigel matrix (BD Biosciences, San Jose, CA). The cells were added into serum-free MEM in the upper chambers, and MEM containing 10% FBS was added to the lower chambers. The cells were incubated in a 5% CO_2 incubator at 37° C for 16 h, followed by the removal of the non-migrated cells from the upper chamber. Each chamber was stained with 0.1% crystal violet after fixing with 3.8% formaldehyde in PBS, and the cells were counted under a microscope (10x objective).

Hypoxic Treatment

MDA-MB-341 and MCF-7 cells (5×10^5/well) were seeded in six-well plates and cultured at 37°C in 5% CO_2 for 24 h. On the second day, the culture medium was replaced with fresh medium and the cells were placed in a hypoxia chamber (in a gas mixture comprising 1% O_2 and 90% N_2/5% CO_2) or in a normal incubator after treatment with various tramadol concentrations for 4 h.

Western Blotting

Cells were washed twice with ice-cold PBS and lysed in a radioimmunoprecipitation assay buffer [100 mM Tris-HCl (pH 8.0), 150 mM NaCl, 0.1% SDS, and 1% Triton X-100] at 4°C. The proteins in the resulting lysate were separated using sodium dodecyl sulphate polyacrylamide gel electrophoresis, and the resolved proteins were immunoblotted with antibodies against β-actin, nuclear factor erythroid 2-related factor 2 (Nrf2), B-cell lymphoma 2 (BCL2) and adenovirus E1B 19-kDa-interacting protein 3 (BNIP-3), p53, Slug (Santa Cruz Biotechnology, Santa Cruz, CA, USA), HIF-1α, α-Smooth muscle actin (α-SMA), transforming growth factor-β (TGF-β), N-cadherin, E-cadherin, Snail, vimentin, poly (ADP-ribose) polymerase (PARP; Cell Signaling Technology, Danvers, MA, USA), γH2A.X, cyclin D1, collagen-I (Abcam, Cambridge, UK), heme-oxidase 1 (HO-1; Enzo Life Sciences, Farmingdale, NY, USA), and differentiated embryonic chondrocyte gene 1 (DEC-1; Bethyl Laboratory, TX, USA).

Statistical Analysis

Values are expressed as the mean ± SD from at least three independent experiments. The Student's *t*-tests was used for all intergroup comparisons. Statistical significance was set at $p < 0.05$.

RESULTS

Tramadol Impeded MDA-MB-231 and MCF-7 Cell Growth

To verify the impact of tramadol on MDA-MB-231 and MCF-7 cells, cell viability assay experimented in cultures treated by tramadol at concentration ranging from 0.01 to 5 mg/mL for 24 hr. The growth of MDA-MB-231 and MCF-7 cells were significantly suppressed at tramadol concentration more than 0.5 and more than 1.0 mg/mL (**Figures 1A, B**), respectively, indicating a dose-dependent inhibition of cell growth following treatment with tramadol in both cell lines. The results showed that the tramadol half-maximal inhibition concentrations (IC_{50}) were determined as 0.8 and 1.1 mg/mL for MDA-MB-231 and MCF-7, respectively. After treatment with the indicated tramadol concentrations for 24 h, the distribution of MDA-MB-231 and MCF-7 cells in different cell-cycle phases were examined. The MDA-MB-231 cells demonstrated a significant dose-dependent decreased in the G2/M phase population and a dose-dependent increase in the G1 phase population (**Figure 1C**). In contrast, there was a significant dose-dependent increase in the G2/M and a significant dose-dependent decreased in the G1 phase populations of MCF-7 cells following treatment with tramadol (**Figure 1D**). Moreover, the sub-G1 phase population showed a significant but slight increase in MCF-7 cells.

Tramadol Suppressed Migration, Colony Formation and Invasion of MDA-MB-231 and MCF-7 Cells

Recurrence and metastases of breast cancer are the key elements of cancer outcomes and related to cancer survival, among which migration of cancer cells plays an important role in metastases. To determine the impact of tramadol on breast cancer cell migration, a wound-healing assay was measured to assess the migration rates. After 24-h treatment with tramadol (concentration more than 0.01 mg/mL), the rate of migration decelerated significantly in MDA-MB-231 cells (**Figure 2A**); in contrast, the suppressive effect of 24-h tramadol treatment (concentration more than 0.1 mg/mL) on the rate of migration was significantly slower in MCF-7 cells (**Figure 2B**).

Colony formation was examined by evaluation of the size of the colony to identify the impact of anchorage-independent growth by tramadol. Compared to the control groups, colony formation of MDA-MB-231 and MCF-7 cells was significantly inhibited following treatment with tramadol (concentration more than 0.2 and more than 0.05 mg/mL; **Figures 3A, B**), respectively. Tramadol inhibited colony formation in both cell lines in a dose-dependent manner (**Figure 3**).

To determine the impact of tramadol on breast cancer cell invasiveness, the amounts of invasive cells were examined using the trans-well assay. The invasiveness of MDA-MB-231 cells was significantly attenuated following tramadol treatment (concentration more than 0.1 mg/mL; **Figures 4A, B**), whereas MCF-7 cells showed no invasive capability (**Figure 4A**).

Effects of Tramadol on Hypoxia, Oxidative Stress, DNA Damage, Cell Death, Cell Cycle and EMT-Related Proteins in MDA-MB-231 and MCF-7 Cells

Hypoxia facilitates EMT at the very beginning of breast cancer invasion and eventually accomplishes distant metastasis with a poor prognosis. To determine the relationship between tramadol

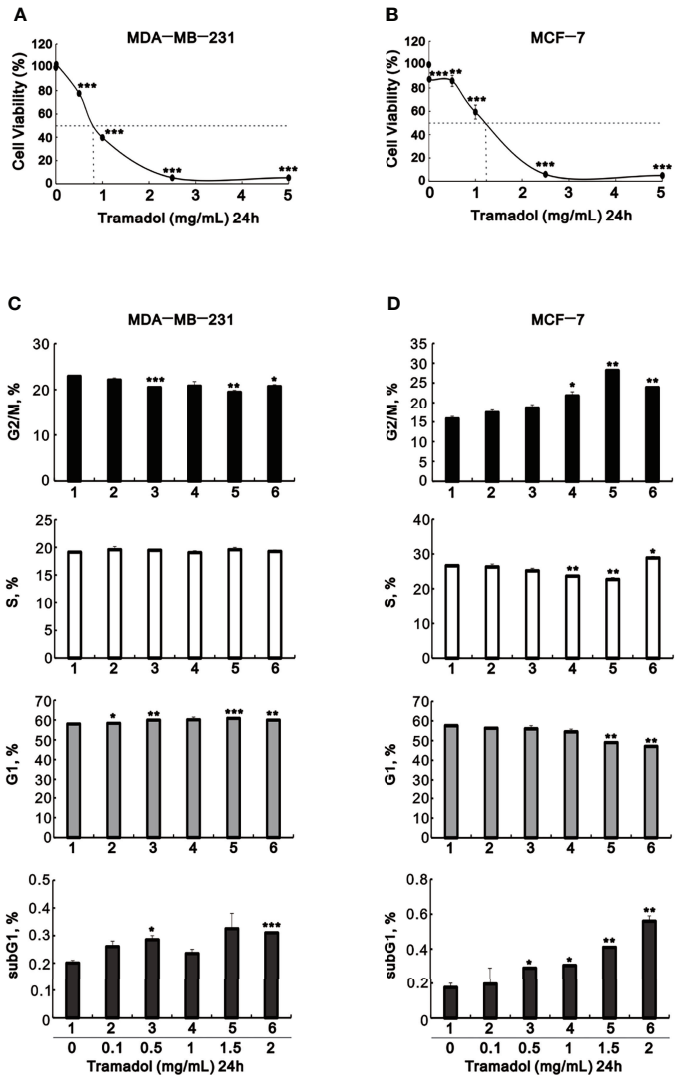

FIGURE 1 | The effects of tramadol on cell viability and the cell-cycle profiles of human breast cancer cells. **(A–D)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.1, 0.5, 1.0, 2.5 and 5 mg/mL) for 24 h. **(A, B)** Cell viability was measured according to the MTT method. **(C, D)** For cell-cycle profiles, the cells were stained with propidium iodide (PI) and analyzed by flow cytometry. Bars depict the mean ± SD of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ (Student's *t*-tests).

and EMT in breast cancer cell invasion, a series of western blot analyses for protein associated with hypoxia, oxidative stress, DNA damage, cell death, cell cycle, and EMT were measured. Under hypoxic conditions, HIF-1α was highly expressed in MDA-MB-231 cells (**Figure 5A**); following treatment with increasing concentrations of tramadol in normoxic conditions, HIF-1α expression was induced, but no further upregulation of HIF-1α expression was observed under hypoxic conditions. Nrf-2 is a well-known transcription factor that plays a role in the maintenance of the cellular redox balance, and HO-1 is one of the targets of Nrf-2 in the mediation of the intracellular antioxidant function. Similar to the HIF-1α expression following tramadol treatment, HO-1 expression, but not Nrf-2 expression, increased in a dose-dependent manner in a normoxic environment in MDA-DB-231 cells (**Figure 5A**). After the tramadol treatment, the expression of γ-H2A.x, a sensitive marker of DNA double-strand breaks and a potential breast cancer biomarker, (19) increased in the normoxic environment (in a dose-dependent manner) but was undetectable in the hypoxic environment.

The expression of three cell death-related proteins—DEC-1, BNIP3, and cleaved PARP—were examined following tramadol treatment and induction of hypoxia in MDA-MB-231 cells. After tramadol treatment, dose-dependent increases in DEC-1 and BNIP3 expressions in a normoxic environment were observed. However, DEC-1 and BNIP3 expressions that were induced in a hypoxic environment diminished in a dose-dependent manner following tramadol treatment. After tramadol treatment and

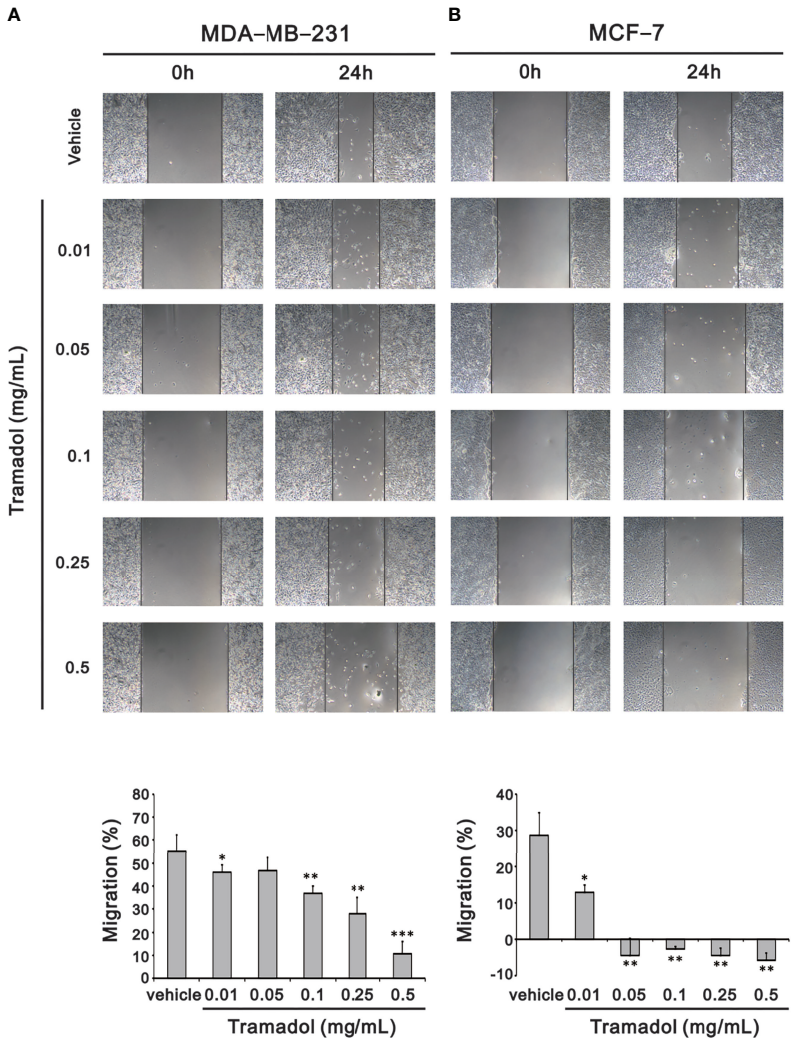

FIGURE 2 | Analysis of the effect of tramadol on the cell migration of human breast cancer cells in a wound-healing assay. **(A, B)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.01, 0.05, 0.1, 0.25 and 0.5 mg/mL) for 24 h. Quantification of the migration area of untreated and tramadol-treated cells within 24 h using Image J Bars depict the mean ± SD of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ (Student's *t*-tests).

induction of hypoxia in MDA-MB-231 cells, the expression of cleaved PARP was undetectable, which suggested the absence of apoptosis. To determine the effects of tramadol treatment and hypoxia in MDA-MB-231 cells, we measured the expression of two cell-cycle-related proteins, p53 and cyclin D1. Tramadol and hypoxia separately induced p53 expression but a further enhancement by a combination of the two treatments was absent. Regardless of normoxia or hypoxia, cyclin D1 expression was inhibited by treatment with tramadol. Finally, we examined the expression of proteins related to EMT, including the epithelial markers E-cadherin, TGF-β, α-SMA and collagen I as well as the mesenchymal markers N-cadherin, vimentin, Snail and Slug in MDA-MB-231 cells. Tramadol treatment resulted in the transition of MDA-MB-231 cells into a mesenchymal state *via* the induction of TGF-β and α-SMA and suppression of E-cadherin and collagen I and the induction of N-cadherin, vimentin, Snail and Slug. Under hypoxic conditions, the effect of tramadol on EMT was eliminated.

Simultaneously, the expression of the abovementioned proteins was examined in MCF-7 cells (**Figure 5B**). The effects of tramadol treatment and hypoxia in MCF-7 cells were similar to those in MDA-MB-231 cells except that vimentin proteins were undetectable in MCF-7 cells and p53 expression was not induced by tramadol and was suppressed by hypoxia.

Synergistic Effect of Tramadol on Doxorubicin-Treated MDA-MB-231 and MCF-7 Cells

Our current findings suggested that tramadol might be a candidate for the combination therapy for breast cancer, especially for TNBC. Doxorubicin is a common chemotherapy drug applied for TNBC. Hence, we designed various amounts of tramadol and doxorubicin

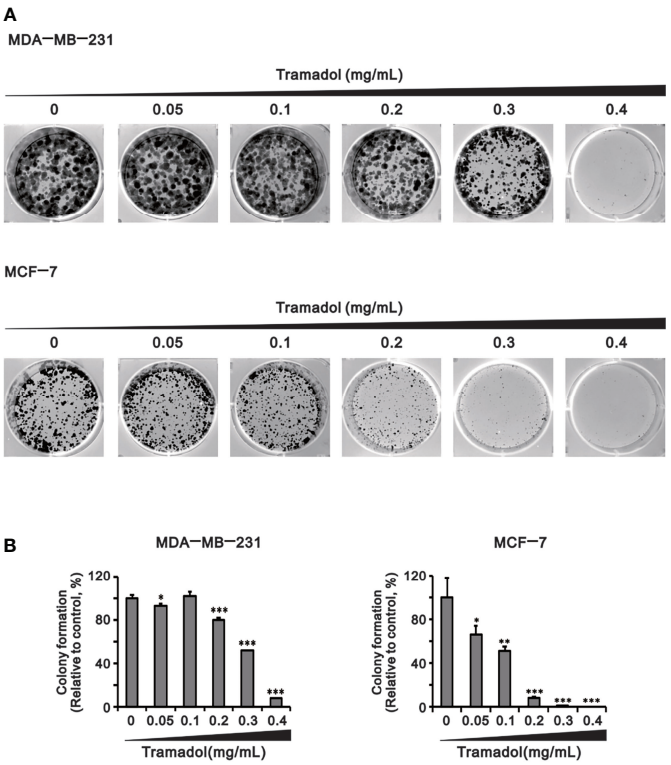

FIGURE 3 | Analysis of the effect of tramadol on the colony-formation ability of human breast cancer cells. **(A, B)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.05, 0.1, 0.2, 0.3 and 0.4 mg/mL) for 14 days. Bars depict the mean ± SD of three independent experiments. * p <0.05, ** p <0.01 and *** p <0.001 (Student's t-tests). Bars depict the mean ± SD of three independent experiments.

for the combination index analysis (**Figure 6**). The CI <1 indicated that all combinations of tramadol and doxorubicin induced synergistic effects in MDA-MD-231 cells (**Figure 6A**). Therefore, combination therapy with tramadol might reduce the effective concentration of doxorubicin from 24 μM to 0.3 μM. Similarly, in MCF-7 cells, combination therapy with tramadol and doxorubicin induced synergistic effects at specific dosage combinations (**Figure 6B**) that facilitated the reduction of the effective doxorubicin concentration from 5.1 to 1.2 μM.

DISCUSSION

The findings of this study show that tramadol has potential cytotoxic properties and inhibits the migration, colony formation and invasion of breast cancer cells. Furthermore, a synergistic effect of tramadol in combination therapy with doxorubicin in breast cancer cell lines was observed.

Tramadol, which is used for acute pain management after breast cancer surgery, is associated with lower risk of tolerance, dependence and respiratory depression. (20, 21) Recent preclinical and clinical studies have shown that tramadol possesses immunostimulatory effects that through NK cell activation and lymphocyte proliferation (22, 23); moreover, tramadol reduces the risk of lung metastasis in rats. (24) Tramadol confers an anti-tumorigenic effect against proliferation, migration and invasion in lung cancer cells by upregulating the phosphatase and tensin homolog and interfering with phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling (25) and by downregulating the α2-receptor in breast cancer cells (MDA-MB-231) (14); our results are consistent with the abovementioned findings. Tumor resection potentially enhances the emergence and seeding of circulating tumor cells through ischemia-reperfusion injury, activation of the sympathetic nervous system, inflammation, induction of a systemic hypercoagulable state, immunosuppression and the effect of anesthetics. (26) Tramadol has positive effects on antioxidant levels in renal injury and in myocardial ischemia-reperfusion injury. (27, 28) In contrast to morphine, tramadol improved postoperative immunosuppression, which might be a desirable feature in a postoperative pain-management option. (22) Likewise, tramadol suppresses sympathetic nervous activity through the inhibition of nicotinic acetylcholine receptors. (29) Furthermore, tramadol induces hypocoagulable changes in patients with gynecologic cancer and may be useful for patients with an impending hypercoagulable state. (30) In our opinion, tramadol, due to its abovementioned properties and anticancer benefits, confers a superior prognosis for patients with breast cancer in addition to pain relief.

Molecular classifications of breast cancer are characterized as five different subtypes: luminal-A, luminal-B, human epidermal

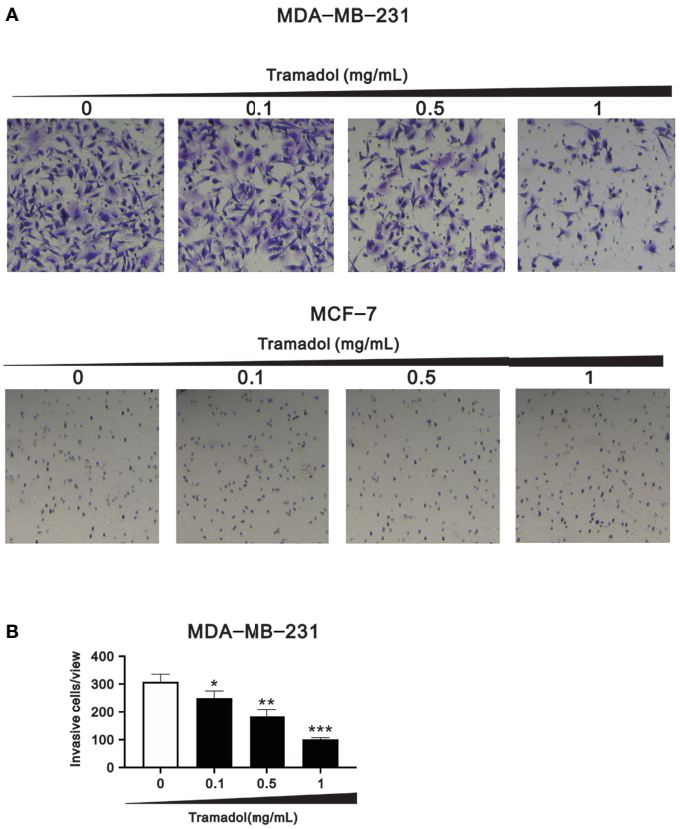

FIGURE 4 | Analysis of the effect of tramadol on the invasiveness of human breast cancer cells. **(A, B)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.1, 0.5 and 1 mg/mL) for 24 h. Bars depict the mean ± SD of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ (Student's *t*-tests). Bars depict the mean ± SD of three independent experiments.

growth factor receptor 2 (HER2)-positive, basal-like and normal breast-like. (31, 32) The basal-like subgroup does not express the estrogen receptor (ER), progesterone receptor (PR) or HER2 and is referred to as triple-negative subtype, which is notorious for its aggressive pattern, a tendency for early relapse and recurrence as well as a paucity of targets for endocrine and anti-HER2 treatment. Some obstacles to surgery and anesthesia in cancer treatment, such as physiological disturbances, tumor-related symptoms and toxicity in traditional chemotherapy treatment, do exist. Consequently, therapy for TNBC poses challenges that emphasize the restricted effect of systemic chemotherapy. The appropriate combination of surgical and anesthetic procedures and medications can reduce perioperative inflammatory and immune changes that could contribute to improved results for cancer patients. (33)

The repurposing strategy of tramadol was applied to the development of therapy for breast cancer. The therapeutic blood levels of tramadol in adults range from 0.1 to 0.3 mg/L, the toxic level is between 1 and 2 mg/L, and the lethal concentration is higher than 2 mg/L. (34) Our working dosages were based on the values of IC_{50} (0.8 and 1.1 mg/mL for MDA-MB-231 and MCF-7, respectively) which were higher than the clinical therapeutic level of tramadol for a centrally acting analgesic but were consistent with the study of Kim and colleagues (8) for anti-tumorigenic effects on breast cancer cells. Furthermore, Kim and colleagues (35) investigated an *in-vivo* experiment for confirmation the anti-tumor effect of tramadol in xenograft mice with orthotopic inoculation of MCF-7 cells and revealed the clinical dosage of tramadol (1.5 and 3 mg/kg/day), could impede tumor growth, the tumor size and weight compared to the control or morphine groups. Kim et al. alternatively provided *in-vivo* evidences of achievable dose of tramadol in clinical settings.

Here, we demonstrated a novel therapeutic strategy by combining tramadol with doxorubicin for the effective treatment of breast cancer. Our results indicate a synergistic effect of tramadol and doxorubicin in breast cancer, despite the predominantly analgesic purpose of tramadol rather than its application in adjuvant chemotherapy. The therapeutic concentrations of 24 μM doxorubicin were decreased to 0.3 μM (at 0.26 mg/mL tramadol) in MDA-MB-231 cells and 5.1 μM doxorubicin were decreased to 1.2 μM (at 0.24 mg/mL tramadol) in MCF-7 cells, which translated to a diminished adverse-effect profile and lower risk of doxorubicin-induced resistance in metastatic breast cancer. However, further *in vivo* and clinical studies are necessary to determine the actual clinical dose of tramadol and doxorubicin in breast cancer, especially for TNBC. In addition, we anticipate that future studies of efficient systems pharmacology platforms containing absorption, distribution,

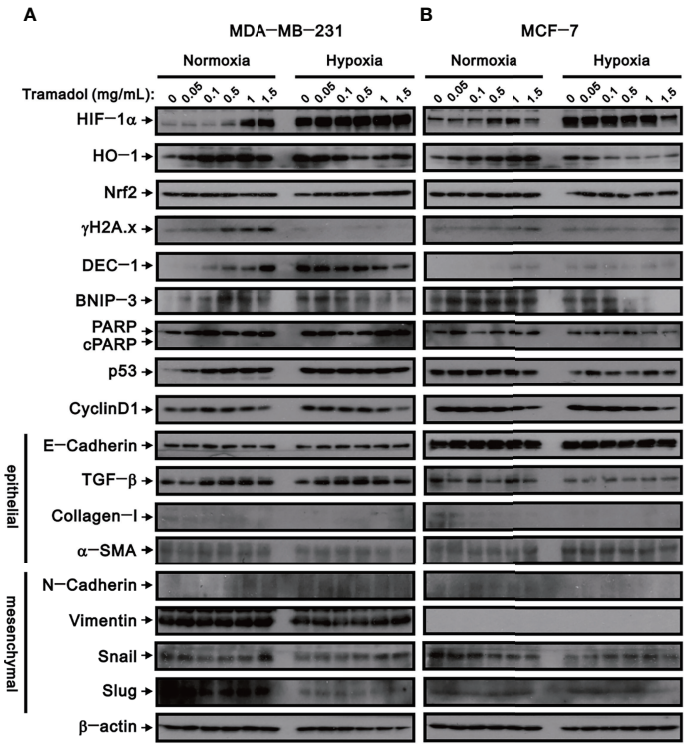

FIGURE 5 | The effects of tramadol on protein expression in human breast cancer cells. **(A, B)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.05, 0.1, 0.5, 1 and 1.5 mg/mL) for 4 h. β-actin (lower panel) served as the loading control.

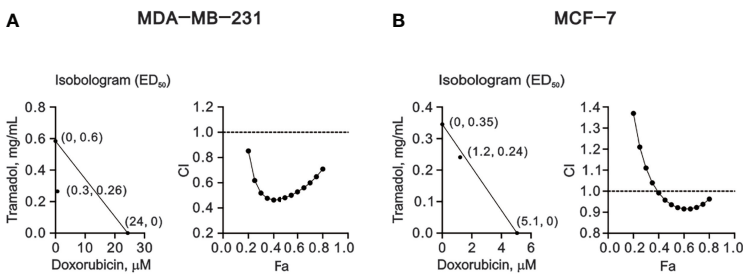

FIGURE 6 | The combination index (CI) of combination treatment of tramadol and doxorubicin in human breast cancer cells. **(A, B)** MDA-MB-231 and MCF-7 cells were treated with tramadol (0, 0.0625, 0.125, 0.25, 0.5, 1, 2 and 4 mg/mL) and doxorubicin (0, 0.0390625, 0.078125, 0.15625, 0.3125, 0.625, 1.25, 2.5, 5 and 10 mM) for 24 h. The experimental points below the line correspond to CI <1, indicating a synergistic effect.

metabolism, and excretion properties will elucidate the optimal dosage of tramadol for the combination therapy.

Turning to the different toxicity of tramadol in MCF-7 and MDA-MB-231 cells, the two cells are infiltrating duct/breast cancer cells, but each own many phenotype/genotype differences: MCF-7 is hormone-dependent (expression of both ER and PR), while MDA-MB-231 is triple negative. Furthermore, MCF-7 cells express markers of the luminal epithelial phenotype, while MDA-MB-231 cells show high expression of vimentin (**Figure 5**), a known marker of the mesenchymal phenotype. The results of xenograft mouse model through MCF-7 by Kim and colleagues (35) have shown that tramadol may have receptor-specific anti-tumor effects through ER, PR and TRPV1. In comparison, MDA-MB-231 cells lack hormone receptors, and the toxicity caused by tramadol must be different from that of MCF-7 cells.

Moreover, dynamic changes in cancer cell plasticity are derived from EMT, which enables tumor cell mobilization and distant metastases. (36) It is clear that the initiation of invasion and metastasis of TNBC, and the resultant cancer mortality, is attributable to EMT progression. (37) HIF-1α expression is highly

induced in hypoxic environments in MDA-MB-231 cells. Thus, hypoxia-induced EMT and HIF-1α expression can regulate the expression of angiogenesis and promote tumor cell metastasis. (16, 38) We found that tramadol, in some way, interfered with the transformation of MDA-MB-231 and MCF-7 cells into the mesenchymal state, which has implications for providing regulatory EMT capacities, and eventually suppressed the migration, colony formation and invasion of breast cancer cells. Both hypoxia and tramadol induced HIF-1α expression; however, no further induction by tramadol in hypoxic MDB-MA-231 and MCF-7 cells was found. HO-1 proteins were induced by tramadol or hypoxia but suppressed by tramadol in hypoxic MDB-MA-231 and MCF-7 cells. The HO-1 gene is a target gene of HIF-1α and tramadol and hypoxia potentially modified HIF-1α expression. Further elucidation of the mechanisms of HIF-1α protein induction by tramadol is required.

On the other hand, one characteristic of cancer is the uncontrolled proliferation of tumor cells caused by the abnormal activity of various cell cycle proteins. Many studies have pointed out that cyclin D1 is overexpressed in more than 50% of breast cancers, and the amplification of the Cyclin D1 gene is related to poor prognosis of patients. (39, 40) In recent years, *in vitro* and *in vivo* studies have identified the new role of cyclin D1 as a controller of cellular invasiveness and aggressiveness. (41, 42) The progression of the G1 phase of the cell cycle is mainly controlled by cyclin D1. Cyclin D1 is located in the nucleus and reaches its highest level before the S phase. At the end of the G1 phase and after entering the S phase, cyclin D1 is exported to the cytoplasm and degraded by the ubiquitin-proteasome system. In our study, tramadol induced a significant dose-dependent decrease in the level of cyclin D1 protein in MCF-7 cells and had no significant effect on MDA-MB-231 cells. This result is consistent with our cell cycle profile. The highest dose of tramadol in MCF-7 cells was shown to induce the S phase and reduce the G1 phase. It also increased cell cycle arrest in the subG1 and G2/M phase. In MDA-MB-231 cells, it was found that the G1, subG1 phase were tramadol-induced without affecting the S phase, and unlike MCF-7, its G2/M phase was reduced. This result indicated that tramadol has different effects on the cell cycle of MCF-7 and MDA-MB-231.

In conclusion, tramadol inhibited cell growth, cell migration, colony formation and invasion; regulated the EMT process; and induced a cytotoxic effect in MDA-MB-231 and MCF-7 cells. These findings suggest that tramadol might be a candidate for combination therapy for breast cancer, especially for TNBC. In addition, co-administration of tramadol might reduce the effective dosage of doxorubicin, which indicates a promising treatment strategy in clinical practice for breast cancer patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Y-HH and S-HS performed experiments, collected data, and wrote the manuscript. Z-SW performed experiments and prepared the figures. S-MH provided cell lines for the experiments and was assistant in data analysis. S-YL collected data. Z-FW designed the experiments, wrote the manuscript, and supervised the work. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Byrne K, Levins KJ, Buggy DJ. Can Anesthetic-Analgesic Technique During Primary Cancer Surgery Affect Recurrence or Metastasis? *Can J Anaesth* (2016) 63(2):184–92. doi: 10.1007/s12630-015-0523-8
3. Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *Int J Med Sci* (2017) 14(10):970–6. doi: 10.7150/ijms.20064
4. Desmedt C, Demicheli R, Fornili M, Bachir I, Duca M, Viglietti G, et al. Potential Benefit of Intra-Operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index. *J Natl Cancer Inst* (2018) 110(10):1115–22. doi: 10.1093/jnci/djy042
5. Lukoseviciene V, Tikuisis R, Dulskas A, Miliauskas P, Ostapenko V. Surgery for Triple-Negative Breast Cancer- Does the Type of Anaesthesia Have an Influence on Oxidative Stress, Inflammation, Molecular Regulators, and Outcomes of Disease? *J BUON* (2018) 23(2):290–5.
6. Forget P, Bouche G, Duhoux FP, Coulie PG, Decloedt J, Dekleermaker A, et al. Intraoperative Ketorolac in High-Risk Breast Cancer Patients. A Prospective, Randomized, Placebo-Controlled Clinical Trial. *PloS One* (2019) 14(12):e0225748. doi: 10.1371/journal.pone.0225748
7. Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, et al. Propofol-Based Total Intravenous Anesthesia did Not Improve Survival Compared to Desflurane Anesthesia in Breast Cancer Surgery. *PloS One* (2019) 14(11): e0224728. doi: 10.1371/journal.pone.0224728
8. Kim MH, Oh JE, Park S, Kim JH, Lee KY, Bai SJ, et al. Tramadol Use is Associated With Enhanced Postoperative Outcomes in Breast Cancer Patients: A Retrospective Clinical Study With *In Vitro* Confirmation. *Br J Anaesth* (2019) 123(6):865–76. doi: 10.1016/j.bja.2019.09.004
9. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/s0140-6736(19)32313-x
10. Chhabra A, Roy Chowdhury A, Prabhakar H, Subramaniam R, Arora MK, Srivastava A, et al. Paravertebral Anaesthesia With or Without Sedation Versus

General Anaesthesia for Women Undergoing Breast Cancer Surgery. *Cochrane Database Syst Rev* (2021) 2:Cd012968. doi: 10.1002/14651858.CD012968.pub2
11. Pang QY, Duan LP, Jiang Y, Liu HL. Comparison of Outcomes After Breast Cancer Surgery Between Inhalational and Propofol-Based Intravenous Anaesthesia: A Systematic Review and Meta-Analysis. *J Pain Res* (2021) 14:2165–77. doi: 10.2147/jpr.S315360
12. Gibson TP. Pharmacokinetics, Efficacy, and Safety of Analgesia With a Focus on Tramadol HCl. *Am J Med* (1996) 101(1a):47s–53s. doi: 10.1016/s0002-9343(96)00138-6
13. Pérez Piñero C, Bruzzone A, Sarappa MG, Castillo LF, Lüthy IA. Involvement of α2- and β2-Adrenoceptors on Breast Cancer Cell Proliferation and Tumour Growth Regulation. *Br J Pharmacol* (2012) 166(2):721–36. doi: 10.1111/j.1476-5381.2011.01791.x
14. Xia M, Tong JH, Zhou ZQ, Duan ML, Xu JG, Zeng HJ, et al. Tramadol Inhibits Proliferation, Migration and Invasion *via* α2-Adrenoceptor Signaling in Breast Cancer Cells. *Eur Rev Med Pharmacol Sci* (2016) 20(1):157–65.
15. Tiwari N, Gheldof A, Tatari M, Christofori G. EMT as the Ultimate Survival Mechanism of Cancer Cells. *Semin Cancer Biol* (2012) 22(3):194–207. doi: 10.1016/j.semcancer.2012.02.013
16. Gao T, Li JZ, Lu Y, Zhang CY, Li Q, Mao J, et al. The Mechanism Between Epithelial Mesenchymal Transition in Breast Cancer and Hypoxia Microenvironment. *BioMed Pharmacother* (2016) 80:393–405. doi: 10.1016/j.biopha.2016.02.044
17. Wong CC, Zhang H, Gilkes DM, Chen J, Wei H, Chaturvedi P, et al. Inhibitors of Hypoxia-Inducible Factor 1 Block Breast Cancer Metastatic Niche Formation and Lung Metastasis. *J Mol Med (Berl)* (2012) 90(7):803–15. doi: 10.1007/s00109-011-0855-y
18. Chou TC. Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies. *Pharmacol Rev* (2006) 58(3):621–81. doi: 10.1124/pr.58.3.10
19. Varvara PV, Karaolanis G, Valavanis C, Stanc G, Tzaida O, Trihia H, et al. Gamma-H2AX: A Potential Biomarker in Breast Cancer. *Tumour Biol* (2019) 41(9):1010428319878536. doi: 10.1177/1010428319878536
20. Kampe S, Wolter K, Warm M, Dagtekin O, Shaheen S, Landwehr S. Clinical Equivalence of Controlled-Release Oxycodone 20 Mg and Controlled-Release Tramadol 200 Mg After Surgery for Breast Cancer. *Pharmacology* (2009) 84 (5):276–81. doi: 10.1159/000242998
21. Besic N, Smrekar J, Strazisar B. Acute Pain and Side Effects After Tramadol in Breast Cancer Patients: Results of a Prospective Double-Blind Randomized Study. *Sci Rep* (2020) 10(1):18766. doi: 10.1038/s41598-020-75961-2
22. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, et al. The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients. *Anesth Analg* (2000) 90(6):1411–4. doi: 10.1097/00000539-200006000-00028
23. Tsai YC, Won SJ. Effects of Tramadol on T Lymphocyte Proliferation and Natural Killer Cell Activity in Rats With Sciatic Constriction Injury. *Pain* (2001) 92(1-2):63–9. doi: 10.1016/s0304-3959(00)00472-3
24. Gaspani L, Bianchi M, Limiroli E, Panerai AE, Sacerdote P. The Analgesic Drug Tramadol Prevents the Effect of Surgery on Natural Killer Cell Activity and Metastatic Colonization in Rats. *J Neuroimmunol* (2002) 129(1-2):18–24. doi: 10.1016/s0165-5728(02)00165-0
25. Xia M, Tong JH, Ji NN, Duan ML, Tan YH, Xu JG. Tramadol Regulates Proliferation, Migration and Invasion *via* PTEN/PI3K/AKT Signaling in Lung Adenocarcinoma Cells. *Eur Rev Med Pharmacol Sci* (2016) 20(12):2573–80.
26. Chen Z, Zhang P, Xu Y, Yan J, Liu Z, Lau WB, et al. Surgical Stress and Cancer Progression: The Twisted Tango. *Mol Cancer* (2019) 18(1):132. doi: 10.1186/s12943-019-1058-3
27. Bilir A, Erkasap N, Koken T, Gulec S, Kaygisiz Z, Tanriverdi B, et al. Effects of Tramadol on Myocardial Ischemia-Reperfusion Injury. *Scand Cardiovasc J* (2007) 41(4):242–7. doi: 10.1080/14017430701227747
28. Şen E, Kaplan DS, Bozdağ Z, Örkmez M, Mızrak A, Şen H, et al. The Effect of Tramadol on Oxidative Stress Total Antioxidant Levels in Rats With Renal Ischemia-Reperfusion Injury. *Turk J Urol* (2020) 46(5):388–92. doi: 10.5152/tud.2020.20227
29. Shiraishi M, Minami K, Uezono Y, Yanagihara N, Shigematsu A, Shibuya I. Inhibitory Effects of Tramadol on Nicotinic Acetylcholine Receptors in Adrenal Chromaffin Cells and in Xenopus Oocytes Expressing Alpha 7 Receptors. *Br J Pharmacol* (2002) 136(2):207–16. doi: 10.1038/sj.bjp.0704703
30. Bilir A, Akay MO, Ceyhan D, Andıc N. Does Tramadol Affect Coagulation Status of Patients With Malignancy? *Indian J Pharmacol* (2014) 46(4):413–5. doi: 10.4103/0253-7613.135954
31. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, et al. Comprehensive Molecular Portraits of Human Breast Tumours. *Nature* (2012) 490(7418):61–70. doi: 10.1038/nature11412
32. Yersal O, Barutca S. Biological Subtypes of Breast Cancer: Prognostic and Therapeutic Implications. *World J Clin Oncol* (2014) 5(3):412–24. doi: 10.5306/wjco.v5.i3.412
33. Watson J, Ninh MK, Ashford S, Cornett EM, Kaye AD, Urits I, et al. Anesthesia Medications and Interaction With Chemotherapeutic Agents. *Oncol Ther* (2021) 9(1):121–38. doi: 10.1007/s40487-021-00149-1
34. Yousef Khan F, Yousef H, Errayes M. Tramadol Toxicity-Induced Rhabdomyolysis. *J Emerg Trauma Shock* (2010) 3(4):421–2. doi: 10.4103/0974-2700.70766
35. Kim MH, Lee JR, Kim KJ, Jun JH, Hwang HJ, Lee W, et al. Identification for Antitumor Effects of Tramadol in a Xenograft Mouse Model Using Orthotopic Breast Cancer Cells. *Sci Rep* (2021) 11(1):22113. doi: 10.1038/s41598-021-01701-9
36. Bakir B, Chiarella AM, Pitarresi JR, Rustgi AK. EMT, MET, Plasticity, and Tumor Metastasis. *Trends Cell Biol* (2020) 30(10):764–76. doi: 10.1016/j.tcb.2020.07.003
37. Al Moustafa AE. Epithelial-Mesenchymal Transition and its Regulators are Major Targets of Triple-Negative Breast Cancer. *Cell Adh Migr* (2013) 7 (5):424–5. doi: 10.4161/cam.26728
38. Lundgren K, Holm C, Landberg G. Hypoxia and Breast Cancer: Prognostic and Therapeutic Implications. *Cell Mol Life Sci* (2007) 64(24):3233–47. doi: 10.1007/s00018-007-7390-6
39. Kenny FS, Hui R, Musgrove EA, Gee JM, Blamey RW, Nicholson RI, et al. Overexpression of Cyclin D1 Messenger RNA Predicts for Poor Prognosis in Estrogen Receptor-Positive Breast Cancer. *Clin Cancer Res* (1999) 5(8):2069–76.
40. Al-Kuraya K, Schraml P, Torhorst J, Tapia C, Zaharieva B, Novotny H, et al. Prognostic Relevance of Gene Amplifications and Coamplifications in Breast Cancer. *Cancer Res* (2004) 64(23):8534–40. doi: 10.1158/0008-5472.Can-04-1945
41. He Y, Franco OE, Jiang M, Williams K, Love HD, Coleman IM, et al. Tissue-Specific Consequences of Cyclin D1 Overexpression in Prostate Cancer Progression. *Cancer Res* (2007) 67(17):8188–97. doi: 10.1158/0008-5472.Can-07-0418
42. Liu Y, Zhang J, Qian W, Dong Y, Yang Y, Liu Z, et al. Gankyrin is Frequently Overexpressed in Cervical High Grade Disease and is Associated With Cervical Carcinogenesis and Metastasis. *PloS One* (2014) 9(4):e95043. doi: 10.1371/journal.pone.0095043

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frontiers in Oncology

REVIEW
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Current Status and Prospects of Anesthesia and Breast Cancer: Does Anesthetic Technique Affect Recurrence and Survival Rates in Breast Cancer Surgery?

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The relationship between the anesthetic technique and cancer recurrence has not yet been clarified in cancer surgery. Surgical stress and inhalation anesthesia suppress cell-mediated immunity (CMI), whereas intravenous (IV) anesthesia with propofol and regional anesthesia (RA) are known to be protective for CMI. Surgical stress, general anesthesia (GA) with inhalation anesthesia and opioids contribute to perioperative immunosuppression and may increase cancer recurrence and decrease survival. Surgical stress and GA activate the hypothalamic-pituitary-adrenal axis and release neuroendocrine mediators such as cortisol, catecholamines, and prostaglandin E_2, which may reduce host defense immunity and promote distant metastasis. On the other hand, IV anesthesia with propofol and RA with paravertebral block or epidural anesthesia can weaken surgical stress and GA-induced immunosuppression and protect the host defense immunity. IV anesthesia with propofol and RA or in combination with GA may reduce cancer recurrence and improve patient survival compared to GA alone. We review the current status of the relationship between anesthesia and breast cancer recurrence using retrospective and prospective studies conducted with animal models and clinical samples, and discuss the future prospects for reducing breast cancer recurrence and improving survival rates in breast cancer surgery.

Keywords: breast cancer, anesthetic technique, recurrence, survival, immune response

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Abbreviations: ALND, axillary lymph node dissection; ARF6, adenosine diphosphate–ribosylation factor 6; BCS, breast-conserving surgery; CMI, cell-mediated immunity; CTC, circulating tumor cell; CTL, cytotoxic T lymphocyte; DEX, dexmedetomidine; ER, estrogen receptor; ERK, extracellular signal–regulated kinase; GA, general anesthesia; HER-2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor-1α; HPA, hypothalamic–pituitary–adrenal; HR, hormone receptor; IL, interleukin; IVA, intravenous anesthesia; LA, local anesthesia; MDSC, myeloid-derived suppressor cell; miR, micro RNA; MMP, matrix metalloproteinase; MOR, μ-opioid receptor; MT, mastectomy; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor κB; NK, natural killer; NLR, neutrophil-to-lymphocyte ratio; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; PGE_2, prostaglandin E_2; PVB, paravertebral block; RA, regional anesthesia; RCT, randomized controlled trial; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy; SNS, sympathetic nervous system; TDSF, tumor-derived soluble factor; Th, T helper; TIVA, total intravenous anesthesia; TN, triple negative; TNF-α, tumor necrosis factor-α; TPVB, total paravertebral block; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

INTRODUCTION

Over the past two decades, the relationship between anesthesia and cancer recurrence has been a controversial issue in the field of oncological surgery because surgical stress and intraoperative anesthesia impair host immunity (1). The first report on anesthesia and cancer recurrence, published in 2000, describes a retrospective analysis of patients with cutaneous melanoma (2). In that study, the survival rate of patients who received local anesthesia (LA) was higher than that of patients who received general anesthesia (GA), suggesting that LA reduces the recurrence of melanoma relative to GA (2). This finding reflects the impairment of cell-mediated immunity (CMI) and host immune responses by inhalation GA (3). Indeed, several preclinical models have shown that inhaled anesthetics inhibit natural killer (NK) cell– and T lymphocyte-mediated immunity, resulting in increased metastasis (4, 5). Immunosuppression by inhalation anesthesia is mediated by the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis, which releases neuroendocrine mediators such as catecholamines, prostaglandin E_2 (PGE_2), cytokines, and cortisol. Other neuroendocrine mediators, such as interleukin 6 (IL-6) and matrix metalloproteinases (MMPs), are also secreted and play critical roles in the regulation of tumor growth and angiogenesis (6). The impairment of CMI may reactivate micrometastases that are already disseminated at the time of surgery, increasing the frequencies of cancer recurrence and distant metastasis (6). In contrast, LA allows the maintenance of spontaneous breathing during surgery and has a weaker immunosuppressive effect than does GA (7).

Other factors that can cause immunosuppression during cancer surgery include surgical stress and opioid use. Surgical stress is limited by the size of the operative field, duration of the operation, and amount of blood loss (8). Opioids are commonly used in combination with inhalation anesthetics as analgesics and sedatives for GA, but non-synthetic and synthetic opioids can suppress CMI, depending on the dose and duration of use (9). In contrast, intravenous anesthesia (IVA) with propofol protects CMI (4, 10), as does regional anesthesia (RA) with paravertebral block (PVB) or epidural anesthesia. RA blocks afferent neurotransmitter pathways from peripheral nerves to the central nervous system and the efferent activation of the sympathetic nervous system (SNS), thereby reducing the release of neuroendocrine mediators such as glucocorticoids and allowing the minimization of opioid use (11).

Retrospective studies of anesthesia and cancer recurrence have yielded positive and negative results, depending on the type of cancer and the anesthetic technique used. Several prospective randomized controlled trials (RCTs) are underway, and preliminary results suggest that the effects of anesthesia on cancer recurrence and survival differ depending on the type of cancer. In this review, we examine the effect of the anesthetic technique used during breast cancer surgery on breast cancer recurrence and survival, and discuss the current status of and future prospects for anesthesia and breast cancer.

EFFECTS OF SURGICAL STRESS AND ANESTHESIA ON IMMUNE FUNCTION AND BREAST CANCER PROGRESSION

Stress caused by surgery and anesthetics is believed to trigger changes in the immune system, the host defense, and tumor formation. The constellation of anesthesia, stress, and immunosuppression effects on breast cancer recurrence is illustrated in **Figure 1**. The hypothetical balancing of recurrence-promoting and -inhibiting factors related to breast cancer surgery is shown in **Figure 2**.

Surgical Stress

In general, the invasiveness of surgery, postoperative pain, and intraoperative bleeding are stress factors in cancer surgery. For thoracic and abdominal surgeries, long operative times, excessive invasiveness, and massive blood loss are major stress factors leading to decreased immunity in patients with cancer. As surgery alters the microenvironments of the nervous, endocrine, inflammatory, and immune systems (12), the stress response induced by surgery may activate angiogenesis and promote tumor growth (13–15). Breast cancer surgery types are breast-conserving surgery (BCS), mastectomy (MT) with or without subsequent reconstruction, sentinel lymph-node biopsy (SLNB), and axillary lymph-node dissection (ALND). BCS is less invasive than MT and yields higher survival rates (16–18), and SLNB is less invasive than ALND. These surgeries usually take 1–2 hours, and those that do not involve reconstruction cause less blood loss. Relative to thoracic and abdominal surgeries, breast cancer surgery is minimally invasive due to its de-escalation based on the concept that breast cancer is a systemic disease, and to the development of adjuvant and neoadjuvant chemotherapies. Nevertheless, surgical resection, even in patients with breast cancer, can increase the expression of MMP-9 and vascular endothelial growth factor (VEGF), which may promote tumor growth and metastasis, as documented in some xenograft models of breast cancer (19). Plasma VEGF levels are increased by surgical stress during MT (13), and plasma transforming growth factor-β levels have been shown to increase and to be associated with lung metastasis after MT in animal models (20). In patients with breast cancer, the acceleration of metastasis due to the proliferation of distant and dormant micrometastases after surgical resection has been observed (21).

Inhalation Anesthesia

In anesthesia-induced immunosuppression, inhalation anesthetics such as sevoflurane suppress CMI and promote tumor cell proliferation and angiogenesis. Sevoflurane induces the apoptosis of T lymphocytes and upregulates the expression of hypoxia-inducible factor-1α (HIF-1α) *in vitro*; other inhalation anesthetics, including isoflurane and desflurane, upregulate HIF-1α expression *in vitro* and *in vivo* (5, 22). Sevoflurane has also been shown to increase

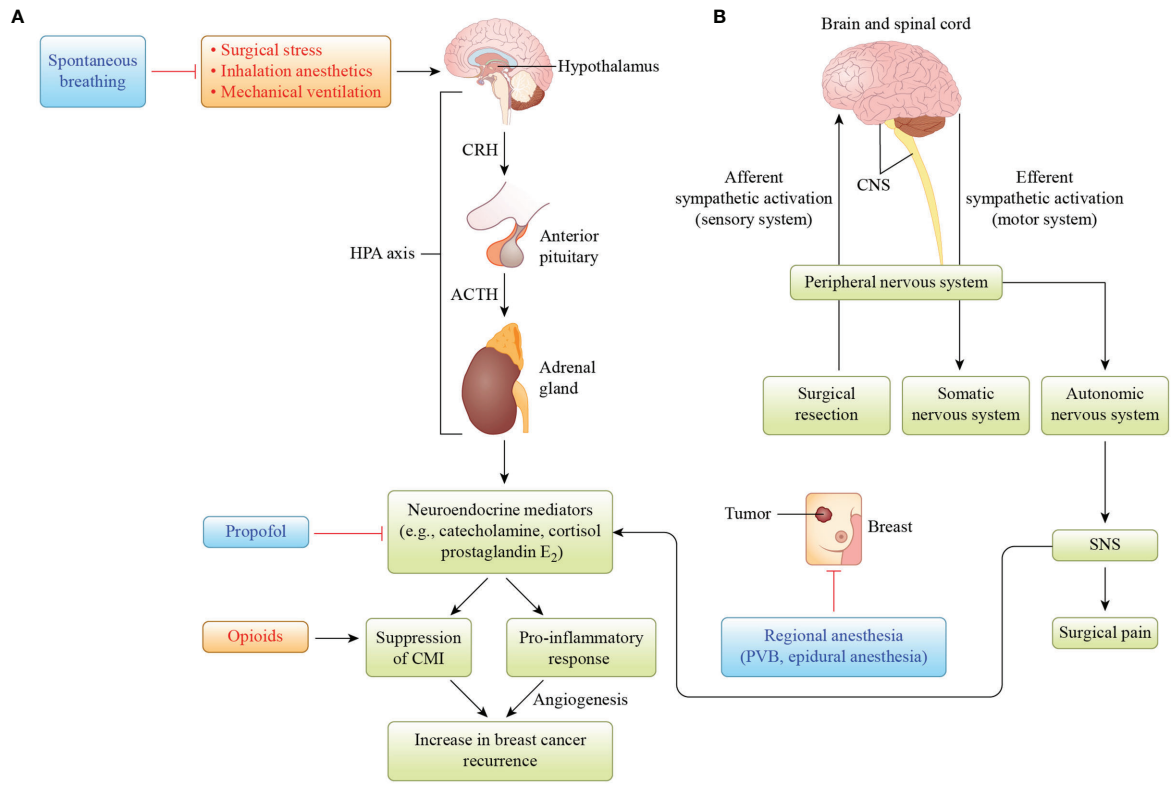

FIGURE 1 | Illustration of the hypothesis that hypothalamus–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) activation by surgical stress, inhalation anesthetics, and mechanical ventilation is involved in increased breast cancer recurrence. **(A)** Activation of the HPA axis results in the release of neuroendocrine mediators such as catecholamine, cortisol, and prostaglandin E_2. These mediators suppress cell-mediated immunity (CMI), resulting in host immunosuppression, and produce pro-inflammatory cytokines to induce angiogenesis, which has been associated with increased breast cancer recurrence. Propofol protects against CMI suppression mediated by neuroendocrine mediators, whereas opioids suppress CMI. **(B)** When breast cancer surgery activates the afferent nervous system from the peripheral to the central nervous system (CNS), it activates the efferent nervous system from the CNS to the peripheral nervous system, autonomic nervous system, and sympathetic nervous system (SNS), which releases neuroendocrine mediators. Regional anesthesia, such as paravertebral blockade (PVB), or epidural anesthesia inhibits the SNS-induced release of neuroendocrine mediators. Reciprocal activation of the HPA axis and SNS by surgical stress and/or inhalation anesthesia may increase breast cancer recurrence. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

the levels of MMP-3 and -9 in patients undergoing breast cancer surgery (23). Surgical stress and inhalation anesthesia may increase distant metastasis in patients with cancer by activating the HPA axis and the SNS *via* the release of neuroendocrine mediators such as cortisol, catecholamines, and PGE_2. Sevoflurane increases the proliferation, migration, and invasion of estrogen receptor (ER)-positive and -negative breast cancer cells (24). Furthermore, serum from patients who received propofol and PVB, but not from those who received sevoflurane and opioids, for breast cancer surgery inhibited the growth of ER-negative breast cancer cells *in vitro* (25). On the other hand, a recent study showed that sevoflurane, especially at high concentrations, inhibits the migration, invasion, and epithelial–mesenchymal transition (EMT) of breast cancer cells, mediated by the upregulation of micro-RNA (miR)-139-5p and down-regulation of adenosine diphosphate–ribosylation factor 6 (ARF6) due to miR-139-5p–ARF6 binding *in vitro* (26). These effects are based on the involvement of miR-139-5p in the metastatic processes of breast cancer cell migration and invasion, and the key functional role of ARF6 in tumor angiogenesis (27, 28).

Opioids

Opioids such as morphine stimulate the growth of tumor cells *in vitro*, and synthetic opioids such as fentanyl and remifentanil also inhibit CMI. Most opioids inhibit the proliferation of T lymphocytes (29). Morphine inhibits NK cell cytotoxicity and T cell proliferation and differentiation, promotes T lymphocyte apoptosis, and decreases the expression of the lipopolysaccharide receptor toll-like receptor 4 on macrophages *in vitro* and *in vivo* (29–32). Similarly, fentanyl was found to decrease NK cell cytotoxicity, resulting in lung metastasis, in an animal model (33), but to increase regulatory T cell (Treg) expression in patients who had undergone breast cancer surgery (34). Remifentanil has also been shown to inhibit NK cell cytotoxicity and T lymphocyte proliferation in a rat model

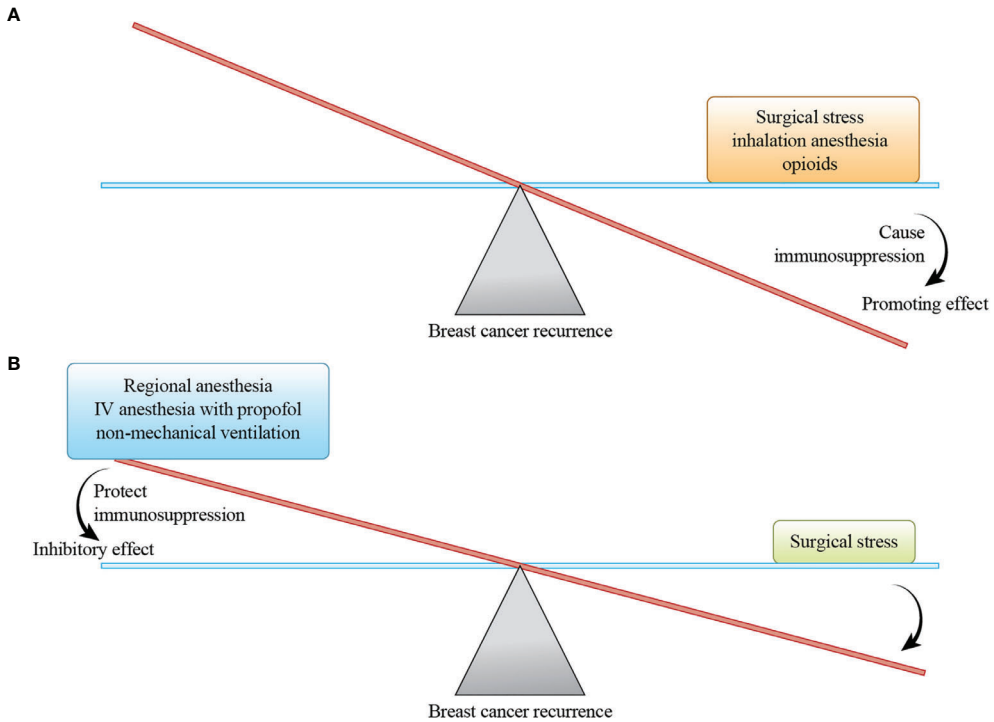

FIGURE 2 | A hypothetical balance of recurrence-promoting and -inhibiting factors related to breast cancer surgery. The magnitude of the promoting effect depends on the size of the breast cancer surgery, and the magnitude of the inhibitory effect depends on the inhibiting factors selected. **(A)** Surgical stress, inhalation anesthesia, and opioids promote breast cancer recurrence by causing immunosuppression. **(B)** Regional anesthesia, intravenous (IV) anesthesia with propofol, and non-mechanical ventilation reduce breast cancer recurrence by protecting immunosuppression.

(35). Opioid analgesics may affect tumor development by modulating cell proliferation and cell death (36–38). Various immunocompetent cells express μ-opioid receptors (MORs) and induce apoptosis under opioid alkaloid treatment, suggesting that opioids suppress the immune response (39). In contrast, the overexpression of MORs, which promotes tumor growth and metastasis, has been observed in several human cancers (40).

The tumor growth–promoting effects of opioids are mediated by a signaling cascade involving Akt and extracellular signal–regulated kinase (ERK), whereas their death-promoting effects are mediated by the inhibition of nuclear factor-κB (NF-κB), increased expression of Fas, stabilization of p53, and activation of p38 and c-Jun-N-terminal kinase (39). In a recent study, morphine promoted angiogenesis and tumor cell proliferation in recurrent breast tumors in nude mice after breast cancer surgery, likely with the involvement of the PI3K/c-Myc signaling pathway (41). In a triple-negative (TN) breast cancer xenograft model, morphine promoted TN breast cancer metastasis and angiogenesis, and the non-steroidal anti-inflammatory drug (NSAID) ketorolac inhibited these effects, possibly due to its enhancement of thrombospondin-1 synthesis and inactivation of the PI3K/Akt/c-Myc pathway (42).

Opioid-induced cell proliferation and cell death are thought to depend on the opioid concentration and duration of exposure. *In vitro*, low concentrations and single doses of opioids promote tumor growth, whereas chronic use and high opioid concentrations inhibit this growth (43). Clinically useful doses of morphine have been shown to promote tumor neovascularization and progression in xenograft models of human breast cancer (38), and to promote angiogenesis and the progression of ER-negative breast cancer *in vitro* and *in vivo* (44). Morphine also stimulates the proliferation of vascular endothelial cells, which is mediated by the mitogen-activated protein kinase pathway, *in vitro* (45). MORs are thought to play important roles in angiogenesis and carcinogenic signaling. On the other hand, the preoperative and postoperative use of morphine as analgesia was found to decrease the tumor-promoting effects of surgery (46) and to significantly suppress the surgery-induced increase in corticosterone production (47) in rat models. These results suggest that preoperative morphine administration plays an important role in the prevention of surgery-induced metastasis. Indeed, a recent study showed that increases in intraoperative opioid doses improved recurrence-free survival (RFS), but not overall survival (OS), in patients with TN breast cancer (48). The authors explained this effect by noting that the expression of opioid receptors in tumor and immune cells was consistent with the protective effect of opioid agonists, with no or decreased expression of protumor receptors and elevated expression of antitumor receptors (48).

Tramadol and Dexmedetomidine

Analgesic use after breast cancer surgery may also affect long-term outcomes. Tramadol is an atypical opioid analgesic that has shown antitumor effects on breast cancer cells *in vitro* and *in vivo* (49, 50). The mechanism by which tramadol exerts these effects involves cell cycle arrest and the induction of apoptosis *via* ERK, due to the decreased expression of 5-hydroxytryptamine$_{2B}$ receptor and transient receptor potential vanilloid-1, as demonstrated by *in-vitro* experiments (49). *In vivo*, tramadol administration decreased the expression of inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF- α), which are involved in tumor growth and invasion, and maintained NK cell activity, unlike morphine (50). Tramadol activates the host immune system by increasing lymphocyte proliferation and NK cell activity in patients with cancer (29). Furthermore, a retrospective analysis showed that tramadol use was associated with reduced breast cancer recurrence and mortality in patients who had undergone breast cancer surgery (49).

Dexmedetomidine (DEX) is a selective α2 adrenergic receptor agonist that has analgesic and antiemetic effects and can be used as an anesthetic adjuvant in cancer surgery. An RCT conducted to evaluate the effect of DEX on perioperative immune function in patients undergoing MT showed that DEX maintains the host immune function, as reflected in the expression of immune cells such as CD4/8 and NK cells, and cytokines such as IL-2, IL-6, and IL-10 (51). Furthermore, a meta-analysis showed that the use of DEX as an adjuvant to anesthetics reduces the use of analgesics such as tramadol, morphine, and fentanyl; prolongs the time to patients' first analgesic request; and relieves postoperative pain (52). The mechanism by which DEX exerts its analgesic effect is unclear, but it may be related to the decreased expression of inflammatory cytokines such as IL-6, TNF-α, and C-reactive protein (53). Furthermore, DEX administration has been shown to enhance host protective immunity, including increases in NK and CD4+ cells and CD4/CD8 and T helper cell (Th)1/Th2 ratios, *via* suppression of the HPA axis and SNS stimulation of the surgical stress response in the setting of cancer surgery (53). Despite its anti-inflammatory effects, however, DEX has also been reported to be tumor promoting. It was shown to promote breast cancer cell proliferation, migration, and invasion *via* activation of the α2B adrenergic receptor/ERK signaling pathway *in vitro* and *in vivo* (54), and to promote the metastasis of breast, lung, and colon cancer cells, mediated by the α2 adrenergic receptor, in animal models (55).

Regional and Intravenous Anesthesia

RA (e.g., PVB and epidural anesthesia) is expected to suppress neuroendocrine stress responses, reduce the need for opioids, decrease immunosuppression, and induce antitumor and anti-inflammatory responses, contributing to the reduction of cancer recurrence, due to the effects of LA on the whole body. Clinical trials suggest that the use of RA and avoidance of opioids is beneficial, but the isolated benefits of abstaining from opioids and adding RA are unclear.

IVA with propofol does not suppress CMI, but it increases cytotoxic T lymphocyte (CTL) activity, decreases inflammatory cytokine levels, and suppresses cyclooxygenase 2 and PGE_2 functions (10, 56, 57). The *in-vitro* activity of CTLs against EL4 tumor cells was significantly greater after propofol injection than after the injection of vehicle (Intralipid; Nihon Pharmaceutical, Co., Ltd., Osaka, Japan) or saline (10). Propofol also inhibited the growth of EL4 tumors inoculated into mice, suggesting that it has an immune-mediated antitumor effect (10). Propofol and lidocaine reduced lung metastasis, whereas methylprednisolone increased such metastasis, in a mouse model of breast cancer surgery under sevoflurane anesthesia (56).

Propofol maintains the host immune defense *via* NK cells and innate immunity, and may increase the survival rate of patients with breast cancer more effectively than do inhalational anesthetics (58). Propofol is thought to have antitumor and tumor-promoting effects, depending on its concentration (58). It has been found to inhibit breast tumor invasion and migration by affecting the expression of MMPs, enzymes that play important roles in the degradation of extracellular proteins and EMT (59), *via* NF-κB inhibition *in vitro* (60). In another *in-vitro* study, propofol inhibited the migration, but not proliferation, of ER-positive and -negative breast cancer cells, mediated by decreased expression of neuroepithelial transforming gene 1, which is associated with enhanced migration (61). *In-vitro* studies have shown that propofol induces apoptosis in breast cancer cells, by decreasing miR-24 expression and increasing the expression of p27 and cleaved caspase-3 (62), and by increasing the expression of pro-apoptotic proteins such as Bax, Bak, and cytochrome c, followed by the activation of the caspase cascade through an intrinsic apoptotic signaling pathway mediated by reactive oxygen species (63). In addition, propofol was shown in an *in-vitro* study to suppress HIF-1 activation and downstream genes such as VEGF using macrophage cells, which is expected to inhibit the systemic inflammatory response to surgery (64). In terms of tumor-promoting effects, propofol has been found to increase the migration of breast cancer cells in association with the activation of the γ-aminobutyric acid type A receptor (65), and to promote the proliferation and migration of human breast cancer cells in association with the inhibition of p53 and activation of nuclear factor E2–related factor-2 *in vitro* (66). The discrepant effects of propofol on breast cancer may be due to the heterogeneity of this type of cancer; propofol may act differently on different types of cancer cell. In addition, the findings may reflect the lack of standardization of experimental parameters such as the propofol concentration and duration of exposure to cancer cells.

Local Anesthesia

Clinically relevant concentrations of lidocaine, the most commonly used local anesthetic, enhance NK cell activity *in vitro via* the release of lytic granules in a variety of human leukemia cells (57). Local anesthetics inhibit the growth of several types of cancer cell, but the mechanism of action is unknown. These anesthetics block voltage-gated sodium channels (67), which are highly expressed in breast cancer and involved in the metastatic process (68). Local anesthetics that

cause channel blockade inhibit tumor growth. Indeed, lidocaine inhibits tumor cell proliferation and differentiation *in vitro*, exhibits cytotoxicity against mesenchymal stem cells, and may inhibit tumor growth and metastasis (69). Clinically useful concentrations of lidocaine induced the apoptosis of breast cancer cells *in vitro* and *in vivo*, suggesting the usefulness of LA for breast cancer surgery (70). Lidocaine, which inhibits the kinesin motor protein, also decreases the formation and function of tubulin microtentacles *in vitro*, suggesting that it has a novel ability to inhibit breast cancer metastasis (71). The use of lidocaine at clinical concentrations *in vitro* causes DNA demethylation as a tumor-suppressive effect on ER-positive and -negative breast cancer cells (72). In addition, lidocaine was shown to inhibit the growth of luminal, TN, and human epidermal growth factor receptor 2 (HER-2)–positive breast cancer cell lines *in vitro*, the migration of breast tumor epithelial cells relative to normal breast epithelial cells, and the anchorage-independent growth of TN breast cancer cells (73). The intraperitoneal administration of lidocaine improved the survival of mice injected intraperitoneally with TN breast cancer cells at doses comparable to those used for analgesia in current clinical practice (73). These results suggest that clinically relevant concentrations of lidocaine directly inhibit the growth and metastasis of breast cancer cells. Other studies have shown that the systemic administration of amide local anesthetics inhibits the biological properties of cancer cells (74, 75); thus, the systemic administration of lidocaine at the time of tumor resection may inhibit cancer progression. In a mouse model of breast cancer, combination lidocaine and sevoflurane (but not ketamine) anesthesia suppressed lung metastasis, possibly due to the anti-inflammatory and anti-angiogenic effects of lidocaine (74). Similarly, in a mouse model of 4T1 breast cancer with surgery performed under sevoflurane anesthesia, the combined administration of cisplatin and lidocaine significantly reduced lung metastasis compared with the control and the administration of cisplatin alone, but did not reduce liver metastasis compared with the control (75). The serum VEGF and IL-6 levels did not differ significantly among these groups, suggesting that lidocaine enhances the metastasis-inhibiting effect of cisplatin under sevoflurane anesthesia (75).

The plasma concentrations of systemically administered lidocaine (as IVA) are significantly higher than those achieved with RA, but not LA. Furthermore, a recent study showed that perioperative lidocaine IVA reduces the postoperative extracellular trapping of neutrophils, an immune and angiogenic factor, and the postoperative expression of MMP-3 in patients undergoing breast cancer surgery, regardless of the GA technique (76). These results suggest that the intravenous administration of lidocaine at the time of breast cancer surgery reduces the risk of postoperative recurrence.

The local anesthetic ropivacaine has a breast cancer–inhibiting effect *in vitro* due to the disruption of mitochondrial function (77). It inhibited the phosphorylation of Akt, mechanistic target of rapamycin (mTOR), rS6, and ErbB3 binding protein 1 in breast cancer cells, suggesting a link between the Akt/mTOR signaling pathway and mitochondrial function in the context of breast cancer (77). This finding helps us to properly understand the mechanism by which local anesthetics reduce the risk of tumor recurrence. In another study, several local anesthetics (bupivacaine, levobupivacaine, and chloroprocaine) had different *in-vitro* effects on breast cancer cell survival and migration, suggesting that these effects depend on the exposure time, anesthetic type, and cell line (78).

Muscle Relaxants

Muscle relaxants are often used for GA. Increases in doses of the chemical reference substances rocuronium bromide and suxamethonium chloride decreased the numbers of normal breast epithelial cells and hormone receptor (HR)-positive breast cancer cells, but not TN breast cancer cells, *in vitro* (79). Furthermore, rocuronium bromide promoted the invasion, adhesion, and proliferation of TN breast cancer cells, whereas vecuronium bromide had no significant effect on breast cancer cell motility or invasion (79). These findings suggest that certain muscle relaxants affect breast cancer progression.

Mechanical Ventilation

The use of mechanical ventilation during cancer surgery has been hypothesized to promote lung metastasis; in a mouse model, it altered the interstitial and tissue environments of the lung to favor tumor formation (80). The mechanical ventilation of mice implanted with breast cancer cell lines during MT under GA significantly increased the number of circulating breast cancer cells remaining in the lung microvasculature and the occurrence of postoperative lung metastasis (80). Immunohistochemical analysis showed increased infiltration of CD68-positive macrophages in the injured lung parenchyma and metastatic tumors, and increased expression of epithelial cell adhesion molecules in metastatic nodules (80). Lung metastasis induced by mechanical ventilation occurs *via* the attraction of circulating tumor cells (CTCs) to the site of lung injury and promotion of the growth of existing lung micrometastases (80). In addition, the paracrine secretion of pro-inflammatory cytokines may induce metastasis to organs other than the lung (81). These observations suggest that the metastasis-promoting effects of mechanical ventilation during breast cancer surgery under GA need to be considered. Non-intubated metastasectomy with video-assisted thoracic surgery induces fewer inflammatory and immune reactions than does conventional surgery with intubation under GA (82). Moreover, with the de-escalation of breast cancer surgery, outpatient procedures can be performed without mechanical ventilation, with the use of lidocaine LA, low-dose propofol IVA, and/or midazolam sedation, which may reduce the recurrence rate; however, this evidence derives from retrospective cohort studies, not studies involving comparison with alternative anesthetic techniques such as standard GA (83, 84). In addition, awake surgery for breast cancer with LA causes less postoperative lymphopenia and may reduce the risk of tumor progression relative to GA (7). Further RCTs comparing total intravenous anesthesia (TIVA) or inhalation anesthesia with mechanical intubation with propofol IVA and/or sedation are needed to clarify the effect of mechanical ventilation on breast cancer recurrence after BCS.

POSSIBLE MECHANISMS BY WHICH SURGICAL STRESS AND ANESTHESIA-INDUCED IMMUNOSUPPRESSION PROMOTE DISTANT METASTASIS IN PATIENTS WITH BREAST CANCER

As most breast cancer surgeries can consist of BCS with axillary management (e.g., SLNB or ALND), the impact of surgical stress on immunosuppression can be limited. MT with ALND may cause more surgical stress, leading to immunosuppression, and increase breast cancer recurrence relative to BCS with SLNB. Similarly, the use of inhalation anesthesia and opioids during breast cancer surgery can lead to immunosuppression, increasing recurrence and decreasing survival rates. Decreased host immunity may promote the growth of residual tumor cells in the surgically resected area, dormant tumor cells in other organs, and CTCs after surgery.

Breast cancer is a systemic disease; at the time of initial diagnosis, cells released from the primary tumor are circulating and present as micrometastases (85). In the perioperative period, breast cancer cells may escape surveillance by components of the innate and adaptive immune responses, such as NK cells and CTLs, which promotes distant metastasis *via* angiogenesis. Tumor dormancy, a quiescent state, is not well understood clinically; it is considered to comprise the lack of angiogenesis and tumor–host immunological equilibrium (86). Under perioperative immunosuppression, dormant cancer (stem) cells may reawaken and regenerate, and they may be detected as clinically visible foci months or years after surgical resection despite adjuvant treatment (86).

Cancer cells produce an immunosuppressive network of tumor-derived soluble factors (TDSFs), such as VEGF, which in turn recruit myeloid-derived suppressor cells (MDSCs), which are involved in CMI suppression, from the bone marrow (87). In the tumor microenvironment, immunosuppression due to the use of inhalational anesthesia may suppress the anti-metastatic effects of CMI and allow cancer cells to spread, affecting cancer recurrence and long-term outcomes. Immunosuppression induced by TDSFs can affect residual tumor cells and existing micrometastases and may lead to the formation of new metastatic foci (6).

EFFECT OF ANESTHETICS ON TUMOR ANGIOGENESIS, IMMUNE FUNCTION, INFLAMMATION, AND THE CLINICAL OUTCOMES OF BREAST CANCER SURGERY

Sevoflurane is thought to promote angiogenesis, whereas propofol inhibits it. Compared with inhalation anesthesia with sevoflurane, TIVA with propofol/remifentanil effectively inhibited the release of VEGF-C induced by breast cancer surgery, but did not significantly affect the 2-year RFS rate, suggesting that it does not affect short-term breast cancer recurrence (88). Because propofol is less immunosuppressive than inhalation anesthetics, it induces changes in immune cells (e.g., Tregs, Th1 and Th17 cells, NK cells, and CTLs) during breast cancer surgery comparable to those induced by sevoflurane, suggesting that anesthetics have minimal effects on perioperative immune activity (89). The effect of propofol on breast cancer recurrence needs to be investigated further, such as in an RCT comparing the use of RA and TIVA with propofol for anesthesia in breast cancer surgery.

MDSCs are immunosuppressive myeloid cells, and the number of these cells present is related closely to the breast cancer stage, clinical treatment response, and prognosis. Anesthesia with sevoflurane and propofol did not significantly alter the number of MDSCs or the prognosis after breast cancer surgery; compared with BCS, MT with a high degree of surgical stress reduced the number of MDSCs but did not significantly alter the prognosis (90). The postoperative presence of CTCs may be an independent factor influencing long-term outcomes in patients with breast cancer. In an RCT, the type of anesthesia (sevoflurane or propofol) did not affect the number of CTCs present over time after breast cancer surgery, but sevoflurane use significantly increased the maximum number of tumor cells postoperatively (91). In addition, NK cell activity was not associated with the number of CTCs (91).

In another RCT, balanced GA with opioid analgesia increased MOR expression, but not the expression of the immune cell markers CD56, CD57, CD4, and CD68, in resected breast tumors relative to paravertebral-propofol anesthesia (92). Propofol use may be superior to the use of inhalation agents for anesthesia during breast cancer surgery in terms of host defense immunity, but it did not alter the immune response (in terms of NK cells, CTLs, TNF-α, IL-6, and IL-10) or the apoptosis rate relative to sevoflurane in co-culture with a breast cancer cell line (93).

Inflammation and immunosuppression due to the elevation of the neutrophil-to-lymphocyte ratio (NLR) reflect breast cancer progression and adverse outcomes. In one study, the postoperative (but not preoperative) NLR was lower in the paravertebral propofol group than in the inhalation anesthesia and opioid groups (94), suggesting that paravertebral-propofol anesthesia inhibits the postoperative NLR elevation that may lead to breast cancer recurrence. In addition, NSAIDs may reduce breast cancer recurrence and act on biological mechanisms present in overweight patients. A retrospective study showed that the intraoperative administration of ketorolac was associated with significantly less distant recurrence than was diclofenac administration in patients with high body mass indices undergoing breast cancer surgery (95).

In an RCT, pectoral nerve II block under GA during breast cancer surgery increased the percentage of peripheral NK cells, NK cell–killing activity, and plasma IL-2 level postoperatively relative to GA (96). These results suggest that pectoral nerve II block had a lesser immunosuppressive effect than GA, thereby improving immunity. In another study, propofol-remifentanil anesthesia and postoperative ketorolac analgesia increased NK cell cytotoxicity relative to baseline, whereas sevoflurane-remifentanil anesthesia and postoperative fentanyl analgesia decreased this cytotoxicity, adversely affecting immune function, in patients undergoing breast cancer surgery (97).

RETROSPECTIVE STUDIES

Thirteen retrospective studies on anesthetic techniques and breast cancer recurrence have been reported (**Table 1**). Inhalation GA has been compared with RA techniques such as PVB-based GA (98, 99, 101–103), intravenous propofol–based GA (100, 104, 105, 107–110), and LA and propofol-based anesthesia (106). In two of these studies, recurrence rates were lower and RFS rates were higher in patients who underwent MT with RA or IV propofol–based GA than in those who underwent the procedure with inhalation-based GA (98, 104). In addition, reduced recurrence and increased survival were observed with RA or intravenous propofol–based GA than with inhalation-based GA for BCS and MT in three studies (99, 100, 110). Propensity score matching with the same variables was used in seven studies, of which one showed a potential benefit of propofol anesthesia (110). These findings suggest that RA and intravenous propofol–based GA reduce breast cancer recurrence compared with inhalation GA. However, the sample size and follow-up period were insufficient to assess breast cancer recurrence in some of the studies.

Two meta-analyses including data on breast cancer and other cancers have been reported (**Table 2**). One meta-analysis showed no OS or RFS benefit of GA/RA over inhalation GA for gastrointestinal, prostate, breast, and ovarian cancer surgeries (111). The other meta-analysis showed that propofol-based TIVA for breast, esophageal, and non-small cell lung cancer surgeries (thus not breast cancer surgery alone) was associated with improved OS and RFS relative to inhalation anesthesia (112). Thus, intravenous propofol–based GA, but not GA/RA, may reduce breast cancer recurrence and increase survival compared with inhalation GA.

PROSPECTIVE STUDIES

Two prospective RCTs examining anesthetic techniques and breast cancer recurrence have been reported (**Table 3**). In the

TABLE 1 | Retrospective analyses of anesthetic technique and breast cancer recurrence.

Ref. (year)	Cancer type (patient *n*)	Surgery type	Anesthetic technique	Outcomes	Benefit/ remarks
98 (2006)	Stage I–III breast (*n* = 129)	Mastectomy and axillary clearance	GA/PVA (*n* = 50) *vs.* GA/opioid anesthesia (*n* = 79)	4-fold reduced recurrence or metastasis risk during 2.5 to 4-year follow-up period with GA/PVA Increased RFS at 3 years with GA/PVA (94% vs. 77%)	Positive
99 (2014)	Stage 0–III breast (*n* = 619)	Breast-conserving surgery or total mastectomy	RA (*n* = 123) *vs.* RA/GA (*n* = 90) *vs.* GA (*n* = 406)	Trend of reduced recurrence with RA, with or without GA	Potential benefit
100 (2014)	Breast, colon, rectal (*n* = 2838)	Radical cancer surgery	Propofol (*n* = 902) *vs.* sevoflurane (*n* = 1935)	Favorable 1- and 5-year OS rates with propofol	Potential benefit
101 (2015)	Stage 0–III breast (*n* = 358)	Partial or total mastectomy without axillary node dissection	GA/PVA (*n* = 193) *vs.* GA (*n* = 165)	No difference in recurrence	Negative
102 (2016)	Stage 0–III breast (*n* = 1107)	Mastectomy or breast-conserving surgery	LRA (*n* = 646) *vs.* GA (*n* = 461); PSM (*n* = 375 each)	No difference in OS, DFS, or LRR	Negative/PSM
103 (2016)	Stage I–III breast (*n* = 792)	Mastectomy with or without axillary node dissection	PVB (*n* = 198) *vs.* opioid-based analgesia (*n* = 594); PSM (*n* = 197 each)	No difference in RFS or OS	Negative/PSM
104 (2016)	Stage I–III breast (*n* = 325)	Modified radical mastectomy	Propofol TIVA (*n* = 173) *vs.* sevoflurane (*n* = 152)	Less recurrence over 5 years with propofol	Positive
105 (2017)	Stage I–III breast (*n* = 2645)	Breast-conserving surgery or mastectomy	Propofol TIVA (*n* = 56) *vs.* inhalation anesthesia (*n* = 2589): PSM (1:5 matching for each inhalation agent)	No difference in RFS or OS	Negative/PSM
106 (2017)	Stage I–II breast (*n* = 91, elderly)	Breast-conserving surgery with SLNB or axillary dissection	LA/midazolam/remifentanil/propofol (*n* = 37) *vs.* GA (*n* = 54)	No difference in locoregional RFS or OS	Negative
107 (2019)	Stage 0–III breast (*n* = 976)	Breast cancer surgery	Propofol (*n* = 344) *vs.* desflurane (*n* = 632); PSM (*n* = 296, 592)	No difference in LRR or 5-year OS	Negative/PSM
108 (2019)	Stage 0–III breast (*n* = 5331)	Breast-conserving surgery or total mastectomy	Propofol TIVA (*n* = 3085) *vs.* inhalation anesthesia (*n* = 2246); PSM (*n* = 1766 each)	No difference in 5-year RFS or OS	Negative/PSM
109 (2020)	Stage 0–III breast (*n* = 1026)	Mastectomy	Propofol TIVA (*n* = 814) *vs.* sevoflurane (*n* = 212); PSM (*n* = 159 each)	No difference in 1-year RFS HR for recurrence or metastasis after sevoflurane vs. propofol was significantly higher for luminal B HER-2 (+) subtype than for other subtypes	Negative/PSM
110 (2020)	Stage 0–IV breast (*n* = 6305)	Total or partial mastectomy, with or without axillary clearance	Propofol (*n* = 3296) *vs.* sevoflurane (*n* = 3209)	Trend toward better 5-year OS with propofol	Potential benefit/PSM

GA, general anesthesia; PVA, paravertebral anesthesia; RFS, recurrence-free survival; RA, regional anesthesia; OS, overall survival; LRA, local or regional anesthesia; PSM, propensity score-matched analysis; DFS, disease-free survival; LRR, locoregional recurrence; PVB, paravertebral block; TIVA, total intravenous anesthesia; SLNB, sentinel lymph-node biopsy; LA, local anesthesia; HR, hazard ratio; HER-2, human epidermal growth factor receptor 2.

TABLE 2 | Meta-analyses of anesthetic technique and breast cancer recurrence.

Ref. (year)	Cancer type (patient *n*)	Surgery type	Anesthetic technique	Outcomes	Benefit/ remarks
111 (2017)	Gastrointestinal, breast, prostate, ovarian (*n* = 67,577)	Cancer surgery	RA/inhalation anesthesia vs. inhalation anesthesia	No difference in OS, RFS, or BRFS Some benefit of OS in RCT on colorectal cancer	Negative
112 (2019)	Breast, esophageal, NSLC (*n* = 7866) Breast, colorectal, gastric, esophageal, NSLC, mixed (*n* = 18,778)	Radical cancer surgery	Propofol TIVA vs. inhalation anesthesia	Improved RFS with TIVA Improved OS with TIVA	Positive

RCT, randomized controlled trial; NSLC, non-small cell lung cancer; BRFS, biochemical recurrence-free survival.

first trial, the use of standardized GA alone, GA plus single-injection thoracic paravertebral block (TPVB), and GA plus TPVB for 72 continuous hours was compared in a total of 180 patients with breast cancer undergoing modified radical MT (113). Neither TPVB technique had a major effect on postoperative local recurrence, metastasis, or 5-year mortality (113). The sample size and follow-up period in that study were insufficient for comprehensive evaluation of the effect of PVB on breast cancer recurrence. In the second RCT, breast cancer recurrence at a median of 36 months did not differ according to the use of PVB/propofol-based GA or sevoflurane/opioid-based GA in a total of 2108 patients who underwent surgery for breast cancer (114). That study was designed based on a retrospective report that GA/PVB reduced breast cancer recurrence at 3 years postoperatively by about one-fourth compared with GA/opioid use in patients who underwent MT with ALND (98), but it did not yield the same results. Several factors may explain this discrepancy. First, there was a large overlap in the use of propofol, sevoflurane, and opioids in both groups in the prospective study. Second, patients in that study did not undergo MT, and more than 30% of BCSs included were performed in China. Third, the median follow-up period was insufficient, as >50% of HR-positive breast cancers recur at >5 years postoperatively. Fourth, the frequency of breast cancer recurrence depends on the tumor subtype; TN and HER-2-positive breast cancers are more likely to recur than are HR-positive breast cancers. However, the randomization variables used in the prospective study pertain only to ER status. These factors may have led to bias and prevent the drawing of an accurate conclusion regarding the effect of PVB on breast cancer recurrence.

Three prospective RCTs (one completed and two ongoing) have been designed to investigate the relationship between anesthesia technique and breast cancer recurrence. A pilot trial (NCT01975064) examined the effects of propofol IVA and sevoflurane anesthesia on survival after radical surgery in patients with breast, colorectal, prostate, melanoma, lung, and other cancers; of 217 eligible patients, 146 were recruited (67.3% recruitment rate), supporting the performance of a large RCT to determine the effect of anesthetic technique on cancer recurrence (115). In the second trial (NCT04074460), the efficacy of propofol IVA and inhalation anesthetics such as sevoflurane, isoflurane, and desflurane is being compared in terms of recruitment (75%) and anesthesia administration (90%) success rates among eligible patients with breast, colorectal, prostate, lung, melanoma, and other cancers. In the third trial (NCT01916317), the effects of the perioperative injection of lidocaine in the setting of breast cancer are being examined as part of the assessment of the *in-vivo* ability of local anesthetics to reduce the dissemination of cancer cells during surgery and improve the disease-free interval (i.e., affect tumor recurrence). Future RCTs must be designed with consideration of the breast cancer surgery type and use of mechanical ventilation, as the use of less-immunosuppressive anesthesia and non-mechanical ventilation may best reduce breast cancer recurrence. For patients who have undergone MT with SLNB or ALND, the effects of propofol IVA with RA and inhalation anesthesia with opioids could be compared. For patients who have undergone BCS with SLNB, the effects of mechanical and non-mechanical ventilation could be compared.

CONCLUDING REMARKS

At this time, RCTs have not provided sufficient evidence that the anesthetic technique is associated with the recurrence rate or long-term outcomes in patients undergoing breast cancer surgery. Preclinical and clinical studies have provided

TABLE 3 | Prospective randomized trials on anesthetic technique and breast cancer recurrence.

Ref. (year)	Cancer type (patient *n*)	Surgery type	Anesthetic technique	Outcomes	Benefit/ remarks
113 (2017)	Stage I–IV breast (*n* = 180)	Modified radical mastectomy	GA (*n* = 58) vs. GA with single-injection TPVB (*n* = 56) vs. GA with continuous TPVB for 72 h postoperatively (*n* = 59)	Little to no effect of TPVB on local recurrence, metastasis, or mortality at 5 years	Negative
114 (2019)	Stage 0–III breast (*n* = 2132)	Breast cancer surgery	RA/propofol (*n* = 1043) vs. sevoflurane/opioids (*n* = 1065)	No difference in recurrence at a median of 36 months	Negative

TPVB, thoracic paravertebral block.

conflicting data on the effects of inhalation anesthetics, propofol, and opioids on the immune response and breast cancer growth. However, RA (e.g., PVB or propofol IVA), LA, and/or non-mechanical ventilation with non-opioid anesthesia may reduce breast cancer recurrence compared with intravenous or inhalation GA, opioid use, and/or mechanical ventilation. As most current breast cancer surgeries, especially BCS, are performed with IVA, the superiority of this technique to inhalation anesthesia may be difficult to evaluate. Nevertheless, such efforts are being made in ongoing RCTs, and we await their results for breast cancer and other cancers. Further such trials are needed for the development of systemic breast cancer therapies, which will bring us closer to a cure for primary breast cancer.

AUTHOR CONTRIBUTIONS

Conceptualization, RK. Resources, RK. Writing—original draft preparation, RK. Writing—review and editing, RK, AK, MW, and TK. All authors contributed to the article and approved it for publication.

REFERENCES

1. Kim R. Anesthetic Technique and Cancer Recurrence in Oncologic Surgery: Unraveling the Puzzle. *Cancer Metastasis Rev* (2017) 36:159–77. doi: 10.1007/s10555-016-9647-8
2. Schlagenhauff B, Ellwanger U, Breuninger H, Stroebel W, Rassner G, Garbe C. Prognostic Impact of the Type of Anaesthesia Used During the Excision of Primary Cutaneous Melanoma. *Melanoma Res* (2000) 10:165–9. doi: 10.1097/00008390-200004000-00009
3. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune Modulation by Volatile Anesthetics. *Anesthesiology* (2016) 125:399–411. doi: 10.1097/ALN.0000000000001195
4. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, But Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth Analg* (2003) 97:1331–9. doi: 10.1213/01.ane.0000082995.44040.07
5. Loop T, Dovi-Akue D, Frick M, Roesslein M, Egger L, Humar M, et al. Volatile Anesthetics Induce Caspase-Dependent, Mitochondria-Mediated Apoptosis in Human T Lymphocytes *In Vitro*. *Anesthesiology* (2005) 102:1147–57. doi: 10.1097/00000542-200506000-00014
6. Kim R. Effects of Surgery and Anesthetic Choice on Immunosuppression and Cancer Recurrence. *J Transl Med* (2018) 16:8. doi: 10.1186/s12967-018-1389-7
7. Vanni G, Materazzo M, Perretta T, Meucci R, Anemona L, Buonomo C, et al. Impact of Awake Breast Cancer Surgery on Postoperative Lymphocyte Responses. *In Vivo* (2019) 33:1879–84. doi: 10.21873/invivo.11681
8. Tang F, Tie Y, Tu C, Wei X. Surgical Trauma-Induced Immunosuppression in Cancer: Recent Advances and the Potential Therapies. *Clin Transl Med* (2020) 10:199–223. doi: 10.1002/ctm2.24
9. Yardeni IZ, Beilin B, Mayburd E, Alcalay Y, Bessler H. Relationship Between Fentanyl Dosage and Immune Function in the Postoperative Period. *J Opioid Manag* (2008) 4:27–33. doi: 10.5055/jom.2008.0005
10. Kushida A, Inada T, Shingu K. Enhancement of Antitumor Immunity After Propofol Treatment in Mice. *Immunopharmacol Immunotoxicol* (2007) 29:477–86. doi: 10.1080/08923970701675085
11. Xuan W, Hankin J, Zhao H, Yao S, Ma D. The Potential Benefits of the Use of Regional Anesthesia in Cancer Patients. *Int J Cancer* (2015) 137:2774–84. doi: 10.1002/ijc.29306
12. Mao L, Lin S, Lin J. The Effects of Anesthetics on Tumor Progression. *Int J Physiol Pathophysiol Pharmacol* (2013) 5:1–10.
13. Looney M, Doran P, Buggy DJ. Effect of Anesthetic Technique on Serum Vascular Endothelial Growth Factor C and Transforming Growth Factor β in Women Undergoing Anesthesia and Surgery for Breast Cancer. *Anesthesiology* (2010) 113:1118–25. doi: 10.1097/ALN.0b013e3181f79a69
14. Baum M, Demicheli R, Hrushesky W, Retsky M. Does Surgery Unfavourably Perturb the "Natural History" of Early Breast Cancer by Accelerating the Appearance of Distant Metastases? *Eur J Cancer* (2005) 41:508–15. doi: 10.1016/j.ejca.2004.09.031
15. Retsky M, Demicheli R, Hrushesky WJ. Does Surgery Induce Angiogenesis in Breast Cancer? Indirect Evidence From Relapse Pattern and Mammography Paradox. *Int J Surg* (2005) 3:179–87. doi: 10.1016/j.ijsu.2005.08.002
16. Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival After Lumpectomy and Mastectomy for Early Stage Invasive Breast Cancer: The Effect of Age and Hormone Receptor Status. *Cancer* (2013) 119:1402–11. doi: 10.1002/cncr.27795
17. Hofvind S, Holen A, Aas T, Roman M, Sebuødegård S, Akslen LA. Women Treated With Breast Conserving Surgery Do Better Than Those With Mastectomy Independent of Detection Mode, Prognostic and Predictive Tumor Characteristics. *Eu J Surg Oncol* (2015) 41:1417–22. doi: 10.1016/j.ejso.2015.07.002
18. de Boniface J, Szulkin R, Johansson ALV. Survival After Breast Conservation vs Mastectomy Adjusted for Comorbidity and Socioeconomic Status: A Swedish National 6-Year Follow-Up of 48 986 Women. *JAMA Surg* (2021) 156:628–37. doi: 10.1001/jamasurg.2021.1438
19. Zhao T, Xia WH, Zheng MQ, Lu CQ, Han X, Sun YJ. Surgical Excision Promotes Tumor Growth and Metastasis by Promoting Expression of MMP-9 and VEGF in a Breast Cancer Model. *Exp Oncol* (2008) 30:60–4.
20. Padua D, Zhang XH, Wang Q, Nadal C, Gerald WL, Gomis RR, et al. TGFbeta Primes Breast Tumors for Lung Metastasis Seeding Through Angiopoietin-Like 4. *Cell* (2008) 133:66–77. doi: 10.1016/j.cell.2008.01.046
21. Demicheli R, Miceli R, Moliterni A, Zambetti M, Hrushesky WJ, Retsky MW, et al. Breast Cancer Recurrence Dynamics Following Adjuvant CMF Is Consistent With Tumor Dormancy and Mastectomy-Driven Acceleration of the Metastatic Process. *Ann Oncol* (2005) 16:1449–57. doi: 10.1093/annonc/mdi280
22. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer Recurrence After Surgery: Direct and Indirect Effects of Anesthetic Agents. *Int J Cancer* (2012) 130:1237–50. doi: 10.1002/ijc.26448
23. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic Technique and the Cytokine and Matrix Metalloproteinase Response to Primary Breast Cancer Surgery. *Reg Anesth Pain Med* (2010) 35:490–5. doi: 10.1097/AAP.0b013e3181ef4d05
24. Ecimovic P, McHugh B, Murray D, Doran P, Buggy DJ. Effects of Sevoflurane on Breast Cancer Cell Function. *vitro Anticancer Res* (2013) 33:4255–60.
25. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of Anaesthetic Technique on Oestrogen Receptor-Negative Breast Cancer Cell Function *In Vitro*. *Br J Anaesth* (2009) 103:685–90. doi: 10.1093/bja/aep261
26. Wu T, Sun L, Wang C, Yu P, Cheng L, Chen Y. Sevoflurane Suppresses the Migration, Invasion, and Epithelial-Mesenchymal Transition of Breast Cancer Cells Through the miR-139-5p/ARF6 Axis. *J Surg Res* (2021) 258:314–23. doi: 10.1016/j.jss.2020.08.051
27. Krishnan K, Steptoe AL, Martin HC, Pattabiraman DR, Nones K, Waddell N, et al. miR-139-5p Is a Regulator of Metastatic Pathways in Breast Cancer. *RNA* (2013) 19:1767–80. doi: 10.1261/rna.042143.113
28. Hongu T, Funakoshi Y, Fukuhara S, Suzuki T, Sakimoto S, Takakura N, et al. Arf6 Regulates Tumour Angiogenesis and Growth Through HGF-Induced Endothelial β1 Integrin Recycling. *Nat Commun* (2015) 6:7925. doi: 10.1038/ncomms8925

29. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, et al. The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients. *Anesth Analg* (2000) 90:1411–4. doi: 10.1097/00000539-200006000-00028
30. Gao M, Sun J, Jin W, Qian Y. Morphine, But Not Ketamine, Decreases the Ratio of Th1/Th2 in CD4-Positive Cells Through T-Bet and GATA3. *Inflammation* (2012) 35:1069–77. doi: 10.1007/s10753-011-9413-6
31. Franchi S, Moretti S, Castelli M, Lattuada D, Scavullo C, Panerai AE, et al. Mu Opioid Receptor Activation Modulates Toll Like Receptor 4 in Murine Macrophages. *Brain Behav Immun* (2012) 26:480–8. doi: 10.1016/j.bbi.2011.12.010
32. Das J, Kumar S, Khanna S, Mehta Y. Are We Causing the Recurrence-Impact of Perioperative Period on Long-Term Cancer Prognosis: Review of Current Evidence and Practice. *J Anaesthesiol Clin Pharmacol* (2014) 30:153–9. doi: 10.4103/0970-9185.129996
33. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B. Effects of Fentanyl on Natural Killer Cell Activity and on Resistance to Tumor Metastasis in Rats. Dose and Timing Study. *Neuroimmunomodulation* (2004) 11:255–60. doi: 10.1159/000078444
34. Gong L, Qin Q, Zhou L, Ouyang W, Li Y, Wu Y, et al. Effects of Fentanyl Anesthesia and Sufentanil Anesthesia on Regulatory T Cells Frequencies. *Int J Clin Exp Pathol* (2014) 7:7708–16.
35. Sacerdote P, Gaspani L, Rossoni G, Panerai AE, Bianchi M. Effect of the Opioid Remifentanil on Cellular Immune Response in the Rat. *Int Immunopharmacol* (2001) 1:713–9. doi: 10.1016/s1567-5769(01)00005-4
36. Hatzoglou A, Bakogeorgou E, Castanas E. The Antiproliferative Effect of Opioid Receptor Agonists on the T47D Human Breast Cancer Cell Line, Is Partially Mediated Through Opioid Receptors. *Eur J Pharmacol* (1996) 296:199–207. doi: 10.1016/0014-2999(95)00703-2
37. Singhal PC, Sharma P, Kapasi AA, Reddy K, Franki N, Gibbons N. Morphine Enhances Macrophage Apoptosis. *J Immunol* (1998) 160:1886–93.
38. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, et al. Morphine Stimulates Angiogenesis by Activating Proangiogenic and Survival-Promoting Signaling and Promotes Breast Tumor Growth. *Cancer Res* (2002) 62:4491–8.
39. Tegeder I, Geisslinger G. Opioids as Modulators of Cell Death and Survival–Unraveling Mechanisms and Revealing New Indications. *Pharmacol Rev* (2004) 56:351–69. doi: 10.1124/pr.56.3.2
40. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-Opioid Receptor Expression in Metastatic Lung Cancer. *Br J Anaesth* (2014) 113 Suppl 1:103–8. doi: 10.1093/bja/aeu165
41. Cheng S, Guo M, Liu Z, Fu Y, Wu H, Wang C, et al. Morphine Promotes the Angiogenesis of Postoperative Recurrent Tumors and Metastasis of Dormant Breast Cancer Cells. *Pharmacology* (2019) 104:276–86. doi: 10.1159/000502107
42. Liu Z, Cheng S, Fu G, Ji F, Wang C, Cao M. Postoperative Administration of Ketorolac Averts Morphine-Induced Angiogenesis and Metastasis in Triple-Negative Breast Cancer. *Life Sci* (2020) 251:117604. doi: 10.1016/j.lfs.2020.117604
43. Lin X, Wang YJ, Li Q, Hou YY, Hong MH, Cao YL, et al. Chronic High-Dose Morphine Treatment Promotes SH-SY5Y Cell Apoptosis *via* C-Jun N-Terminal Kinase-Mediated Activation of Mitochondria-Dependent Pathway. *FEBS J* (2009) 276:2022–36. doi: 10.1111/j.1742-4658.2009.06938.x
44. Bimonte S, Barbieri A, Rea D, Palma G, Luciano A, Cuomo A, et al. Morphine Promotes Tumor Angiogenesis and Increases Breast Cancer Progression. *BioMed Res Int* (2015) 2015:161508. doi: 10.1155/2015/161508
45. Leo S, Nuydens R, Meert TF. Opioid-Induced Proliferation of Vascular Endothelial Cells. *J Pain Res* (2009) 2:59–66. doi: 10.2147/jpr.s4748
46. Page GG, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine Attenuates Surgery-Induced Enhancement of Metastatic Colonization in Rats. *Pain* (1993) 54:21–8. doi: 10.1016/0304-3959(93)90095-7
47. Page GG, McDonald JS, Ben-Eliyahu S. Pre-Operative Versus Postoperative Administration of Morphine: Impact on the Neuroendocrine, Behavioural, and Metastatic-Enhancing Effects of Surgery. *Br J Anaesth* (1998) 81:216–23. doi: 10.1093/bja/81.2.216
48. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative Opioids Are Associated With Improved Recurrence-Free Survival in Triple-Negative Breast Cancer. *Br J Anaesth* (2021) 126:367–76. doi: 10.1016/j.bja.2020.10.021
49. Kim MH, Oh JE, Park S, Kim JH, Lee KY, Bai SJ, et al. Tramadol Use Is Associated With Enhanced Postoperative Outcomes in Breast Cancer Patients: A Retrospective Clinical Study With *In Vitro* Confirmation. *Br J Anaesth* (2019) 123:865–76. doi: 10.1016/j.bja.2019.09.004
50. Kim MH, Yoo JH, Cho HJ, Ko KJ, Jun KW, Han KD, et al. Identification for Antitumor Effects of Tramadol in a Xenograft Mouse Model Using Orthotopic Breast Cancer Cells. *Ann Surg Treat Res* (2021) 101:291–8. doi: 10.4174/astr.2021.101.5.291
51. Yang XH, Bai Q, Lv MM, Fu HG, Dong TL, Zhou Z. Effect of Dexmedetomidine on Immune Function of Patients Undergoing Radical Mastectomy: A Double Blind and Placebo Control Study. *Eur Rev Med Pharmacol Sci* (2017) 21:1112–6.
52. Liu C, Wang W, Shan Z, Zhang H, Yan Q. Dexmedetomidine as an Adjuvant for Patients Undergoing Breast Cancer Surgery: A Meta-Analysis. *Med (Baltimore)* (2020) 99:e23667. doi: 10.1097/MD.0000000000023667
53. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of Dexmedetomidine on Perioperative Stress, Inflammation, and Immune Function: Systematic Review and Meta-Analysis. *Br J Anaesth* (2019) 123:777–94. doi: 10.1016/j.bja.2019.07.027
54. Xia M, Ji NN, Duan ML, Tong JH, Xu JG, Zhang YM, et al. Dexmedetomidine Regulate the Malignancy of Breast Cancer Cells by Activating α2-Adrenoceptor/ERK Signaling Pathway. *Eur Rev Med Pharmacol Sci* (2016) 20:3500–6.
55. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120:188–96. doi: 10.1016/j.bja.2017.11.004
56. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine, Propofol and Steroids on Pulmonary Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers (Basel)* (2019) 11:613. doi: 10.3390/cancers11050613
57. Ramirez MF, Tran P, Cata JP. The Effect of Clinically Therapeutic Plasma Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. *Reg Anesth Pain Med* (2015) 40:43–8. doi: 10.1097/AAP.0000000000000191
58. Li R, Liu H, Dilger JP, Lin J. Effect of Propofol on Breast Cancer Cell, the Immune System, and Patient Outcome. *BMC Anesthesiol* (2018) 18:77. doi: 10.1186/s12871-018-0543-3
59. Gialeli C, Theocharis AD, Karamanos NK. Roles of Matrix Metalloproteinases in Cancer Progression and Their Pharmacological Targeting. *FEBS J* (2011) 278:16–27. doi: 10.1111/j.1742-4658.2010.07919.x
60. Li Q, Zhang L, Han Y, Jiang Z, Wang Q. Propofol Reduces MMPs Expression by Inhibiting NF-κb Activity in Human MDA-MB-231 Cells. *BioMed Pharmacother* (2012) 66:52–6. doi: 10.1016/j.biopha.2011.10.006
61. Ecimovic P, Murray D, Doran P, Buggy DJ. Propofol and Bupivacaine in Breast Cancer Cell Function *In Vitro* - Role of the NET1 Gene. *Anticancer Res* (2014) 34:1321–31.
62. Yu B, Gao W, Zhou H, Miao X, Chang Y, Wang L, et al. Propofol Induces Apoptosis of Breast Cancer Cells by Downregulation of miR-24 Signal Pathway. *Cancer Biomark* (2018) 21:513–9. doi: 10.3233/CBM-170234
63. Wang H, Zhao L, Wu J, Hong J, Wang S. Propofol Induces ROS-Mediated Intrinsic Apoptosis and Migration in Triple-Negative Breast Cancer Cells. *Oncol Lett* (2020) 20:810–6. doi: 10.3892/ol.2020.11608
64. Tanaka T, Takabuchi S, Nishi K, Oda S, Wakamatsu T, Daijo H, et al. The Intravenous Anesthetic Propofol Inhibits Lipopolysaccharide-Induced Hypoxia-Inducible Factor 1 Activation and Suppresses the Glucose Metabolism in Macrophages. *J Anesth* (2010) 24:54–60. doi: 10.1007/s00540-009-0829-1
65. Garib V, Lang K, Niggemann B, Zänker KS, Brandt L, Dittmar T. Propofol-Induced Calcium Signalling and Actin Reorganization Within Breast Carcinoma Cells. *Eur J Anaesthesiol* (2005) 22:609–15. doi: 10.1017/s026502150500102x
66. Meng C, Song L, Wang J, Li D, Liu Y, Cui X. Propofol Induces Proliferation Partially *via* Downregulation of P53 Protein and Promotes Migration *via* Activation of the Nrf2 Pathway in Human Breast Cancer Cell Line MDA-MB-231. *Oncol Rep* (2017) 37:841–8. doi: 10.3892/or.2016.5332
67. Baptista-Hon DT, Robertson FM, Robertson GB, Owen SJ, Rogers GW, Lydon EL, et al. Potent Inhibition by Ropivacaine of Metastatic Colon

Cancer SW620 Cell Invasion and NaV1.5 Channel Function. *Br J Anaesth* (2014) 113 Suppl 1:i39–48. doi: 10.1093/bja/aeu104
68. Fraser SP, Diss JK, Chioni AM, Mycielska ME, Pan H, Yamaci RF, et al. Voltage-Gated Sodium Channel Expression and Potentiation of Human Breast Cancer Metastasis. *Clin Cancer Res* (2005) 11:5381–9. doi: 10.1158/1078-0432.CCR-05-0327
69. Lucchinetti E, Awad AE, Rahman M, Feng J, Lou PH, Zhang L, et al. Antiproliferative Effects of Local Anesthetics on Mesenchymal Stem Cells: Potential Implications for Tumor Spreading and Wound Healing. *Anesthesiology* (2012) 116:841–56. doi: 10.1097/ALN.0b013e31824babfe
70. Chang YC, Liu CL, Chen MJ, Hsu YW, Chen SN, Lin CH, et al. Local Anesthetics Induce Apoptosis in Human Breast Tumor Cells. *Anesth Analg* (2014) 118:116–24. doi: 10.1213/ANE.0b013e3182a94479
71. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. Local Anesthetics Inhibit Kinesin Motility and Microtentacle Protrusions in Human Epithelial and Breast Tumor Cells. *Breast Cancer Res Treat* (2011) 129:691–701. doi: 10.1007/s10549-010-1239-7
72. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine Time- and Dose-Dependently Demethylates Deoxyribonucleic Acid in Breast Cancer Cell Lines *In Vitro*. *Br J Anaesth* (2012) 109:200–7. doi: 10.1093/bja/aes128
73. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, et al. Antitumor Effects of Lidocaine on Human Breast Cancer Cells: An *In Vitro* and *In Vivo* Experimental Trial. *Anticancer Res* (2018) 38:95–105. doi: 10.21873/anticanres.12196
74. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Ketamine-Xylazine Anaesthesia for Breast Tumour Resection in a Murine Model. *Br J Anaesth* (2018) 121:76–85. doi: 10.1016/j.bja.2017.12.043
75. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. *Anticancer Res* (2018) 38:5599–606. doi: 10.21873/anticanres.12894
76. Galos EV, Tat TF, Popa R, Efrimescu CI, Finnerty D, Buggy DJ, et al. Neutrophil Extracellular Trapping and Angiogenesis Biomarkers After Intravenous or Inhalation Anaesthesia With or Without Intravenous Lidocaine for Breast Cancer Surgery: A Prospective, Randomised Trial. *Br J Anaesth* (2020) 125:712–21. doi: 10.1016/j.bja.2020.05.003
77. Gong X, Dan J, Li F, Wang L. Suppression of Mitochondrial Respiration With Local Anesthetic Ropivacaine Targets Breast Cancer Cells. *J Thorac Dis* (2018) 10:2804–12. doi: 10.21037/jtd.2018.05.21
78. Li R, Xiao C, Liu H, Huang Y, Dilger JP, Lin J. Effects of Local Anesthetics on Breast Cancer Cell Viability and Migration. *BMC Cancer* (2018) 18:666. doi: 10.1186/s12885-018-4576-2
79. Jiang A, Zhao H, Cai J, Jiang WG. Possible Effect of Muscle-Relaxant Anaesthetics on Invasion, Adhesion and Migration of Breast Cancer Cells. *Anticancer Res* (2016) 36:1259–65.
80. Huang Y, Pan L, Helou K, Xia Q, Parris TZ, Li H, et al. Mechanical Ventilation Promotes Lung Metastasis in Experimental 4T1 Breast Cancer Lung-Metastasized Models. *Cancer Manag Res* (2018) 10:545–55. doi: 10.2147/CMAR.S142650
81. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity* (2019) 51(1):27–41. doi: 10.1016/j.immuni.2019.06.025
82. Mineo TC, Sellitri F, Vanni G, Gallina FT, Ambrogi V. Immunological and Inflammatory Impact of Non-Intubated Lung Metastasectomy. *Int J Mol Sci* (2017) 18:1466. doi: 10.3390/ijms18071466
83. Kim R, Kawai A, Wakisaka M, Funaoka Y, Nishida Y, Yasuda N, et al. Outcomes of Outpatient Breast Cancer Surgery at a Private Breast Clinic. *Breast J* (2018) 24:628–32. doi: 10.1111/tbj.13012
84. Kim R, Kawai A, Wakisaka M, Sawada S, Shimoyama M, Yasuda N, et al. Outpatient Breast-Conserving Surgery for Breast Cancer: Use of Local and Intravenous Anesthesia and/or Sedation May Reduce Recurrence and Improve Survival. *Ann Med Surg (Lond)* (2020) 60:365–71. doi: 10.1016/j.amsu.2020.10.072
85. Fisher B. Laboratory and Clinical Research in Breast Cancer: A Personal Adventure—The David A. Karnofsky Memorial Lecture. *Cancer Res* (1980) 40:3863–74.
86. Sistigu A, Musella M, Galassi C, Vitale I, De Maria R. Tuning Cancer Fate: Tumor Microenvironment's Role in Cancer Stem Cell Quiescence and Reawakening. *Front Immunol* (2020) 11:2166:2166. doi: 10.3389/fimmu.2020.02166
87. Kim R, Emi M, Tanabe K, Arihiro K. Tumor-Driven Evolution of Immunosuppressive Networks During Malignant Progression. *Cancer Res* (2006) 66:5527–36. doi: 10.1158/0008-5472.CAN-05-4128
88. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of Propofol/Remifentanil-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Release of VEGF-C and TGF-β and Prognosis After Breast Cancer Surgery: A Prospective, Randomized and Controlled Study. *BMC Anesthesiol* (2018) 18:131. doi: 10.1186/s12871-018-0588-3
89. Oh CS, Lee J, Yoon TG, Seo EH, Park HJ, Piao L, et al. Effect of Equipotent Doses of Propofol Versus Sevoflurane Anesthesia on Regulatory T Cells After Breast Cancer Surgery. *Anesthesiology* (2018) 129:921–31. doi: 10.1097/ALN.0000000000002382
90. Yan T, Zhang GH, Cheng YZ, Wu LX, Liu XY, Sun YL, et al. Effects of Anesthetic Technique and Surgery on Myeloid-Derived Suppressor Cells and Prognosis in Women Who Underwent Breast Cancer Surgery: A Prospective Study. *Cancer Manag Res* (2019) 11:5513–22. doi: 10.2147/CMAR.S183519
91. Hovaguimian F, Braun J, Z'graggen BR, Schläpfer M, Dumrese C, Ewald C, et al. Anesthesia and Circulating Tumor Cells in Primary Breast Cancer Patients: A Randomized Controlled Trial. *Anesthesiology* (2020) 133:548–58. doi: 10.1097/ALN.0000000000003409
92. Levins KJ, Prendeville S, Conlon S, Buggy DJ. The Effect of Anesthetic Technique on μ-Opioid Receptor Expression and Immune Cell Infiltration in Breast Cancer. *J Anesth* (2018) 32:792–6. doi: 10.1007/s00540-018-2554-0
93. Lim JA, Oh CS, Yoon TG, Lee JY, Lee SH, Yoo YB, et al. The Effect of Propofol and Sevoflurane on Cancer Cell, Natural Killer Cell, and Cytotoxic T Lymphocyte Function in Patients Undergoing Breast Cancer Surgery: an. *Vitro analysis BMC Cancer* (2018) 18:159. doi: 10.1186/s12885-018-4064-8
94. Ní Eochagáin A, Burns D, Riedel B, Sessler DI, Buggy DJ. The Effect of Anaesthetic Technique During Primary Breast Cancer Surgery on Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Return to Intended Oncological Therapy. *Anaesthesia* (2018) 73:603–11. doi: 10.1111/anae.14207
95. Desmedt C, Demicheli R, Fornili M, Bachir I, Duca M, Viglietti G, et al. Potential Benefit of Intra-Operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index. *J Natl Cancer Inst* (2018) 110:1115–22. doi: 10.1093/jnci/djy042
96. Cui X, Zhu C, Chen P, Qu M, Zhang B, Li H. Effect of Pectoral Nerve Block Type II Under General Anesthesia on the Immune Function of Patients With Breast Cancer. *Am J Surg* (2020) 220:938–44. doi: 10.1016/j.amjsurg.2020.03.008
97. Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *Int J Med Sci* (2017) 14:970–6. doi: 10.7150/ijms.20064
98. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105:660–4. doi: 10.1097/00000542-200610000-00008
99. Koonce SL, Mclaughlin SA, Eck DL, Porter S, Bagaria S, Clendenen SR, et al. Breast Cancer Recurrence in Patients Receiving Epidural and Paravertebral Anesthesia: A Retrospective, Case-Control Study. *Middle East J Anesthesiol* (2014) 22:567–71.
100. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The Choice of Anaesthetic–Sevoflurane or Propofol–and Outcome From Cancer Surgery: A Retrospective Analysis. *Ups J Med Sci* (2014) 119:251–61. doi: 10.3109/03009734.2014.922649
101. Starnes-Ott K, Goravanchi F, Meininger JC. Anesthetic Choices and Breast Cancer Recurrence: A Retrospective Pilot Study of Patient, Disease, and Treatment Factors. *Crti Care Nurs Q* (2015) 38:200–10. doi: 10.1097/CNQ.0000000000000062
102. Tsigonis AM, Al-Hamadani M, Linebarger JH, Vang CA, Krause FJ, Johnson JM, et al. Are Cure Rates for Breast Cancer Improved by Local and Regional Anesthesia? *Reg Anesth Pain Med* (2016) 41:339–47. doi: 10.1097/AAP.0000000000000379

103. Cata JP, Chavez-MacGregor M, Valero V, Black W, Black DM, Goravanchi F, et al. The Impact of Paravertebral Block Analgesia on Breast Cancer Survival After Surgery. *Reg Anesth Pain Med* (2016) 41:696–703. doi: 10.1097/AAP.0000000000000479
104. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of Propofol-Based Total Intravenous Anesthesia on Recurrence and Overall Survival in Patients After Modified Radical Mastectomy: A Retrospective Study. *Korean J Anesthesiol* (2016) 69:126–32. doi: 10.4097/kjae.2016.69.2.126
105. Kim MH, Kim DW, Kim JH, Lee KY, Park S, Yoo YC. Does the Type of Anesthesia Really Affect the Recurrence-Free Survival After Breast Cancer Surgery? *Oncotarget* (2017) 8:90477–87. doi: 10.18632/oncotarget.21014
106. Karanlik H, Kılıç B, Yıldırım I, Bademler S, Ozgur I, Ilhan B, et al. Breast-Conserving Surgery Under Local Anesthesia in Elderly Patients With Severe Cardiorespiratory Comorbidities: A Hospital-Based Case-Control Study. *Breast Care (Basel)* (2017) 12:29–33. doi: 10.1159/000455003
107. Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, et al. Propofol-Based Total Intravenous Anesthesia Did Not Improve Survival Compared to Desflurane Anesthesia in Breast Cancer Surgery. *PloS One* (2019) 14: e0224728. doi: 10.1371/journal.pone.0224728
108. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, et al. Total Intravenous Anesthesia Versus Inhalation Anesthesia for Breast Cancer Surgery: A Retrospective Cohort Study. *Anesthesiology* (2019) 130:31–40. doi: 10.1097/ALN.0000000000002491
109. Shiono S, Shibata SC, Kabata D, Shintani A, Ikeda T, Fujino Y. Comparison of 1-Year Recurrence-Free Survival Between Sevoflurane and Propofol Use for General Anesthesia Management in Primary Breast Cancer Surgery. *J Anesth* (2020) 34:694–701. doi: 10.1007/s00540-020-02806-7
110. Enlund M, Berglund A, Ahlstrand R, Walldén J, Lundberg J, Wärnberg F, et al. Survival After Primary Breast Cancer Surgery Following Propofol or Sevoflurane General Anesthesia-A Retrospective, Multicenter, Database Analysis of 6305 Swedish Patients. *Acta Anaesthesiol Scand* (2020) 64:1048–54. doi: 10.1111/aas
111. Grandhi RK, Lee S, Abd-Elsayed A. The Relationship Between Regional Anesthesia and Cancer: A Metaanalysis. *Ochsner J* (2017) 17:345–61.
112. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B. Global Onco-Anesthesia Research Collaboration Group. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anaesth* (2019) 66:546–61. doi: 10.1007/s12630-019-01330-x
113. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival Analysis of Patients With Breast Cancer Undergoing a Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: A 5-Year Follow-Up of a Randomized Controlled Trial. *Anticancer Res* (2017) 37:5813–20. doi: 10.21873/anticanres.12024
114. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Breast Cancer Recurrence Collaboration. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394:1807–15. doi: 10.1016/S0140-6736(19)32313-X
115. Dubowitz JA, Cata JP, De Silva AP, Braat S, Shan D, Yee K, et al. Global Onco-Anaesthesia Research Collaboration Group. Volatile Anaesthesia and Peri-Operative Outcomes Related to Cancer: A Feasibility and Pilot Study for a Large Randomised Control Trial. *Anaesthesia* (2021) 76:1198–206. doi: 10.1111/anae.15354

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REVIEW
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Emerging Trends on the Correlation Between Neurotransmitters and Tumor Progression in the Last 20 Years: A Bibliometric Analysis *via* CiteSpace

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Background: Bibliometric analysis is used to gain a systematic understanding of developments in the correlation between *neurotransmitters and tumor progression* in research hotspots over the past 20 years.

Methods: Relevant publications from the Web of Science Core Collection (WoSCC) were downloaded on August 1, 2021. Acquired data were then analyzed using the Online Analysis Platform of Literature Metrology (http://biblimetric.com) and the CiteSpace software to analyze and predict trends and hot spots in this field.

Results: A total of 1310 publications on *neurotransmitters and tumor progression* were identified, and 1285 qualified records were included in the final analysis. The country leading the research was the United States of America. The University of Buenos Aires featured the highest number of publications among all institutions. Co-citation cluster labels revealed the characteristics of 10 main clusters: beta-adrenergic receptors (β-AR), glutamate, neurotransmitters, serotonin, drd2, histamine, glycine, interleukin-2, neurokinin receptor-1, and nicotinic acetylcholine receptors (AchRs). Keywords and references burst detection indicated that apart from β-AR, dopamine receptor and cancer types like gastric cancer and glioblastoma are the newly emerging research hotspots.

Conclusions: This study analyzed 1285 publications and 39677 references covering the topic of *neurotransmitters and tumor progression* and showed that while β-AR has always been a hot topic in this field, dopamine receptor is an emerging target for this research field, and gastric cancer and glioblastoma are the top two tumors that have garnered increasing attention and have become the focal point of recent studies.

Keywords: neurotransmitters, cancer, Citespace, bibliometric analysis, anesthesia and tumor

Abbreviations: WHO, World Health Organization; WoSCC, Web of Science Core Collection; USA, United States of America; Ach, Acetylcholine; nAchRs, Nicotinic acetylcholine receptors; GABA, Gamma-aminobutyric acid; NMDA, N-methyl-D-aspartic acid receptor; NE, Norepinephrine; E, Epinephrine; NPY, Neuropeptide Y; HR, Hazard ratio; CI, Confidence interval; BC, Breast cancer; TNBC, Triple negative breast cancer; IL-2, Inerleukin-2; B-AR, Beta-adrenergic receptors; B2-AR, Beta2-adrenergic receptors; α2-AR, Alfa2- adrenergic receptor; DRD2, Dopamine receptor D2; DRD1, Dopamine receptor D1; Dex, Dexmedetomidine; HIF-1, Hypoxia-inducible factor 1; TI, Title; TS, Topical subject; IF, Impact factors; LSR, least square filtering.

INTRODUCTION

Cancer has always been a major problem plaguing the health of the global population, and according to the latest data released by the World Health Organization in 2021, the total number of new patients with cancer worldwide in 2020 was about 19.29 million. In 2018, China had the highest number of tumor incidence and deaths across the world, which has brought a heavy medical burden to the country (1). Therefore, exploring more deeply the causes and finding effective cures for patients with cancer are clinically important.

Neurotransmitters are chemicals that transmit information between neurons and other types of cells, such as muscle and glandular cells. Based on their specific chemical structure, neurotransmitters are divided into four categories: 1) acetylcholine (Ach); 2) amino acids, including glutamate, aspartic acid, glycine, and gamma-aminobutyric acid (GABA); 3) biogenic amines, consisting of dopamine, norepinephrine (NE), epinephrine (E), and serotonin; and 4) neuropeptides, including but not limited to neuropeptide Y (NPY), neurotensin, and many others (2).

Neuromodulation in cancer is universal and involves complex mechanisms, which are not fully understood. As important messengers of neural signaling, neurotransmitters and their receptors contribute to tumor proliferation, angiogenesis and tumor metastasis (3–6). Additionally, neurotransmitter receptors are widely expressed on the surface of immune cells and regulated by their corresponding neurotransmitters, thus affecting tumor immune responses (7, 8).

For clinical anesthesia, the primary targets of many narcotics are various neurotransmitter receptors. For example, propofol is closely associated with GABA and N-methyl-D-aspartate (NMDA) receptors, and inhalational anesthetics, including sevoflurane desflurane, may mostly have a strong link with ionotropic neurotransmitter receptors. Muscle relaxants exert action through Ach receptors, whereas dexmedetomidine (Dex) mainly acts on α2-adrenergic receptors (α2-AR), among others. However, whether and how anesthetics affect tumor progression through neurotransmitter receptors remains unsettled.

Many authors worldwide have published research findings on neurotransmitters and tumor malignancy. Since many kinds of neurotransmitters are involved in the various types of cancer, the general direction of this body of research is challenging to grasp, and launching investigations in this field is difficult with little or no prior knowledge. Thus, collecting data from relevant publications is highly necessary to assist investigators in analyzing the vast amount of literature on this subject.

Bibliometric analysis is a method used to analyze large amounts of heterogeneous literature and is largely dependent on visualizing processing tools, like CiteSpace. The latter helps gather data on contributions to a certain field in diverse perspectives, including different countries/regions, institutions, journals, co-cited authors, co-cited networks, and detailed research trends or hot spots (9).

We aimed to provide a comprehensive understanding of the developments in the research on neurotransmitters and tumor progression by analyzing the remarkable achievements in the past 20 years. The patterns of the research publications in this field were mapped to determine journals, countries, institutions, co-cited authors, co-cited references, research topics, research trends, and emerging areas of research on neurotransmitters and tumor progression.

MATERIALS AND METHODS

Data Sources and Search Strategies

A literature search was conducted using the Web of Science Core Collection (WoSCC) database on August 1, 2021, to reduce bias incurred by database updating. The search strategy employed was as follows: TI = ("neurotransmitter" or "neurotransmitter receptor" or "5-HT" or "Serotonin" or "Cholinergic" or "Ach" or "Muscarinic acetylcholine receptor" or "GABA" or "gamma-aminobutyric acid" or "histamine" or "glycine or glutamate" or "NMDA" or AMPA" or "aspartic acid" or "dopamine" or "adrenergic" or "norepinephrine" or epinephrine" or "Neurokinin") AND TS = ("tum*r" or "neoplasm" or "cancer" or "carcinoma") NOT TS = ("non-cancer" or "chronic pain") AND TS = ("prognos*s" or "outcome" or "recurrence" or "overall survival" or "recurrence free survival" or "relapse-free survival" or "proliferation" or "invasion" or "metastas*s") NOT TI = ("guideline" or "recommendation" or "consensus" or "case report" or "meta" or "review") AND Language = English. Document Type was set to include "Articles" only from 2001 to 2021. After the primary data search, two researchers (Y Shi and J Luo) screened all manuscripts individually to ensure that they were relevant to the subject of this study.

Bibliometric Online Platform Analysis

Web of Science (https://wcs.webofknowledge.com) was used to analyze the search results and plot a histogram showing the publication trend. Then, the WoSCC data were converted to UTF-8 format and imported into the Online Analysis Platform of Bibliometrics (http://bibliometric.com/), we chose "total literature analysis" option for different countries' publication trends analysis and "partnership analysis" option for intercountry/regional analysis, respectively.

CiteSpace Software Analysis

Full records and cited references of these publications were downloaded from the WoSCC database, saved in.TXT format, and then imported into the CiteSpace software V5.6R5 SE, 64 bits (Drexel University, Philadelphia, PA, USA) using the following settings: Time slicing from January 2001 to June 2021 at 1 year per slice. The selection uses a modified g-index in each slice: k = 25. For interinstitutional analysis, "Institution" was chosen in the Node Types parameter area, and the remaining settings were all the default values. For co-authorship network analysis, "Cited-author" was chosen from the Node Types as after importing data into CiteSpace. For document co-citation, the related parameters were set as the following: choosing

"References" as the Node Type, choosing "Cosine" to calculate relationship strength, and choosing "Pathfinder" and "Pruning the merged network" for Pruning parameters area to simplify the network and highlight its important structural features (10). For keywords and references burst detection, "Keywords" and "References" were chosen for Node Type, respectively. After removing keywords with little significance (like cells, mice, etc.), the top 20 keywords with the strongest citation bursts were identified and presented using Microsoft Excel 2019. The references with the strongest citation bursts were displayed without deletion.

RESULTS

Quantity and Trend Analysis of Published Papers

A total of 1310 publications met the inclusion criteria using our search strategy. The number of articles actually published each year was calculated using Online Analysis Platform of Bibliometrics (http://bibliometric.com/) (**Figure 1A**). The early stage (2000–2010) saw fluctuations in the number of publications above or below 50, with exceptions in 2005, 2008, and 2009. The number of papers published on the subject reached a peak in 2020, indicating that *neurotransmitters and cancer progression* have become a research hotspot and has captured global research attention.

To identify the countries/regions leading the research in the field, further analysis of publications in different countries and regions was conducted. The bar chart (**Figure 1B**) presents the top 10 countries/regions in terms of the total number of published articles in the past 20 years. Based on the number of publications and still increasing steadily, the USA was identified as a groundbreaker in the field. We also found that the annual publications in China have been increasing rapidly, outstripping the USA from early 2016.

Journal Analysis

The WoSCC search showed that the 1310 papers included in the current analysis were published in 562 different journals over the last 20.5 years since 2001. Bibliometrics online analysis was used to analyze the influence of journals. The top 10 most cited journals are listed in **Supplementary Table 1**, among which, seven publishers are located in the USA, while the other three are located in Switzerland, Greece, and Netherlands, respectively. *Cancer Research*, which demonstrated the highest number of total citations (220) with an IF of 12.701, ranked first in the research field of the neurotransmitters and tumor progression.

Analysis of Intercountry/Regional and Interinstitutional Cooperation

To determine the research institutional and interinstitutional cooperation in neurotransmitters and cancer research, we

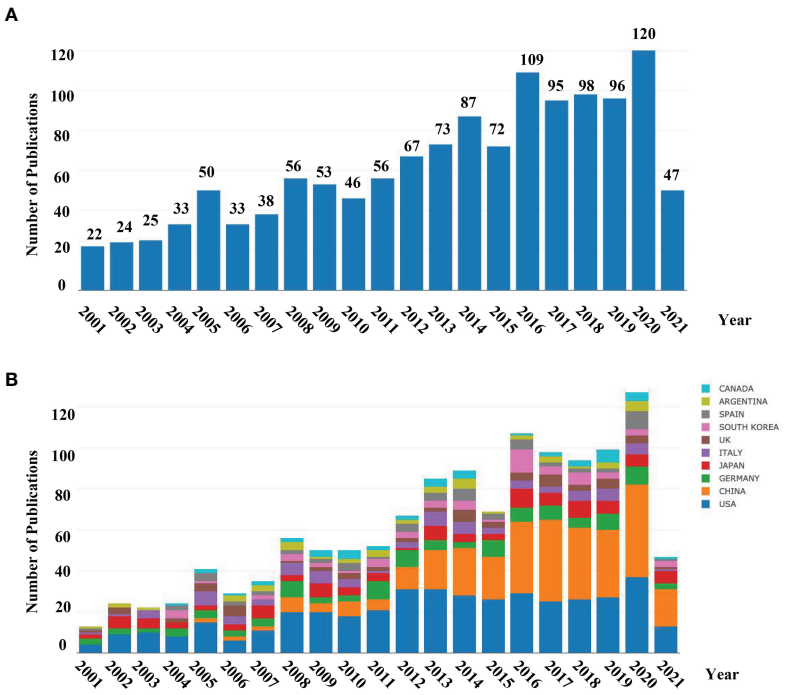

FIGURE 1 | **(A)** Number of annual research publications and growth trends on the topic of neurotransmitters and tumor progression from 2001 to the first half of 2021, export of results from the Online Analysis Platform of Literature Metrology (http://biblimetric.com); **(B)** Number of annual publications and growth trends of the top 10 countries/regions on research in neurotransmitters and tumor progression from 2001 to 2021, export of results from the Online Analysis Platform of Literature Metrology (http://bibliometric.com). Bar chart reflects number of online articles online per year.

performed intercountry/regional and interinstitutional analyses using CiteSpace. After removing duplicate entries, 1275 published articles, 1 book chapter, 10 early-access articles, and 24 proceedings papers were identified, among which, 1285 (1275 published articles + 10 early-access articles) were included in the final analysis.

Results of the intercountry/regional cooperation suggested that 68 countries have established partnerships, with 239 links among one other. USA and China possessed the best partnerships in this area. However, China showed less international cooperation than the USA (**Figure 2A**).

The top 10 most productive institutions are presented in **Figure 2B**. The size of the concentric circles signifies the number of publications, and the institution with more published articles tends to present larger concentric circles. Links between two institutions means they have jointly published articles. The boldness of lines indicates the strength of their cooperation. Collaborative relationship analysis among the different institutions yielded 534 nodes and 601 links. Institutions located in China and USA make up a substantial amount of the total. The University of Buenos Aires from Argentina was the most prolific institution. The second and the third productive institutions, the University of California Los Angeles and the University of Texas MD Anderson Cancer Center, were both located in the USA, followed by a Chinese institution, Shanghai Jiao Tong University.

Author and Document Co-Citation Analysis

Co-citation analysis can reveal the research trends on *neurotransmitters and tumor progression*. We performed cited-author and cited-references analyses to find the top 10 most cited authors and references, which can provide important clues. A co-citation relationship among authors is established when two (or more) authors are cited in one or more subsequent papers at the same time. We can obtain a clear picture of core authors and their contributions to a certain field by analyzing the authors' co-cited networks, the strength of which indicates the degree of participation of the authors. CiteSpace was used to analyze the 1285 original articles and 39677 valid and distinct references obtained from them to identify the top 10 most cited authors and references on *neurotransmitters and tumor progression*. In the author co-citation analysis, 858 nodes and 2775 links were obtained. The node size was positively associated with the cited counts of the authors, and the thickness of the lines between every two nodes represented the frequency of being co-cited between those two authors. The top 10 most-cited authors in this research area are shown in **Figure 3A**. HM Schuller from the University of Tennessee was the most-cited author and has been cited 88 times in 2007. SW Cole from the University of California Los Angeles has been cited 82 times in 2011 and thus ranks the second highest in most-cited authors. The other eight major research teams are also presented in **Figure 3A** (EK Sloan from the University of Melbourne, A Melhem-Bertrandt from the University of Texas, AK Sood from the MD Anderson Cancer Center, A Jemal and RL Siegel from American Cancer Society, PH Thaker from Washington University, DG Powe from Nottingham Trent University, and TI Barron from St. James' Hospital in Ireland).

As for the document co-citation analysis, the year and the first author of the top 10 most-cited publications are shown in **Figure 3B**. The size of the circle is positively correlated with the frequency of citations, whereas the thickness of the lines between every two nodes represents the co-occurrence of citations. The details of these 10 articles are listed in **Supplementary Table 2**.

Since studies are usually cited to bolster the conceptions of the authors, a high citation frequency would reflect that the reference

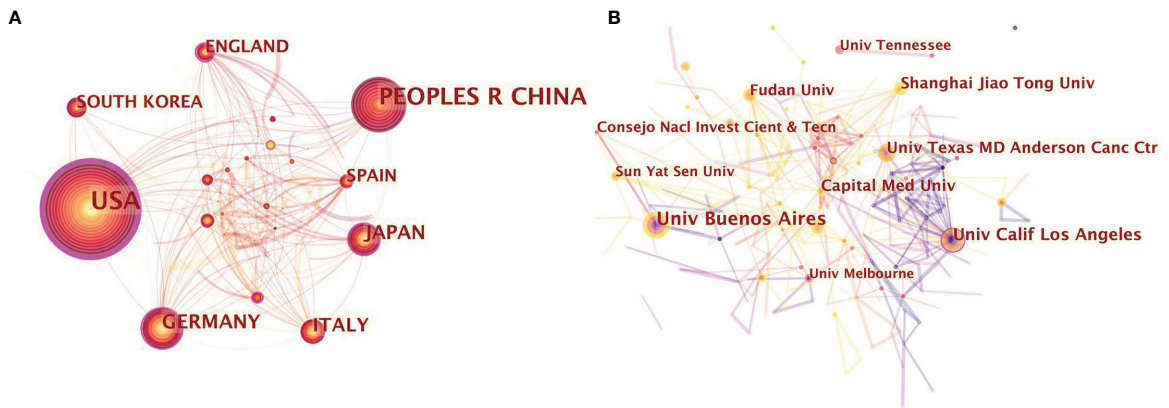

FIGURE 2 | **(A)** Citespace network map of 68 countries involved in neurotransmitters and tumor progression research; **(B)** Citespace network map of institutions involved in neurotransmitters and tumor progression research. Each circle represents an institution. Size of circle is positively correlated with the number of articles published by institutions, and links between two circles represents a collaboration between two institutions on the same article. Line thickness is positively correlated with frequency of collaborations. Top 10 institutions with the most publications are shown. (the University of Buenos Aires, the University of California Los Angeles, the University of Texas MD Anderson Cancer Center, Shanghai Jiao Tong University, Fudan University, the University of Tennessee, Sun-Yat Sen University, Capital Medical University, the University of Melbourne, Consejo Nacl Investigation Cientificas & Tecn). Timespan: 2001-2021; Slice length=1.

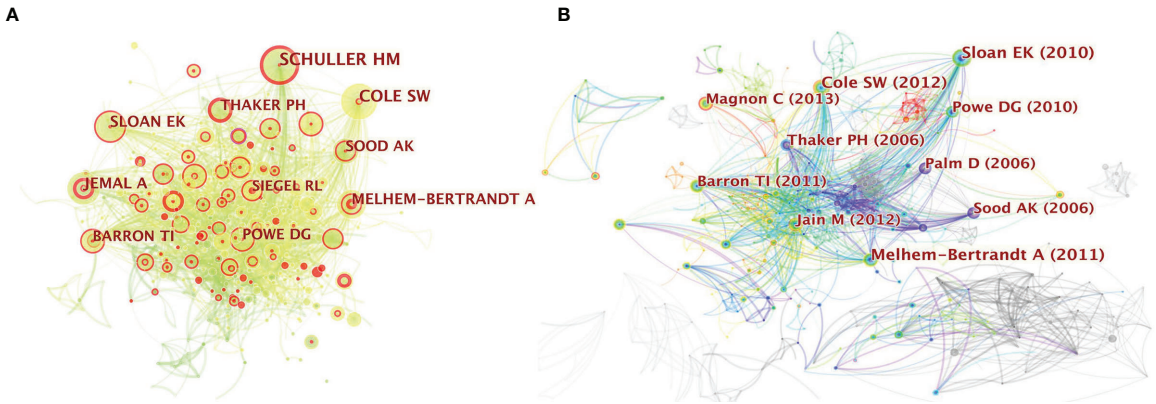

FIGURE 3 | **(A)** Citespace network of co-cited authorship in the field of neurotransmitters and tumor progression research. Each circle represents one author. Size of circle is positively correlated with cited counts of the authors, and links between two circles represents a collaboration between two authors on the same article. Line thickness is positively correlated with frequency of collaborations. Top 10 most-cited authors are shown. Timespan: 2001-2021; Slice length=1; **(B)** Citespace co-citation map of 39677 references on neurotransmitters and tumor progression research, filter option showing the largest connected component only. Each circle represents a reference. Size of circle is positively correlated with frequency of citations, and links between two circles represent two references that were cited in the same article. Year and first author of the top 10 most-cited publications are shown. Timespan: 2001-2021; Slice length=1.

has made wide contributions in the field with highly proven peer recognition. Interestingly, the top 10 most-cited studies were mainly on the stress-correlated adrenaline system (11–20). Furthermore, breast cancer (BC) and prostate cancer have become the focus in this area, with the frequency of 6 for BC and 3 for prostate cancer. For example, the highest-ranking article published in the *Journal of Clinical Oncology* in 2011 (11) demonstrated that beta-blocker intake was associated with improved relapse-free survival (RFS) in 1413 patients with BC [hazard ratio (HR), 0.52; 95% confidence interval (CI), 0.31–0.88; P = 0.008] and in 377 patients with triple-negative breast cancer (TNBC) (HR, 0.30; 95% CI, 0.10–0.87; P = 0.027), indicating the protective function of beta-blockers. These were consistent with the results of the article with the second highest citation, released by *Cancer Research* (12), which discussed that stress-induced neuroendocrine activation induced a 30-fold increase in metastasis to distant tissues. Accordingly, treatment with the beta-antagonist propranolol inhibited tumor spread.

Clustered Network in Co-Analysis

Next, we performed clustered network analysis to conduct a more in-depth study of those co-citations. If two publications have many common references, they are inclined to be homogenous. Based on this logic, we could divide 1285 articles into several clusters. After filter disposal by choosing "show the largest connected component only" node (which could explain why the displayed clustering numbers are not continuous), 10 major clusters generated from the co-citation networks of 39677 references cited by 1285 publications were identified. Cluster labels were salient noun phrases extracted from keywords using least square filtering (LSR) algorithm, including #0 beta-adrenergic receptors, #1 glutamate, #2 neurotransmitters, #3 serotonin, #4 DRD2, #6 histamine, #7 glycine, #10 inerleukin-2, #13 neurokinin receptor-1, and #14 nAchRs. The number of cluster tags as reversely correlated with the number of articles for each cluster included. Simply put, the cluster of #0 contains the largest number of articles (**Figure 4A**).

A timeline view of the distinct co-citations is shown in **Figure 4B** to present all the cited literature more clearly. The bold timeline indicates that the clustering topic was a hotspot during this period. Citation tree-rings with different sizes on the timeline represent some key articles with a high citation frequency.

We found that in the research on neurotransmitters and tumor progression, beta-adrenergic receptors (β-AR) has been a hot topic since 2004, reaching its peak moment in 2010. Studies on glutamate first appeared in 1999 and made a robust comeback in 2009. Serotonin was an emerging research field in 2013 and has attracted increasing attention recently. To our interest, inerleukin-2 (IL-2) is the only cytokine in the 10 major clusters post filtration, indicating that IL-2 may be an important cytokine related to the mechanism underlying the influence of neurotransmitters on tumor progression.

Research Trend Analysis *via* Burst Detection With Keywords and References

Keywords burst detection was applied to acquire a quick glimpse of future research trends (**Figure 5A**). The red line indicates that the use of a keyword increased suddenly during the relevant period. In contrast, a blue line means relative unpopularity. The keywords burst detection identified histamine as a hot topic during 2001–2014, and researchers in this area have given increasing attention on mechanisms related to stem cells or autophagy (21); moreover, gastric cancer and glioblastoma have been the top two focal points of recent studies.

The top 25 references with the strongest citation bursts were also identified *via* a document co-citation strength analysis, which is another method for determining research trends (**Figure 5B**).

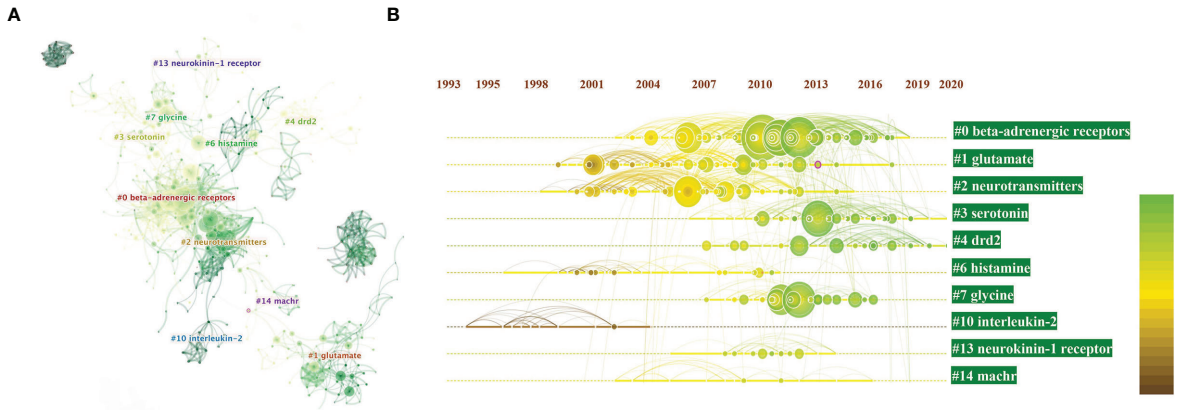

FIGURE 4 | **(A)** Clustered networks of co-citation status of the investigated 39677 references and the 1285 citing articles *via* CiteSpace. The top 10 largest clusters of citing articles are shown; **(B)** Timeline view of the top 10 largest clusters of citing articles in the field of neurotransmitters and tumor progression research. Machr also known as nAchRs. Right side = cluster labels.

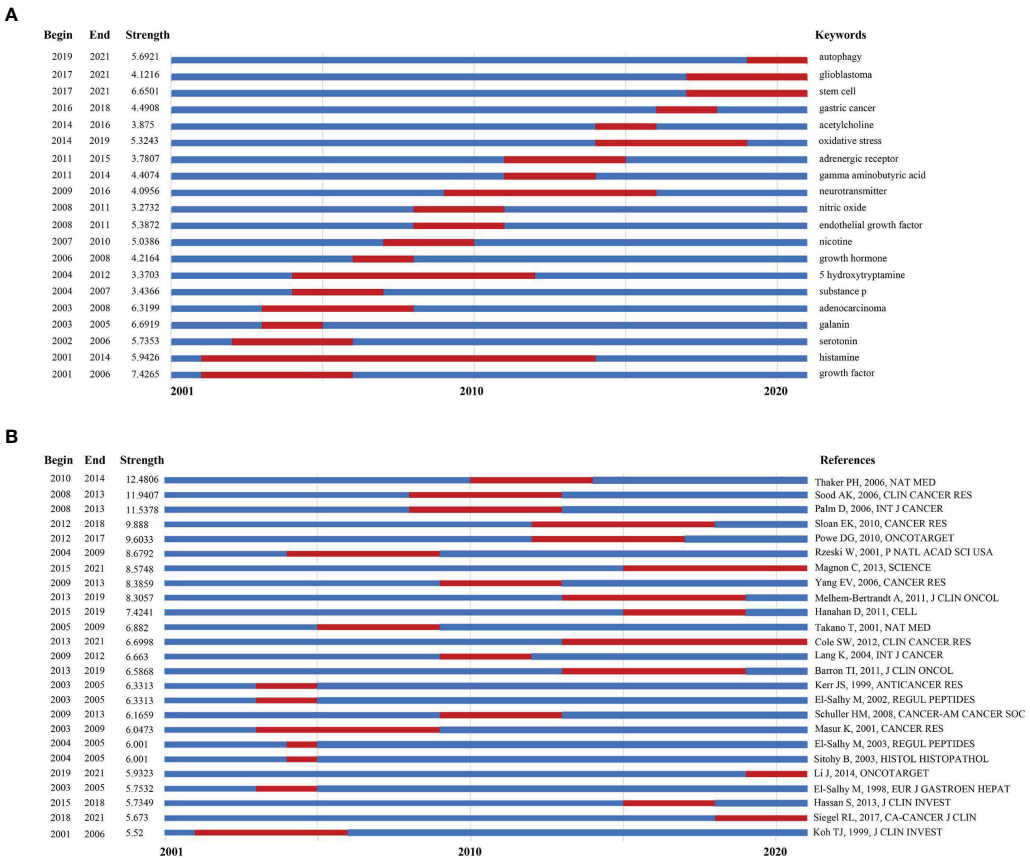

FIGURE 5 | **(A)** Keywords with the strongest burst strength of the 1285 citing articles on neurotransmitters and tumor progression research between 2001 and 2021. Keywords marked in red indicates a sudden increase in the usage frequency of this keyword during that period. Blue represents a relatively unpopular time period; **(B)** References with the strongest burst strength of the 39677 references on neurotransmitters and tumor progression research between 2001 and 2021. References marked in red indicates a sudden increase in cited frequency of this article during that period. Blue represents a relatively unpopular time period.

The article with the strongest citation burst was published in Nature Medicine in 2006, which demonstrated that in ovarian cancer (22), beta-2-adrenergic receptor (β2-AR) activation mediated by chronic stress promotes tumor growth and angiogenesis, consistent with the results of the study by Sood et al. (18). While β2-AR has always been a hotspot in this research area since the early 2010s (14), dopamine receptor is also likely to be an emerging target for cancer development. An article aiming to clarify the role of dopamine receptor D2 (DRD2) in glioblastoma progression was cited consistently for 2 years since 2019 (23). The details of these 25 articles are listed in **Supplementary Table 3**.

DISCUSSION

This study visualized the citation analysis of research articles on *neurotransmitters and tumor progression* from 2001 to 2021. Our search strategy provides a comprehensive picture of neurotransmitters and their receptors in different descriptions. The number of published articles on this topic rapidly increased after 2016 and reached 120 articles per year in 2020. Using an online bibliometric analysis platform and CiteSpace, our study analyzed the publications on neurotransmitters and tumor progression from multiple dimensions and showed a systematic view for understanding this field over the past 20 years. These findings can guide future studies. Researchers new to this field can easily gain useful and relevant information from our bibliometric analysis.

USA, China, and Germany are the top three countries that have focused research on *neurotransmitters and tumor progression*. Notably, by 2016, the number of articles from China had outstripped those from the USA, making China the most prolific country in the field. The top three most fruitful research institutions were located in Argentina and the USA, respectively, followed by Shanghai Jiao Tong University from China. However, Chinese researchers were not in the top 10 most-cited authors, indicating that the quality and influence of their research can still improve. Interestingly, the top 10 most-cited studies were mainly on the stress-correlated adrenaline system, and BC and prostate cancer are the most commonly studied diseases in this area.

The timeline view of the 39677 related references and burst detection of keywords and references both indicated the research trends on neurotransmitters and tumor progression. We found that β2-AR, which is strongly linked with stress, was the most frequently studied neurotransmitter receptor since the early 2010s. Interestingly, chronic stress and acute stress seem to play distinct roles in tumor development and progression. While blocking chronic adrenergic signaling with beta-blockers shows protective potential in patients with cancer, activating acute adrenergic signaling through exercise also seems beneficial (24). Other neurotransmitter receptors, like dopamine receptors, have been increasingly studied since 2019. Dopamine can inhibit liver cancer cell growth and metastasis by activating dopamine receptors (25). Discrepant studies have also shown that patients with liver cancer with a high dopamine receptor D1 (DRD1) expression had worse prognosis, and the usage of the DRD1-specific antagonist SCH23390 significantly inhibited cell invasion and migration *in vitro* and tumor growth *in vivo* (26). IL-2, the only cytokine appeared in the 10 largest clusters of citing articles, seems to exert a synergistic effect with antihistamine treatments in patients with acute myeloid leukemia and other cancers (27, 28). When administered together, antihistamines could enables the activation of T cells and NK cells by IL-2, resulting in the killing of tumor cells of various cancers (29), indicating a close connection between IL-2 and histamine signaling pathway in tumor development. The clustered network analysis also revealed that gastric cancer and glioblastoma have increasingly gained attention and have become the focal points of recent studies.

The explored connection between the nervous system and tumor tissue is not surprising, as they share a reciprocal impact. On the one hand, nerve fibers or neurotransmitters in tumor tissues not only can act on fibroblasts in the microenvironment by modulating the extracellular matrix synthesis or shaping synaptic-like connections with tumor cells (30) but also has a direct effect on immune cells, thereby regulating the infiltration of immune cells into tumors (7, 8). On the other hand, the invasion of the surrounding nerves by cancer cells also provides a route for metastasis and promotes tumorigenesis *via* the crosstalk between neuron cells and tumor cells (31, 32). A recent study has shown that perineural invasion (PNI) contributed to the immune-suppressive microenvironment in pancreatic ductal adenocarcinoma through the hyperactivation of PNI-associated cholinergic signaling (33).

The perioperative time period is a dangerous window for tumor metastasis, during which anesthesia contributes a significant part (34). Whether anesthetics or different anesthetic techniques influence the prognosis of patients with cancer has been a topic of interest recently (35–39). First, patients with cancer show higher stress and anxiety levels than other patients (40, 41). The use of anesthetics reduces patients' pain and relieves the stress caused by the surgery. Second, anesthetics themselves would directly affect the malignancy of tumor cells. Most fundamental studies focusing on anesthetics have proven that propofol, midazolam, and local anesthetics exert potential anti-cancer properties, whereas inhalants and opioids promote cancer development. The potential mechanisms underlying the effects of anesthetics are more or less associated with neurotransmitters or their receptors because the primary targets of many anesthetics are neurotransmitter receptors.

Among these, GABA receptors are most closely associated with anesthesia and sedation. Propofol, inhaled anesthetics, etomidate, and benzodiazepine sedatives can all act on GABA receptors. In a mouse model of lung metastasis from colon cancer, Xie et al. (42) found that propofol could downregulate the expression of the ubiquitination regulatory protein TRIM21 by activating GABAA receptors on the tumor surface, thereby upregulating Src protein and increasing the adhesion of tumor cells to vascular endothelial cells, which ultimately promotes

distal metastasis of tumor cells to the lung. However, strong data have been presented that support the inhibitive impact of propofol on tumor development by acting on GABA receptors. In glioma studies, propofol, etomidate, and diazepam modulated GABA receptor function and inhibited glioma cell proliferation by inducing cell cycle arrest (43, 44). The involvement of NMDA receptors in propofol-induced inhibition of tumor growth and metastasis has also been reported in other studies (45, 46). Besides GABA and NMDA, the connection among anesthetics, other neurotransmitters, and tumor progression has also been demonstrated. Dexmedetomidine (Dex) is an alpha-2-adrenergic receptor (α2-AR) agonist, also a sedative drug commonly used in clinical anesthesia. Studies have suggested that the perioperative use of Dex or α2-AR activation promotes tumor cell proliferation (47, 48). Wang et al. (49) demonstrated that Dex could promote tumor cell migration by activating the α2-AR/STAT3 pathway and the secretion of the exosomal protein TMPRSS2 in breast cancer. We also previously found that postoperative serum from patients administered with Dex during surgery promoted BC cell proliferation, migration, and invasion, indicating that Dex worsens the prognosis of patients with BC (50). Additionally, there is a paucity of studies on the prognostic effects of muscle relaxants, a blocker of the binding between Ach and nAchRs, in patients with cancer. A few studies have found that cis-atracurium has some anti-colon cancer effects *in vitro*, however, the link between its anti-cancer effects and nAchRs is unclear (51, 52).

This study has several limitations. First, the data were retrieved from a single database. Second, only articles with English keywords or abstracts in the database were considered in our analysis, and articles in other languages were thus excluded. Third, bibliometrics studies are a type of quantitative analysis of scholarly publications that can only be conducted with publications in journals that are cited and indexed but not unpublished studies or publications in non-indexed journals, dissertations, books, or government reports. In future studies, we may use multimethod evaluations to gain a more in-depth understanding of this research field.

The findings from this bibliometric study provided insights into research trends on neurotransmitters and tumor progression in the past 20 years. The study provides new directions and ideas for clinical tumor treatment by targeting neurotransmitters and their receptors and for the optimization of anesthetic techniques and medications in patients with cancer. Priority should be given to anesthetics that may be beneficial to the prognosis of patients with cancer. Furthermore, the effects of perioperative stress, anxiety, and depression and other psychiatric factors on the nervous system should be fully considered to reduce risk factors that may accelerate tumor progression.

AUTHOR CONTRIBUTIONS

Conception and design: YS. Administrative support: HZ, WY, DS, and JT. Collection and assembly of data: YS and JL. Data analysis and interpretation: XW, YZ, and HZ. Manuscript writing: All authors. Final approval of manuscript: All authors.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: Cancer J Clin* (2018) 68 (6):394–424. doi: 10.3322/caac.21492
2. Jiang S, Hu L, Wang X, Li J, Zhang Z. Neurotransmitters: Emerging Targets in Cancer. *Oncogene* (2020) 39(3):503–15. doi: 10.1038/s41388-019-1006-0
3. Boilly B, Faulkner S, Jobling P, Hondermarck H. Nerve Dependence: From Regeneration to Cancer. *Cancer Cell* (2017) 31(3):342–54. doi: 10.1016/j.ccell.2017.02.005
4. Hanoun M, Maryanovich M, Arnal-Estapé A, Frenette PS. Neural Regulation of Hematopoiesis, Inflammation, and Cancer. *Neuron* (2015) 86(2):360–73. doi: 10.1016/j.neuron.2015.01.026
5. Entschladen F, Palm D, Niggemann B, Zaenker KS. The Cancer's Nervous Tooth: Considering the Neuronal Crosstalk Within Tumors. *Semin Cancer Biol* (2008) 18(3):171–5. doi: 10.1016/j.semcancer.2007.12.004
6. Monje M, Borniger J, D'Silva N, Deneen B, Dirks P, Fattahi F, et al. Roadmap for the Emerging Field of Cancer Neuroscience. *Cell* (2020) 181(2):219–22. doi: 10.1016/j.cell.2020.03.034
7. Cervantes-Villagrana R, Albores-García D, Cervantes-Villagrana A, García-Acevez S. Tumor-Induced Neurogenesis and Immune Evasion as Targets of Innovative Anti-Cancer Therapies. *Signal Transduct Targeted Ther* (2020) 5 (1):99. doi: 10.1038/s41392-020-0205-z
8. Jiang S, Zhang X, Hu L, Wang X, Li Q, Zhang X, et al. Systemic Regulation of Cancer Development by Neuro-Endocrine-Immune Signaling Network at Multiple Levels. *Front Cell Dev Biol* (2020) 8:586757:586757. doi: 10.3389/fcell.2020.586757

9. Liu DD, Liu SL, Zhang JH. Visualization Analysis of Research Hotspots Based on CiteSpace II: Taking Medical Devices as an Example. *Med Devices (Auckl)* (2014) 7:357–61. doi: 10.2147/mder.S69685
10. Synnestvedt M, Chen C, Holmes J. CiteSpace II: Visualization and Knowledge Discovery in Bibliographic Databases. *AMIA Annu Symposium Proc AMIA Symposium* (2005) 2005:724–8.
11. Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown E, Lee R, Meric-Bernstam F, et al. Beta-Blocker Use is Associated With Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer. *J Clin Oncol* (2011) 29(19):2645–52. doi: 10.1200/jco.2010.33.4441
12. Sloan E, Priceman S, Cox B, Yu S, Pimentel M, Tangkanangnukul V, et al. The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer. *Cancer Res* (2010) 70(18):7042–52. doi: 10.1158/0008-5472.Can-10-0522
13. Powe D, Voss M, Zänker K, Habashy H, Green A, Ellis I, et al. Beta-Blocker Drug Therapy Reduces Secondary Cancer Formation in Breast Cancer and Improves Cancer Specific Survival. *Oncotarget* (2010) 1(7):628–38. doi: 10.18632/oncotarget.101009
14. Cole S, Sood A. Molecular Pathways: Beta-Adrenergic Signaling in Cancer. *Clin Cancer Res* (2012) 18(5):1201–6. doi: 10.1158/1078-0432.Ccr-11-0641
15. Barron T, Connolly R, Sharp L, Bennett K, Visvanathan K. Beta Blockers and Breast Cancer Mortality: A Population- Based Study. *J Clin Oncol* (2011) 29 (19):2635–44. doi: 10.1200/jco.2010.33.5422
16. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza A, et al. Metabolite Profiling Identifies a Key Role for Glycine in Rapid Cancer Cell Proliferation. *Sci (New York NY)* (2012) 336(6084):1040–4. doi: 10.1126/science.1218595
17. Magnon C, Hall S, Lin J, Xue X, Gerber L, Freedland S, et al. Autonomic Nerve Development Contributes to Prostate Cancer Progression. *Sci (New York NY)* (2013) 341(6142):1236361. doi: 10.1126/science.1236361
18. Sood A, Bhatty R, Kamat A, Landen C, Han L, Thaker P, et al. Stress Hormone-Mediated Invasion of Ovarian Cancer Cells. *Clin Cancer Res* (2006) 12(2):369–75. doi: 10.1158/1078-0432.Ccr-05-1698
19. Palm D, Lang K, Niggemann B, Drell T, Masur K, Zaenker K, et al. The Norepinephrine-Driven Metastasis Development of PC-3 Human Prostate Cancer Cells in BALB/c Nude Mice is Inhibited by Beta-Blockers. *Int J Cancer* (2006) 118(11):2744–9. doi: 10.1002/ijc.21723
20. Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, et al. Behavioral Stress Accelerates Prostate Cancer Development in Mice. *J Clin Invest* (2013) 123(2):874–86. doi: 10.1172/jci63324
21. Marisetty A, Lu L, Veo B, Liu B, Coarfa C, Kamal M, et al. REST-DRD2 Mechanism Impacts Glioblastoma Stem Cell-Mediated Tumorigenesis. *Neuro-oncology* (2019) 21(6):775–85. doi: 10.1093/neuonc/noz030
22. Thaker P, Han L, Kamat A, Arevalo J, Takahashi R, Lu C, et al. Chronic Stress Promotes Tumor Growth and Angiogenesis in a Mouse Model of Ovarian Carcinoma. *Nat Med* (2006) 12(8):939–44. doi: 10.1038/nm1447
23. Li J, Zhu S, Kozono D, Ng K, Futalan D, Shen Y, et al. Genome-Wide shRNA Screen Revealed Integrated Mitogenic Signaling Between Dopamine Receptor D2 (DRD2) and Epidermal Growth Factor Receptor (EGFR) in Glioblastoma. *Oncotarget* (2014) 5(4):882–93. doi: 10.18632/oncotarget.1801
24. Jensen A, Carnaz Simões A, Thor Straten P, Holmen Olofsson G. Adrenergic Signaling in Immunotherapy of Cancer: Friend or Foe? *Cancers* (2021) 13 (3):394. doi: 10.3390/cancers13030394
25. Zhang QB, Zhang BH, Zhang KZ, Meng XT, Jia QA, Zhang QB, et al. Moderate Swimming Suppressed the Growth and Metastasis of the Transplanted Liver Cancer in Mice Model: With Reference to Nervous System. *Oncogene* (2016) 35(31):4122–31. doi: 10.1038/onc.2015.484
26. Yan Y, Pan J, Chen Y, Xing W, Li Q, Wang D, et al. Increased Dopamine and its Receptor Dopamine Receptor D1 Promote Tumor Growth in Human Hepatocellular Carcinoma. *Cancer Commun (Lond)* (2020) 40(12):694–710. doi: 10.1002/cac2.12103
27. Li H, Xiao Y, Li Q, Yao J, Yuan X, Zhang Y, et al. The Allergy Mediator Histamine Confers Resistance to Immunotherapy in Cancer Patients *via* Activation of the Macrophage Histamine Receptor H1. *Cancer Cell* (2022) 40(1):36–52.e9. doi: 10.1016/j.ccell.2021.11.002
28. Lindnér P, Rizell M, Mattsson J, Hellstrand K, Naredi P. Combined Treatment With Histamine Dihydrochloride, Interleukin-2 and Interferon-Alpha in Patients With Metastatic Melanoma. *Anticancer Res* (2004) 24:1837–42.
29. Yang L, Perry C. Spotlight on Histamine Dihydrochloride in Acute Myeloid Leukaemia. *Drugs Aging* (2011) 28(4):325–9. doi: 10.2165/11206810-000000000-00000
30. Zeng Q, Michael I, Zhang P, Saghafinia S, Knott G, Jiao W, et al. Synaptic Proximity Enables NMDAR Signalling to Promote Brain Metastasis. *Nature* (2019) 573(7775):526–31. doi: 10.1038/s41586-019-1576-6
31. Liebig C, Ayala G, Wilks J, Berger D, Albo D. Perineural Invasion in Cancer: A Review of the Literature. *Cancer* (2009) 115(15):3379–91. doi: 10.1002/cncr.24396
32. Jurcak N, Rucki A, Muth S, Thompson E, Sharma R, Ding D, et al. Axon Guidance Molecules Promote Perineural Invasion and Metastasis of Orthotopic Pancreatic Tumors in Mice. *Gastroenterology* (2019) 157 (3):838–850.e6. doi: 10.1053/j.gastro.2019.05.065
33. Yang M, Tao L, Jiang Y, Yang J, Huo Y, Liu D, et al. Perineural Invasion Reprograms the Immune Microenvironment Through Cholinergic Signaling in Pancreatic Ductal Adenocarcinoma. *Cancer Res* (2020) 80(10):1991–2003. doi: 10.1158/0008-5472.Can-19-2689
34. Baum M, Demicheli R, Hrushesky W, Retsky M. Does Surgery Unfavourably Perturb the "Natural History" of Early Breast Cancer by Accelerating the Appearance of Distant Metastases? *Eur J Cancer (Oxf Engl 1990)* (2005) 41 (4):508–15. doi: 10.1016/j.ejca.2004.09.031
35. Buggy D, Wall T. Can Anaesthetic-Analgesic Technique During Cancer Surgery of Curative Intent Influence Recurrence or Metastasis? An Update. *Br J Anaesthesia* (2019) 123(6):e525–6. doi: 10.1016/j.bja.2019.07.023
36. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic Technique may Affect Prognosis for Ovarian Serous Adenocarcinoma: A Retrospective Analysis. *Br J Anaesthesia* (2011) 106(6):814–22. doi: 10.1093/bja/aer055
37. Gottschalk A, Ford J, Regelin C, You J, Mascha E, Sessler D, et al. Association Between Epidural Analgesia and Cancer Recurrence After Colorectal Cancer Surgery. *Anesthesiology* (2010) 113(1):27–34. doi: 10.1097/ALN.0b013e3181de6d0d
38. Wigmore T, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/aln.0000000000000936
39. Exadaktylos A, Buggy D, Moriarty D, Mascha E, Sessler D. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008
40. Mitchell A, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of Depression, Anxiety, and Adjustment Disorder in Oncological, Haematological, and Palliative-Care Settings: A Meta-Analysis of 94 Interview-Based Studies. *Lancet Oncol* (2011) 12(2):160–74. doi: 10.1016/s1470-2045(11)70002-x
41. Honda K, Goodwin R. Cancer and Mental Disorders in a National Community Sample: Findings From the National Comorbidity Survey. *Psychother Psychosomat* (2004) 73(4):235–42. doi: 10.1159/000077742
42. Liu Q, Sheng Z, Cheng C, Zheng H, Lanuti M, Liu R, et al. Anesthetic Propofol Promotes Tumor Metastasis in Lungs *via* GABA(A) R-Dependent TRIM21 Modulation of Src Expression. *Adv Sci (Weinh)* (2021) 8(18):e2102079. doi: 10.1002/advs.202102079
43. Chen J, Ouyang Y, Cao L, Zhu W, Zhou Y, Zhou Y, et al. Diazepam Inhibits Proliferation of Human Glioblastoma Cells Through Triggering a G0/G1 Cell Cycle Arrest. *J Neurosurg Anesthesiol* (2013) 25(3):285–91. doi: 10.1097/ANA.0b013e31828bac6a
44. Babateen O, Jin Z, Bhandage A, Korol SV, Westermark B, Forsberg Nilsson K, et al. Etomidate, Propofol and Diazepam Potentiate GABA-Evoked GABAA Currents in a Cell Line Derived From Human Glioblastoma. *Eur J Pharmacol* (2015) 748:101–7. doi: 10.1016/j.ejphar.2014.12.001
45. Chen X, Wu Q, You L, Chen S, Zhu M, Miao C. Propofol Attenuates Pancreatic Cancer Malignant Potential *via* Inhibition of NMDA Receptor. *Eur J Pharmacol* (2017) 795:150–9. doi: 10.1016/j.ejphar.2016.12.017
46. Qi J, Wu Q, Zhu X, Zhang S, Chen X, Chen W, et al. Propofol Attenuates the Adhesion of Tumor and Endothelial Cells Through Inhibiting Glycolysis in Human Umbilical Vein Endothelial Cells. *Acta Biochim Biophys Sin (Shanghai)* (2019) 51(11):1114–22. doi: 10.1093/abbs/gmz105
47. Tian H, Hou L, Xiong Y, Cheng Q. Dexmedetomidine Upregulates microRNA-185 to Suppress Ovarian Cancer Growth *via* Inhibiting the

SOX9/Wnt/β-Catenin Signaling Pathway. *Cell Cycle* (2021) 20(8):765–80. doi: 10.1080/15384101.2021.1897270
48. Wang C, Datoo T, Zhao H, Wu L, Date A, Jiang C, et al. Midazolam and Dexmedetomidine Affect Neuroglioma and Lung Carcinoma Cell Biology *In Vitro* and *In Vivo*. *Anesthesiology* (2018) 129(5):1000–14. doi: 10.1097/aln.0000000000002401
49. Chi M, Shi X, Huo X, Wu X, Zhang P, Wang G. Dexmedetomidine Promotes Breast Cancer Cell Migration Through Rab11-Mediated Secretion of Exosomal TMPRSS2. *Ann Transl Med* (2020) 8(8):531. doi: 10.21037/atm.2020.04.28
50. Liu Y, Sun J, Wu T, Lu X, Du Y, Duan H, et al. Effects of Serum From Breast Cancer Surgery Patients Receiving Perioperative Dexmedetomidine on Breast Cancer Cell Malignancy: A Prospective Randomized Controlled Trial. *Cancer Med* (2019) 8(18):7603–12. doi: 10.1002/cam4.2654
51. Yabasin I, Lu Z, Yu J, Wen Q. Cisatracurium-Induced Proliferation Impairment and Death of Colorectal Cancer Cells, HCT116 is Mediated by P53 Dependent Intrinsic Apoptotic Pathway*In Vitro*. *Biomed Pharmacother = Biomed Pharmacother* (2017) 91:320–9. doi: 10.1016/j.biopha.2017.04.044
52. Yabasin I, Sanches J, Ibrahim M, Huidan J, Williams W, Lu Z, et al. Cisatracurium Retards Cell Migration and Invasion Upon Upregulation of P53 and Inhibits the Aggressiveness of Colorectal Cancer. *Front Physiol* (2018) 9:941:941. doi: 10.3389/fphys.2018.00941

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REVIEW
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Application of Anesthetics in Cancer Patients: Reviewing Current Existing Link With Tumor Recurrence

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Surgery remains the most effective cancer treatment, but residual disease in the form of scattered micro-metastases and tumor cells is usually unavoidable. Whether minimal residual disease results in clinical metastases is a function of host defense and tumor survival and growth. The much interesting intersection of anesthesiology and immunology has drawn increasing clinical interest, particularly, the existing concern of the possibility that the perioperative and intraoperative anesthetic care of the surgical oncology patient could meaningfully influence tumor recurrence. This paper examines current data, including recent large clinical trials to determine whether the current level of evidence warrants a change in practice. Available pieces of evidence from clinical studies are particularly limited, largely retrospective, smaller sample size, and often contradictory, causing several questions and providing few answers. Recent randomized controlled clinical trials, including the largest study (NCT00418457), report no difference in cancer recurrence between regional and general anesthesia after potentially curative surgery. Until further evidence strongly implicates anesthesia in future clinical trials, clinicians may continue to choose the optimum anesthetic-analgesic agents and techniques in consultation with their cancer patients, based on their expertise and current best practice.

Keywords: anesthesia, cancer, tumor recurrence, perioperative factors, inhalational anesthetic, intravenous anesthetic

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INTRODUCTION

Cancer constitutes an enormous burden on society in both poor and rich global economies alike. Factors contributing to the increasing occurrence of cancer include the growth and aging of the population, as well as an increasing prevalence of established risk factors such as smoking, physical inactivity, overweight, and changing reproductive patterns associated with urbanization and economic development (1). Some of the most common cancers contributing to high mortality include malignant tumors of the lung, breast, prostate, and colorectum. Surgical removal of malignant tumors remains the primary and most effective treatment option for cancer; however, the surgical procedure results in a significant systemic release of tumor cells (2). The potential of these cells to lead to metastases is largely dependent on the balance between the resilience of the

Abbreviations: NK cells, natural killer cells; DCs, dendritic cells; MOR, μ-opioid receptor; SP, substance P; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor-1; EMT, epithelial-mesenchymal transition.

body's immunity and the aggressiveness of tumor cells (2). Several factors including surgical stress, anesthetic agents, and opioid analgesics can compromise immune function and might shift the balance towards the progression of minimal residual disease.

Metastatic disease is the most important cause of cancer-related death in patients after malignant tumor surgery (3). The hypothesis that anesthesia may influence cancer recurrence after surgical removal was first proposed in 2006 (4) and has since gained traction as one of the most important research questions in this field (5). In recent years, many studies have investigated the rate of tumor resurgence regarding the different anesthesia techniques and agents, and the significance of anti-inflammatory, anti-cancer, and anti-metastatic effects in the context of anesthesia, providing insights into potential mechanisms by which anesthesia might influence malignant cells. This review examines recent experimental, preclinical, and clinical studies of the different types and techniques of anesthesia used during cancer surgery regarding their influence on the long-term survival or rate of tumor recurrence in patients undergoing cancer surgery.

ANESTHESIA IN CANCER PATIENTS

The perioperative use of anesthesia forms a crucial part of daily clinical practice in patients undergoing surgery. In cancer surgery, the perioperative period constitutes an important stage for the further course of the disease, as circulating tumor cells shed from the primary tumor into the patient's bloodstream might form new micro-metastases independent of complete tumor removal (6). Various studies have investigated the potential beneficial effect or otherwise of the different anesthesia techniques regarding outcome (overall and/or recurrence-free survival) in patients undergoing cancer surgery. **Figure 1** presents the three main anesthesia techniques employed in tumor surgery and an overview of their effects as discussed below.

Local Anesthesia

Local anesthesia is employed to numb a small part of the body when surgery is minor and does not require general or regional anesthesia. Local anesthetics are common medication and a mainstay of anesthesia since the introduction of cocaine in 1884 and are administered systemically or used as part of regional anesthesia techniques for a variety of reasons. They are effective in pain relief due to their ability to block the voltage-gated sodium channel, thus inhibiting nerve cell depolarization (7, 8), and may contribute to reducing postoperative nausea and vomiting (9) and enhancing early recovery after surgery (10). Local anesthetics may exert a certain degree of influence on circulating tumor cells shed during surgery through direct or indirect means because of their strong anti-inflammatory properties. For example, they could contribute to blunting the inflammatory stress response induced by the surgical stimulus (6).

On the other hand, certain local anesthetics have been demonstrated to preserve immune cell function and exhibit anti-metastatic effects. They can reduce the viability and proliferation of cancer cells *in vitro*, and efficient to target residual disease or cells that form micro-metastasis. Lidocaine, one of the most applied local anesthetics in clinical settings, has been shown to exhibit multi-activities, including the potential in cancer therapy. Growing evidence shows that lidocaine might not only work as a chemosensitizer that induces other conventional chemotherapies to eliminate certain resistant cancer cells but could also suppress cancer cell growth by single-use at different doses or concentrations (11). *In vitro* studies show that lidocaine improves the activity of NK cells and the intravenous administration of lidocaine as part of the

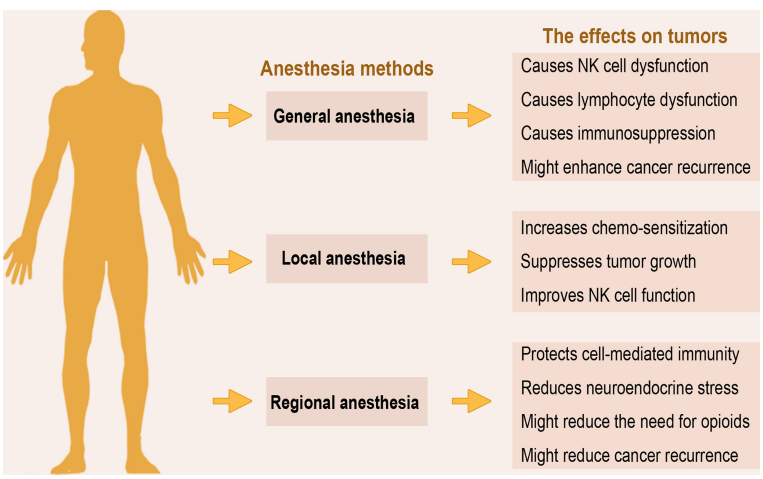

FIGURE 1 | Anesthesia methods and overview of their effects on tumors. The three main anesthesia methods applied in surgery exert varying effects on the host's immunity and ability to clear residual tumor cells. The overview of current data from animal models, *in vitro*, and human studies, suggests that regional anesthesia may be more preferred to general anesthesia due to its immunoprotective effects.

perioperative anesthesia regimen, bears the potential to reduce the risk of cancer progression or recurrence in patients undergoing cancer surgery (12).

Regional Anesthesia

Regional anesthesia is applied to block pain in a particular region of the body. Some studies have asserted that regional anesthesia methods provide perioperative pain relief, hence reduce the number of systemic anesthetic agents and opioids administered (13). Epidural anesthesia, a form of regional anesthesia, blocks the nerve impulses from the lower spinal segments to induce analgesia or pain relief. In epidural anesthesia, one or more drugs are injected into the epidural space bordering on the spinal dura mater to induce a "central" and/or "neuraxial" block (14, 15). Surgical operations carried under general anesthesia result in the bombardment of the central nervous system with nociceptive input and responses, with a neurohumoral stress response that stimulates the sympathetic nervous system and hypothalamic-pituitary axis. The use of regional anesthesia *via* blockade of nociceptive afferents might inhibit much of this neurohumoral response and its subsequent impact on the immune system. In animal studies, the addition of spinal anesthesia to a halothane anesthetic (16) and sevoflurane anesthetic (17), preserved the immune response and reduced hepatic metastases of tumor cells, while preserving liver mononuclear cell function, and attenuating the downward shift in T helper 1/T helper 2 cytokine balance.

Preclinical and retrospective studies highlight a potential benefit of regional anesthesia as it protects cell-mediated immunity and reduces the surgical neuroendocrine stress response by blocking afferent neural transmission that stimulates the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, hence reducing the need for opioids and volatile anesthetics and therefore reducing cancer recurrence (18, 19). The administration of regional anesthesia results in reduced use of certain anesthesia and pain medications that are given intravenously or inhaled into the lung, and as well attenuate surgical stress (13). Therefore, many studies have suggested that regional anesthesia might reduce the risk of long-term cancer recurrence.

General Anesthesia

General anesthesia is a combination of medications that put a patient in a sleep-like or unconscious state and inactivates response to pain signals or reflexes of the autonomic nervous system before surgery. It uses intravenous anesthetics, inhalational (volatile gasses) anesthetics or a combination of both. Opioids and benzodiazepines are often employed as adjuvants during general anesthesia (20, 21). The most frequently applied method in general anesthesia is intravenous anesthesia and uses anesthetic agents such as propofol, sodium thiopental, and ketamine. Volatile anesthetics often used to induce and maintain general anesthesia include sevoflurane, isoflurane, and desflurane. There is evidence that these two general anesthesia methods influence the immune system *via* cellular and molecular (cytokine) modulation, or activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, and possibly contribute to long-term tumor recurrence after surgical intervention (22–24).

Concerning cancer patients, the immunosuppression associated with general anesthesia, including the dysfunction of natural killer (NK) cells and lymphocytes, could promote the immune evasion, growth, and metastasis of residual cancer cells, hence worsening patients' prognoses (25, 26). For example, volatile anesthetics have varying influence on immunity through their effects on components such as NK cells, neutrophils, dendritic cells (DCs), and macrophages (25), and inhibit cytokine release, reduce lymphocyte proliferation, trigger lymphocyte apoptosis, and inhibit the function of neutrophils in a dose-dependent manner (27). In a controlled trial, patients undergoing elective reconstructive surgery for tongue cancer were randomized to receive general anesthesia of either propofol induction and maintenance, sevoflurane induction and maintenance, or propofol induction and sevoflurane maintenance (mixed). Results showed that NK cells, B lymphocytes, and T lymphocyte subsets such as CD3(+) cells, CD3(+)CD4(+) cells, and CD4(+)/CD8(+) ratio significantly reduced in all groups. However, further analysis indicated that propofol had slightly less effect on cellular immune responses than sevoflurane (28). These studies indicate the immunosuppressive effects of anesthesia on host immunity, a possible promoter of tumor recurrence.

PERIOPERATIVE FACTORS ASSOCIATED WITH CANCER PROMOTION

Anesthetics

Perioperative anesthesia and analgesia exacerbate immunosuppression in the already immunocompromised cancer microenvironment in patients. NK cells are a critical part of anti-tumor immunity and are responsible for the phenomenon of immune surveillance, which includes the detection of circulating tumor cells (29). However, the innate immune system, especially NK cell activity is known to be significantly impaired by certain anesthetic agents such as sevoflurane-fentanyl (30). Local anesthetics, especially the amide anesthetics, possess strong anti-inflammatory ability through their effects on cells of the immune system, as well as on others such as microorganisms, thrombocytes, and erythrocytes, which have been extensively studied (31, 32). Although there are different effects regarding volatile anesthetic agents on cancer promotion, the majority of *in vitro* studies suggest that these agents are associated with elevated expression of tumorigenic markers, and increased migration and proliferation of cancer cells (33, 34). For example, enflurane and halothane reversibly and dose-dependently impair NK cell function, and isoflurane and halothane prevent interferon-stimulated NK cell activities (35–37).

Volatile anesthetics not only cause immune cell dysfunction but apoptosis of neutrophils and T-lymphocytes (38, 39), as sevoflurane, one of the most commonly used inhalation anesthetics, induces apoptosis and oxidative stress in lymphocytes (40). In another study, although there were no

significant differences in tumor size or survival between sevoflurane and control mice, *in vitro* study showed that the proliferation of Lewis lung carcinoma cells exposed to sevoflurane increased by 9.2% compared to the controls (41). This implies that sevoflurane exposure might enhance the proliferation of tumor cells *in vitro* environment, but might not affect proliferation *in vivo*, suggesting that the effects of anesthetics on *in vitro* studies of cancer do not necessarily translate into *in vivo* or clinical studies.

The administration of general anesthesia alone is known to impair immune function; however, the addition of pectoral nerve II block under general anesthesia increases the proportion of NK cells, improves tumor cell killing activity, and upregulates postoperative IL-2 concentration in patients' plasma (42). Ketamine, a dissociative anesthetic agent with excellent analgesic properties and a favorable safety profile, effectively reduces postoperative pain, blunts hyperalgesia, lowers opiate consumption, and even decreases chronic persistent postoperative pain (43, 44). However, ketamine has tumor modulatory and anti-inflammatory effects, including, promoting tumor growth *via* decreasing NK cells and increasing tumor cell retention (35) and generally inducing immunosuppression (45). **Figure 2** summarizes the complex immunosuppressive effects of anesthesia that aid tumor progression.

Opioid Analgesics

Opioid analgesics are well-known inhibitors of both cellular and humoral immunity (46, 47). Their effects are primarily modulated by the μ-opioid receptor (MOR) as demonstrated in the evidence that MOR-deficient mice do not exhibit immunosuppression with morphine, and that naloxone blocks morphine-related immunosuppression (36, 48). Morphine has both tumor growth-promoting and -inhibiting effects as reported in many studies (49, 50). In its tumor-promoting influence, morphine stimulates angiogenesis to enhance cancer progression. In one of such studies, the effect of morphine on tumor onset, development, and survival of animal models, as well as whether MOR, mast cell stimulation, lymphangiogenesis, and substance P (SP) are linked with tumor-enhancing effects of morphine was investigated. The outcome indicates that, although morphine does not influence the onset of tumor development, it significantly enhances the growth of existing tumors, and decreases overall survival in mice. The activation of mast cells by morphine may participate in increasing SP and cytokine levels, resulting in cancer progression, while MOR might be linked with morphine-induced cancer progression (51). On the other hand, morphine was shown to inhibit the migration of tumor-infiltrating leukocytes and suppress angiogenesis associated with tumor growth in mice (52).

In general, reports on the effects of opioids on tumor cell migration, proliferation, and apoptosis are contradictory and appear to reflect the influence of multiple factors of tumor biology and drug administration. In these reports, tumor growth either decreases, increases, or remains unaffected by opioid analgesics.

Surgical Stress

The surgical removal of tumors induces stress which results in depressed cell-mediated immunity and decreased concentrations of tumor-associated antiangiogenic factors such as angiostatin and endostatin (**Figure 3**). The surgically induced suppression of cell-mediated immunity is a summation of both direct cell-mediated influence and indirect paracrine-mediated effects *via* dysregulation of cytokine signaling. Surgery or anesthesia-induced activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system provides immunosuppression through several

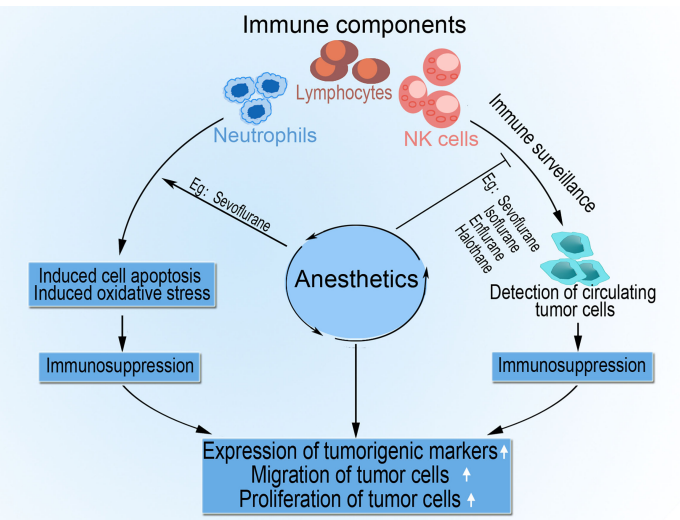

FIGURE 2 | The role of anesthesia in tumor progression. Anesthetic agents impair cell-mediated immunity by direct or indirect inhibition of components such as NK cells, lymphocytes, and neutrophils. Anesthesia also impedes immune surveillance of circulating tumor cells by NK cells and activates apoptosis and oxidative stress in lymphocytes and neutrophils. The resultant immunosuppression encourages tumor cell migration, proliferation, and upregulated expression of tumorigenic markers.

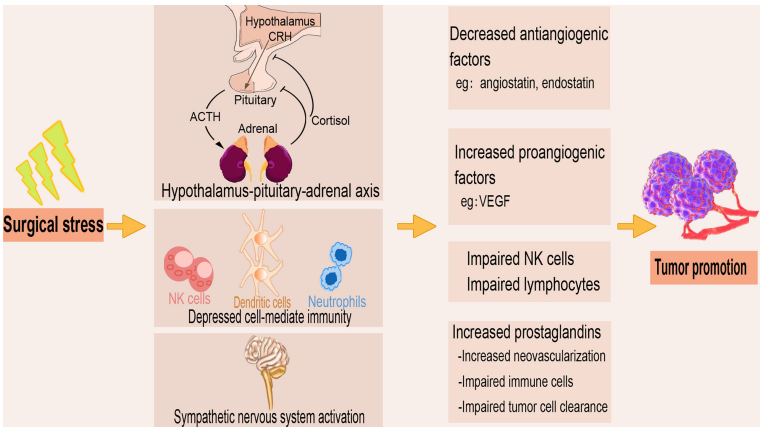

FIGURE 3 | The tumor-promoting effect of surgical stress. The stress produced during the surgical removal of tumors activates the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis and as well depresses the cell-mediated immunity. Surgical stress also decreases antiangiogenic factors, increases proangiogenic factors, and upregulates prostaglandins, leading to impaired immune cell function and tumor cell clearance.

soluble factors (33, 53). Surgical stress upregulates the concentration of proangiogenic factors, including vascular endothelial growth factor (VEGF), and triggers the release of growth factors that promote local and distant growth of malignant tissue (54, 55). Innate immune components such as NK cells play a crucial role in eliminating circulating tumor cells and preventing metastasis (56), where reduced expression of circulating NK cell phenotypes are associated with tumor progression (57). Many studies report reduced postoperative NK cell and certain lymphocyte subsets functions, and an inverse correlation of NK cell function with tumor stage and metastatic growth (58, 59).

The robustness of an individual's perioperative cell-mediated immunity plays an important function in postoperative cancer outcomes. In other words, the oncologic outcome after surgery does not only depends on the extent, invasiveness, and type of cancer but the level of the patient's perioperative immune status and function (60). Cytokines such as interleukins, interferons, and tumor necrosis factors, among other chemical mediators, constitute a complex signaling network that modulates the diverse and interdependent immune cells. In addition to NK cells, other primary effector cells such as macrophages, and adaptive immune system cytotoxic lymphocytes play crucial roles in the tumor outcome (61, 62). In addition to the prostaglandins expressed in abundance due to surgical trauma, tumor cells also produce prostaglandins that together alter the tumor microenvironment, enhance neovascularization, and impair immune cells, adversely affecting the capability to clear residual disease after cancer surgery (63–65).

ANESTHESIA AND TUMOR RECURRENCE

Following the hypothesis that anesthetic and analgesic techniques during cancer surgery influence recurrence or metastasis, the first set of original investigations and a short overview encompassing a consensus statement were published to highlight concerns and drive more investigations (5, 66). These investigations sought to examine the direct effects of anesthetic and analgesic drugs on cancer cell biology, the effect of anesthetic technique in randomized cancer surgery patients on perioperative host immunity and cancer metastatic function, and new retrospective clinical data on perioperative factors associated with subsequent recurrence or metastasis. Recently, several clinical trials have also been published. While volatile anesthetics and opioids generally suppress cell-mediated immunity and enhance the proliferation of cancer cells and angiogenesis, propofol appears to rather support cell-mediated immunity and inhibit tumor angiogenesis (33).

Preclinical Trial Studies

Studies on the effects of anesthesia on tumor cells differ depending on the type and technique employed. While some anesthetic agents enhance tumor cell survival, others inhibit their progression. Anesthetic agents vary in their capability to trigger immunomodulation and potentiation of tumorigenic growth factors, including hypoxia-inducible factor-1 (HIF-1α) and insulin-like growth factors (67–69). Reports indicate that isoflurane enhances the malignant potential of ovarian cancer cells (69), and glioblastoma stem cells (70) through the up-regulation of markers associated with the cell cycle, angiogenesis, and proliferation. In a similar study, isoflurane-induced upregulation of HIF-1α, consequently increasing tumor malignancy with increased proliferation and migration, as well as the development of chemoresistance in prostate cancer cells (67). In a rat model of pulmonary metastasis, ketamine, thiopental, and halothane inhibited NK activity and promoted tumor metastasis (35). On the other hand, propofol mitigates malignant effects such as epithelial-mesenchymal transition (EMT) and HIF-1α effects (71), postpones colorectal cancer development through circ_0026344/miR-645/Akt/mTOR signal pathway (72), and inhibits the proliferation, migration, and

stem-like properties of bladder cancer by suppressing the hedgehog pathway (73).

The local anesthetics, lidocaine, and ropivacaine decrease the viability and proliferation of cancer cells and increase their apoptosis. Mechanistically, lidocaine upregulates the mRNA level of adenomatous polyposis coli, which serves as an inhibitor of the Wnt/β-catenin pathway, while ropivacaine reduces the mRNA level of important cell cycle modulators such as cyclin A2, cyclin B1, cyclin B2, cyclin-dependent kinase 1, and the nuclear marker of cell proliferation MKI67 (74). Lidocaine inhibits the growth of hepatocellular carcinoma cells in a dose- and time-dependent manner by arresting cells in the G0/G1 phase of the cell cycle, and inducing apoptosis. It suppressed tumor development and improved the sensitivity of cisplatin (75). In another study, during sevoflurane anesthesia, the addition of lidocaine to cisplatin significantly reduced metastatic lung but not liver colony count compared to sevoflurane alone and cisplatin alone. Additionally, serum interleukin-6 and VEGF levels were not significantly different (76). This indicates that under sevoflurane anesthesia, lidocaine capably enhances the metastasis-inhibiting function of cisplatin in a murine model of breast cancer surgery. Moreover, mice that receive lidocaine with sevoflurane exhibit reduced lung metastatic colony count, as well as decreased serum pro-inflammatory and angiogenic cytokine expression (77).

Metastatic colon and breast cancer cells express adult and neonatal splice variants of NaV1.5 voltage-activated Na(+) channels. Blockade of these channels inhibits cell invasion. Local anesthetics employed during surgical tumor excision inhibit NaV1.5 voltage-activated Na(+) channels activity on nociceptive neurons, providing regional anesthesia (78, 79). Ropivacaine inhibits both NaV1.5 channel activity and metastatic colon cancer cell invasion (80). Moreover, lidocaine and levobupivacaine potently inhibit aNaV1.5, where higher concentrations of either levobupivacaine (100 μM) or lidocaine (300 μM) result in significantly more tonic block at -120 mV (78). These findings indicate that low concentrations of local anesthetics exhibit an inactivation-dependent block of NaV1.5, and could provide a rationale for their application to safely impede the migration and invasion of metastatic cancer cells without cardiotoxicity.

Retrospective Studies

Several human studies, mainly retrospective, have shown different effects of anesthetics on cancer cell growth and recurrence after surgical removal. These studies mainly compare the different patient outcomes between anesthesia techniques or anesthetic agents. A systematic review of the overall mortality and post-surgery complications after tumor surgery with intravenous and inhalational anesthesia techniques reported that four propensity-adjusted retrospective studies show intravenous anesthesia to be the preferred technique in tumor surgery (81). The result of similar meta-analyses of the effects of propofol (intravenous) and volatile (inhalational gas) anesthesia on cancer recurrence and survival suggested that propofol-based total intravenous anesthesia use might be associated with enhanced recurrence-free survival and overall survival in patients having cancer surgery (82, 83). Another study found volatile inhalational anesthesia to be associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis of known confounders (84). This implies an association between the type of anesthetic delivered and patients' survival. However, these pieces of evidence suffer moderate to serious risk of bias and of low quality, hence randomized clinical trials are needed for concrete confirmation of these findings.

Volatile anesthetic agents have been implicated in metastasis-enhancing effects on cancer cells. Notwithstanding, Xenon, but not sevoflurane, inhibits the migration of both estrogen receptor-negative and positive breast adenocarcinoma cells, and reduces the release of the pro-angiogenic factor RANTES (regulated upon activation, normal T Cell expressed and presumably secreted) (85). In a retrospective cohort study of patients who received elective, open pancreatic cancer surgery, the effect of anesthetic techniques (propofol vs. desflurane) on patients' outcomes has been reported. Propofol anesthesia was associated with enhanced survival in matched analysis and significantly better cancer-specific survival in subgroup analyses. Moreover, propofol was linked with less postoperative recurrence, but not fewer postoperative metastases formation compared to desflurane (86). In a similar retrospective cohort study of colon cancer patients, propofol anesthesia had better survival than desflurane, irrespective of lower tumor-node-metastasis stage, or higher tumor-node-metastasis stage, and the presence or absence of metastases (87). Another report indicates that the five-year survival rate of patients that underwent general anesthesia during bladder tumor surgery is 87.5% compared to 96.3% for regional anesthesia. The authors conclude that although partial correlation analysis showed a higher five-year survival under regional than general anesthesia, the association was not significant in the chi-square test and logistic regression analysis (88).

However, several others studies have reported no significant difference between the type or method of anesthesia used during tumor surgery. For example, in non-randomized retrospective analysis, neither propofol nor desflurane anesthesia for breast cancer surgery exhibited any significant effect on patient prognosis and survival (89). Again, no obvious relationship was found between epidural anesthesia use and long-term survival according to the Cox model, but the Kaplan-Meier analysis showed an association among younger patients (15). A recent cohort study found no association between the type of anesthesia used (total IV anesthesia vs inhalation anesthesia) and the long-term prognosis of breast cancer after surgery (22). However, in a similar study that evaluated the influence of regional anesthesia on cancer-specific outcomes in a radical cystectomy cohort of patients, the authors concluded that epidural anesthesia using sufentanil is linked with worse recurrence and disease-free survival in bladder cancer patients treated with surgery. The cumulative risk of recurrence at two years was 25.2% for epidural analgesia with general anesthesia compared to 20.0% for general anesthesia alone. This could be due to the use of epidural sufentanil or the increased total morphine equivalents patient received as a consequence of the sufentanil (90). **Table 1** summarizes preclinical and retrospective studies concerning the outcome of various anesthetic agents on tumors.

Clinical Trial Studies

The largest available randomized controlled trial at 13 hospitals in Austria, Argentina, China, Ireland, Germany, New Zealand, USA, and Singapore was carried out from 2007 to 2018 and involved 2132 women with breast cancer. Participants were assigned to undergo regional anesthesia-analgesia (1043 patients) using paravertebral blocks and the anesthetic propofol and general anesthesia (1065 patients) using the volatile anesthetic sevoflurane and opioid analgesia. Results showed that 102 (10%) of patients who underwent regional anesthesia-analgesia had breast cancer recurrences compared to 111 (10%) of those allocated to general anesthesia. Moreover, incisional pain was reported by 442 (52%) of 856 patients and 239 (28%) of 854 patients in the regional anesthesia-analgesia group at 6 and 12 months respectively, compared to 456 (52%) of 872 patients and 232 (27%) of 852 patients in the general anesthesia group. Neuropathic breast pain did not also differ by the anesthetic technique used (92). Based on this study, regional anesthesia-analgesia does not decrease breast cancer recurrence after potentially curative surgery compared to general anesthesia, and the severity and frequency of persistent incisional breast pain are unaffected by the anesthetic technique employed.

Another clinical trial that assessed postoperative circulating tumor cell count in breast cancer patients to determine how anesthesia might indirectly affect prognosis has been documented. In that randomized controlled trial, 210 participants were

TABLE 1 | Preclinical and retrospective studies on anesthesia effects on tumor cells.

Anesthesia agent/ technique	Study model	Tumor type	Outcome	Reference
Ropivacaine	SW620 cells *in vitro*	Colon	Ropivacaine causes a concentration-dependent blockade of NaV1.5 variants, inhibiting migration and invasion of metastatic cancer cells	(80)
Xenon and sevoflurane	*In vitro*	Breast	Xenon, but not sevoflurane, inhibits tumor cell migration and expression of angiogenesis biomarkers, RANTES	(85)
Lidocaine and sevoflurane	4T1 murine model (female BALB/c mice)	Breast	Under sevoflurane anesthesia, lidocaine enhances the metastasis-inhibiting action of cisplatin	(76)
Lidocaine and sevoflurane	4T1 murine model (female BALB/c mice)	Breast	Lidocaine decreases pulmonary metastasis combined with sevoflurane, perhaps *via* anti-inflammatory and anti-angiogenic effects	(77)
Lidocaine	*In vitro* and xenograft model *in vivo*	Hepatocellular (HepG2 cells)	Lidocaine exerts potent antitumor activity in hepatocellular carcinoma	(75)
Lidocaine and levobupivacaine	HEK-293 cells *in vitro*	–	Lidocaine and levobupivacaine potently inhibited aNaV1.5, inhibiting migration and invasion of metastatic cancer cells	(78)
Sevoflurane with/ without bupivacaine and morphine	C57BL/6 mice	Liver	The addition of spinal block to sevoflurane general anesthesia attenuates the suppression of the tumoricidal function of liver mononuclear cells, and preserves Th1/Th2 balance, hence reducing the promotion of tumor metastasis.	(16)
Sevoflurane	*In vitro* and *in vivo* mice model	Lung	Promotes the proliferation of Lewis lung carcinoma cells *in vitro* but may not affect proliferation *in vivo*	(41)
Isoflurane	*In vitro* use of ovarian cancer (SK-OV3) cells	Ovarian	Isoflurane exposure significantly increases angiogenic markers vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-1 and IGF-1R expression, cell cycle progression, and cell proliferation in tumor cells	(69)
Isoflurane and propofol.	*In vitro* use of prostate cancer (PC3) cell line	Prostate	Isoflurane increases tumor malignancy *via* modulation of the HIF-1α pathway	(67)
Propofol	*In vitro* and nude mice (bladder cancer stem cells)	Bladder	Blocks the activation of the Hedgehog pathway to repress the growth of cancer cells and the tumor formation	(73)
Propofol and desflurane	A retrospective cohort study in human	Pancreatic	Propofol is associated with improved survival compared with desflurane	(86)
Propofol and desflurane	A retrospective cohort study in human	Colon	Propofol is associated with better survival irrespective of tumor-node-metastasis stage	(87)
Total IV anesthesia and inhalation anesthesia	A retrospective cohort study in human	Breast	No significant difference in recurrence-free survival or overall survival between the two groups	(22)
Desflurane or propofol	Retrospective comparative study	Breast	Neither propofol nor desflurane anesthesia for breast cancer surgery by an experienced surgeon affects patient prognosis and survival	(89)
Volatile IV Anesthesia	Retrospective comparative study	Several types	There is an association between the type of anesthetic delivered and patients' survival.	(84)
Inhalation vs intravenous anesthesia	Retrospective study	Colorectal	Inhalation anesthesia is associated with an increased risk of recurrence after colorectal cancer surgery	(91)

assigned to either sevoflurane (107 patients) or propofol (103 patients) anesthesia. Results showed that anesthesia type did not affect circulating tumor cell counts over time or positivity. However, in one secondary analysis, the administration of sevoflurane was associated with a significant increase in maximal tumor cell counts postoperatively. There was no link between NK cell activity and circulating tumor cell counts (93). CD 39 and CD73, enzymes expressed on the surface of regulatory T cells, promote cancer recurrence and metastasis by suppressing immune cells. In a randomized trial, the immunosuppressive effect of propofol and volatile sevoflurane-based anesthesia, regarding CD39 and CD73 expression on regulatory T cells was examined. Results indicated no difference in CD39 and CD73 expression on regulatory T cells between the two anesthetic agents used, as well as in helper T cell type 1 (Th1), Th17, NK cells, cytotoxic T cells, cytokines, and the neutrophil-to-lymphocyte ratio (94). This study implies similar effects regarding postoperative changes in immune cells after the use of propofol and sevoflurane in cancer surgery. Another randomized trial that investigated the effect of propofol and desflurane anesthesia on the surgery-induced immune perturbation in patients undergoing breast cancer surgery reported that, although both anesthetic agents preserved the CD4(+)/CD8(+) T cell and IL-2/IL-4 ratio, the propofol group had lower leukocytes count (with a significant reduction in NK cells) than the desflurane group (95).

Several small-sized clinical trials have also been documented. These include the report that propofol/remifentanil-based total intravenous anesthesia effectively prevents the expression of VEGF-C induced by breast surgery compared to sevoflurane-based inhalational anesthesia, but appears to be non-beneficial in the short-term recurrence rate of breast cancer (24). The clinical trial studies discussed above, among others, are summarized in **Table 2**.

DISCUSSION

Surgery remains a central component of treatment for patients with many types of cancer. However, it is well documented that surgery, regardless of how extensive it is applied, cannot eliminate all cancer cells from the patient. Certain anesthesia, surgical stress, and pain medications commonly given during anesthesia for cancer surgery are known to suppress body defenses. In addition to any pre-existing micro-metastases, surgical removal of tumors results in spillage of tumor cells locally and into the bloodstream and lymphatics system. Multiple peri-operative factors, inflammatory and neurohumoral factors, patient's physiologic response to surgery, and care of the patient after the procedure, can encourage the invasiveness and proliferation of residual tumor cells while enhancing neo-angiogenesis to support the growth. Parallel to these effects on the tumor cells, the factors could also inhibit cell-mediated immunity, the body's capability to eliminate these tumor cells, within this same vulnerable period. Therefore, surgery and anesthesia might contribute to long-term cancer recurrence. Current laboratory experimental data show that perioperative interventions influence cancer recurrence or metastasis by affecting cancer cell signaling, immune response, and regulating the neuroendocrine stress response.

TABLE 2 | Clinical trial studies on anesthesia and its effects on tumor cells.

Anesthesia agent/technique	Tumor type	Clinical trial-type	Key observation	Reference
Regional anesthesia-analgesia (paravertebral blocks and anesthetic propofol) and general anesthesia (sevoflurane and opioid analgesia)	Breast	Randomized controlled	Regional anesthesia-analgesia did not reduce cancer recurrence after potentially curative surgery compared with general anesthesia	(92)
Sevoflurane and propofol	Breast	Randomized controlled	No difference between sevoflurane and propofol concerning circulating tumor cell counts over time	(93)
Sevoflurane and propofol	Breast	Randomized controlled	Both induce a favorable immune response in terms of preserving IL-2/IL-4 and CD4(+)/CD8(+) T cell ratio Reduced leukocytes and NK cells in propofol anesthesia	(95)
Sevoflurane-based inhalational anesthesia and propofol/remifentanil-based total intravenous anesthesia	Breast	Randomized controlled	Propofol/remifentanil inhibit the release of VEGF-C No significant differences in the preoperative and postoperative TGF-β concentrations between the two groups	(24)
General anesthesia vs combined epidural-general anesthesia	Gallbladder	Randomized controlled	Combined epidural-general anesthesia might attenuate intraoperative hemodynamic responses and improve postoperative cellular immunity	(96)
Volatile general anesthesia or propofol general anesthesia combined with paravertebral regional anesthesia	Breast	Randomized single-blind	The anesthetic technique did not affect neutrophil extracellular trapping expression, hence not a viable marker of the effect of anesthetic technique on breast cancer recurrence.	(97)
Sevoflurane, sevoflurane plus i.v. lidocaine, propofol, and propofol plus i.v. lidocaine	Breast	Randomized controlled	Regardless of the general anesthetic technique, lidocaine decreased postoperative expression of neutrophil extracellular trapping and MMP3, hence might reduce recurrence.	(98)
General anesthesia or combined general/epidural anesthesia	Adenocarcinoma Prostate cancer	Randomized controlled	No difference was observed between the groups in disease-free survival at a median follow-up time of 4.5 years.	(99)
Intraperitoneal local anesthetic vs placebo	Colon	Randomized controlled	There was no significant difference in overall survival or all-cause mortality. There was a higher incidence of cancer-specific mortality in the local anesthetic group	(100)

In effect, both anesthesia and surgery depress cell-mediated immunity and upregulate angiogenesis and could therefore enhance the proliferation and metastasis of tumor cells during the perioperative period. Declined levels of circulating anti-inflammatory cytokines and alterations in the function of NK cells are among the mechanisms by which anesthetic agents and techniques can influence immune function. Other studies have asserted that the use of regional analgesia, including epidural and paravertebral block, is effective in reducing inflammation and preventing immunosuppression in patients undergoing cancer surgery. However, there are reports of no significant difference between the types or methods of anesthesia used and cancer recurrence or patients' outcomes. Unfortunately, current evidence from clinical studies is particularly limited, largely retrospective, smaller sample size, and often contradictory, causing several questions and providing few answers. Moreover, these pieces of evidence suffer moderate to serious risk of bias and of low quality, hence randomized clinical trials are needed for concrete confirmation of these findings. In the phase of the limited data in clinical trials upon which to make concrete recommendations, clinicians and anesthesiologists may seek optimal anesthesia and analgesia for their cancer patients based on the best available evidence on outcomes and individual risk-benefit analysis.

CONCLUSION

Available evidence from experimental cell culture and animal model studies, as well as clinical retrospective studies, indicate that current data are sufficient only to generate a hypothesis that anesthetic or analgesic agents contribute to cancer recurrence and metastasis. Moreover, recent randomized controlled clinical trials, including the largest study (NCT00418457), report no difference in cancer recurrence between regional and general anesthesia after potentially curative surgery. Again, the severity and frequency of persistent incisional pain are unaffected by the anesthetic technique. Until further evidence strongly implicates anesthesia in clinical trials, clinicians may continue to choose the optimum anesthetic-analgesic agents and techniques in consultation with their cancer patients, based on their expertise and current best practice.

AUTHOR CONTRIBUTIONS

XL designed the study and participated in manuscript writing. QW constructed the tables and figures and revised the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. *CA Cancer J Clin* (2015) 65:87–108. doi: 10.3322/caac.21262
2. Orriach JLG, Raigon-Ponferrada A, Buggy DJ. Can Anaesthesia and Analgesia Interventions During Cáncer Surgery Influence Recurrence or Metástasis? *Curr Pharm Des* (2019) 25:2997–7. doi: 10.2174/1381612825281910071555536
3. Snyder GL, Greenberg S. Effect of Anaesthetic Technique and Other Perioperative Factors on Cancer Recurrence. *Br J Anaesth* (2010) 105:106–15. doi: 10.1093/bja/aeq164
4. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105:660–4. doi: 10.1097/00000542-200610000-00008
5. Buggy DJ, Hemmings HC. Special Issue on Anaesthesia and Cancer. *Br J Anaesth* (2014) 113:i1–3. doi: 10.1093/bja/aeu261
6. Müller SD, Ziegler JSH, Piegeler T. Local Anesthetics and Recurrence After Cancer Surgery-What's New? A Narrative Review. *J Clin Med* (2021) 10:719. doi: 10.3390/jcm10040719
7. Nordenskjöld J, Waldén M, Kjellin A, Franzén H, Atroshi I. Benefit of Local Anesthesia in Reducing Pain During Collagenase Injection for Dupuytren's Contracture. *Plast Reconstr Surg* (2017) 140:565–9. doi: 10.1097/PRS.0000000000003583
8. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, et al. Molecular Mechanisms of Action of Systemic Lidocaine in Acute and Chronic Pain: A Narrative Review. *Br J Anaesth* (2019) 123:335–49. doi: 10.1016/j.bja.2019.06.014
9. Colque A, Eisemann ML. Breast Augmentation and Augmentation-Mastopexy With Local Anesthesia and Intravenous Sedation. *Aesthetic Surg J* (2012) 32:303–7. doi: 10.1177/1090820X12436601
10. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Efficacy and Safety of Intravenous Lidocaine for Postoperative Analgesia and Recovery After Surgery: A Systematic Review With Trial Sequential Analysis † †This Review Is an Abridged Version of a Cochrane Review Previously Published in the Cochrane Databas. *Br J Anaesth* (2016) 116:770–83. doi: 10.1093/bja/aew101
11. Zhou D, Wang L, Cui Q, Iftikhar R, Xia Y, Xu P. Repositioning Lidocaine as an Anticancer Drug: The Role Beyond Anesthesia. *Front Cell Dev Biol* (2020) 8:565. doi: 10.3389/fcell.2020.00565
12. Chamaraux-Tran T-N, Piegeler T. The Amide Local Anesthetic Lidocaine in Cancer Surgery—Potential Antimetastatic Effects and Preservation of Immune Cell Function? A Narrative Review. *Front Med* (2017) 4:235. doi: 10.3389/fmed.2017.00235
13. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic Techniques for Risk of Malignant Tumour Recurrence. *Cochrane Database Syst Rev* (2014) (11):CD008877. doi: 10.1002/14651858.CD008877.pub2
14. Liu F, Zhang J, Zeng XQ, Zhao YQ, Zuo YX. Application of General Anesthesia Combined With Epidural Anesthesia/Analgesia in Rehabilitation After Gastric Cancer Resection. *Zhonghua Yi Xue Za Zhi* (2017) 97:1089–92. doi: 10.3760/cma.j.issn.0376-2491.2017.14.013
15. Wang J, Guo W, Wu Q, Zhang R, Fang J. Impact of Combination Epidural and General Anesthesia on the Long-Term Survival of Gastric Cancer Patients: A Retrospective Study. *Med Sci Monit* (2016) 22:2379–85. doi: 10.12659/MSM.899543
16. Wada H, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, et al. Combined Spinal and General Anesthesia Attenuates Liver Metastasis by Preserving Th1/Th2 Cytokine Balance. *Anesthesiology* (2007) 106:499–506. doi: 10.1097/00000542-200703000-00014
17. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the Tumor-Promoting Effect of Surgery by Spinal Blockade in Rats. *Anesthesiology* (2001) 94:1066–73. doi: 10.1097/00000542-200106000-00022
18. Fodale V, D'Arrigo MG, Triolo S, Mondello S, La Torre D. Anesthetic Techniques and Cancer Recurrence After Surgery. *Sci World J* (2014) 2014:1–10. doi: 10.1155/2014/328513
19. Cata JP, Hernandez M, Lewis VO, Kurz A. Can Regional Anesthesia and Analgesia Prolong Cancer Survival After Orthopaedic Oncologic Surgery? *Clin Orthop Relat Res* (2014) 472:1434–41. doi: 10.1007/s11999-013-3306-y
20. Brown EN, Lydic R, Schiff ND. General Anesthesia, Sleep, and Coma. *N Engl J Med* (2010) 363:2638–50. doi: 10.1056/NEJMra0808281
21. Mandel JE. Considerations for the Use of Short-Acting Opioids in General Anesthesia. *J Clin Anesth* (2014) 26:S1–7. doi: 10.1016/j.jclinane.2013.11.003
22. Yoo S, Lee H-B, Han W, Noh D-Y, Park S-K, Kim WH, et al. Total Intravenous Anesthesia Versus Inhalation Anesthesia for Breast Cancer Surgery. *Anesthesiology* (2019) 130:31–40. doi: 10.1097/ALN.0000000000002491

23. Makito K, Matsui H, Fushimi K, Yasunaga H. Volatile Versus Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery. *Anesthesiology* (2020) 133:764–73. doi: 10.1097/ALN.0000000000003440
24. Yan T, Zhang G-H, Wang B-N, Sun L, Zheng H. Effects of Propofol/Remifentanil-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Release of VEGF-C and TGF-β and Prognosis After Breast Cancer Surgery: A Prospective, Randomized and Controlled Study. *BMC Anesthesiol* (2018) 18:131. doi: 10.1186/s12871-018-0588-3
25. Kurosawa S, Kato M. Anesthetics, Immune Cells, and Immune Responses. *J Anesth* (2008) 22:263–77. doi: 10.1007/s00540-008-0626-2
26. Kurosawa S. Anesthesia in Patients With Cancer Disorders. *Curr Opin Anaesthesiol* (2012) 25:376–84. doi: 10.1097/ACO.0b013e328352b4a8
27. Eltzschig HK, Carmeliet P. Hypoxia and Inflammation. *N Engl J Med* (2011) 364:656–65. doi: 10.1056/NEJMra0910283
28. Zhang T, Fan Y, Liu K, Wang Y. Effects of Different General Anaesthetic Techniques on Immune Responses in Patients Undergoing Surgery for Tongue Cancer. *Anaesth Intensive Care* (2014) 42:220–7. doi: 10.1177/0310057X1404200209
29. López-Soto A, Gonzalez S, Smyth MJ, Galluzzi L. Control of Metastasis by NK Cells. *Cancer Cell* (2017) 32:135–54. doi: 10.1016/j.ccell.2017.06.009
30. Cho JS, Lee M-H, Kim SIL, Park S, Park HS, Oh E, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *Int J Med Sci* (2017) 14:970–6. doi: 10.7150/ijms.20064
31. Cassuto J, Sinclair R, Bonderovic M. Anti-Inflammatory Properties of Local Anesthetics and Their Present and Potential Clinical Implications. *Acta Anaesthesiol Scand* (2006) 50:265–82. doi: 10.1111/j.1399-6576.2006.00936.x
32. Hollmann MW, Durieux ME, Fisher DM. Local Anesthetics and the Inflammatory Response. *Anesthesiology* (2000) 93:858–75. doi: 10.1097/00000542-200009000-00038
33. Kim R. Anesthetic Technique and Cancer Recurrence in Oncologic Surgery: Unraveling the Puzzle. *Cancer Metastasis Rev* (2017) 36:159–77. doi: 10.1007/s10555-016-9647-8
34. Byrne K, Levins KJ, Buggy DJ. Can Anesthetic-Analgesic Technique During Primary Cancer Surgery Affect Recurrence or Metastasis? *Can J Anesth Can d'anesthésie* (2016) 63:184–92. doi: 10.1007/s12630-015-0523-8
35. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, But Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth Analg* (2003) 97:1331–9. doi: 10.1213/01.ANE.0000082995.44040.07
36. Ben-David B. Anaesthesia in Cancer Surgery: Can it Affect Cancer Survival? *Curr Clin Pharmacol* (2016) 11:4–20. doi: 10.2174/1574884711666160122093154
37. Tazawa K, Koutsogiannaki S, Chamberlain M, Yuki K. The Effect of Different Anesthetics on Tumor Cytotoxicity by Natural Killer Cells. *Toxicol Lett* (2017) 266:23–31. doi: 10.1016/j.toxlet.2016.12.007
38. Loop T, Dovi-Akue D, Frick M, Roesslein M, Egger L, Humar M, et al. Volatile Anesthetics Induce Caspase-Dependent, Mitochondria-Mediated Apoptosis in Human T Lymphocytes *In Vitro*. *Anesthesiology* (2005) 102:1147–57. doi: 10.1097/00000542-200506000-00014
39. Wong CH, Liu T-Z, Chye S-M, Lu F-J, Liu Y-C, Lin Z-C, et al. Sevoflurane-Induced Oxidative Stress and Cellular Injury in Human Peripheral Polymorphonuclear Neutrophils. *Food Chem Toxicol* (2006) 44:1399–407. doi: 10.1016/j.fct.2006.03.004
40. Zhou Y, Li E, Li Y, Liu S. Attenuating Sevoflurane-Induced Cellular Injury of Human Peripheral Lymphocytes by Propofol in a Concentration-Dependent Manner. *Arch Pharm Res* (2011) 34:1535–43. doi: 10.1007/s12272-011-0916-3
41. Kim Y, Yun S, Shin K-A, Chung W, Ko Y, Kim Y-H, et al. Effects of Sevoflurane on Lewis Lung Carcinoma Cell Proliferation *In Vivo* and *In Vitro*. *Medicina (Kaunas)* (2021) 57:45. doi: 10.3390/medicina57010045
42. Cui X, Zhu C, Chen P, Qu M, Zhang B, Li H. Effect of Pectoral Nerve Block Type II Under General Anesthesia on the Immune Function of Patients With Breast Cancer. *Am J Surg* (2020) 220:938–44. doi: 10.1016/j.amjsurg.2020.03.008
43. Prakash S, Gupta AK, Meena JP, Seth R. A Review of the Clinical Applications of Ketamine in Pediatric Oncology. *Pediatr Blood Cancer* (2021) 68:e28785. doi: 10.1002/pbc.28785
44. Cheung KWA, Chan PC, Lo SH. The Use of Ketamine in the Management of Refractory Cancer Pain in a Palliative Care Unit. *Ann Palliat Med* (2020) 9:4478–89. doi: 10.21037/apm.2019.09.09
45. Liu F-L, Chen T-L, Chen R-M. Mechanisms of Ketamine-Induced Immunosuppression. *Acta Anaesthesiol Taiwanica* (2012) 50:172–7. doi: 10.1016/j.aat.2012.12.001
46. Eisenstein TK. The Role of Opioid Receptors in Immune System Function. *Front Immunol* (2019) 10:2904. doi: 10.3389/fimmu.2019.02904
47. Juneja R. Opioids and Cancer Recurrence. *Curr Opin Support Palliat Care* (2014) 8:91–101. doi: 10.1097/SPC.0000000000000056
48. Feng Y, He X, Yang Y, Chao D, H. Lazarus L, Xia Y. Current Research on Opioid Receptor Function. *Curr Drug Targets* (2012) 13:230–46. doi: 10.2174/138945012799201612
49. Tuerxun H, Cui J. The Dual Effect of Morphine on Tumor Development. *Clin Transl Oncol* (2019) 21:695–701. doi: 10.1007/s12094-018-1974-5
50. Zhang X, Liang Y, Yan Y, Dai Z, Chu H. Morphine: Double-Faced Roles in the Regulation of Tumor Development. *Clin Transl Oncol* (2018) 20:808–14. doi: 10.1007/s12094-017-1796-x
51. Nguyen J, Luk K, Vang D, Soto W, Vincent L, Robiner S, et al. Morphine Stimulates Cancer Progression and Mast Cell Activation and Impairs Survival in Transgenic Mice With Breast Cancer. *Br J Anaesth* (2014) 113:i4–i13. doi: 10.1093/bja/aeu090
52. Koodie L, Yuan H, Pumper JA, Yu H, Charboneau R, Ramkrishnan S, et al. Morphine Inhibits Migration of Tumor-Infiltrating Leukocytes and Suppresses Angiogenesis Associated With Tumor Growth in Mice. *Am J Pathol* (2014) 184:1073–84. doi: 10.1016/j.ajpath.2013.12.019
53. Kim R. Effects of Surgery and Anesthetic Choice on Immunosuppression and Cancer Recurrence. *J Transl Med* (2018) 16:8. doi: 10.1186/s12967-018-1389-7
54. Duff S, Connolly C, Buggy DJ. Adrenergic, Inflammatory, and Immune Function in the Setting of Oncological Surgery. *Int Anesthesiol Clin* (2016) 54:48–57. doi: 10.1097/AIA.0000000000000120
55. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of Perioperative Anaesthetic and Analgesic Interventions on Oncological Outcomes: A Narrative Review. *Br J Anaesth* (2019) 123:135–50. doi: 10.1016/j.bja.2019.04.062
56. Dianat-Moghadam H, Mahari A, Heidarifard M, Parnianfard N, Pourmousavi-Kh L, Rahbarghazi R, et al. NK Cells-Directed Therapies Target Circulating Tumor Cells and Metastasis. *Cancer Lett* (2021) 497:41–53. doi: 10.1016/j.canlet.2020.09.021
57. Han B, Mao F-Y, Zhao Y-L, Lv Y-P, Teng Y-S, Duan M, et al. Altered NKp30, NKp46, NKG2D, and DNAM-1 Expression on Circulating NK Cells Is Associated With Tumor Progression in Human Gastric Cancer. *J Immunol Res* (2018) 2018:6248590. doi: 10.1155/2018/6248590
58. Tai L-H, Zhang J, Scott KJ, de Souza CT, Alkayyal AA, Ananth AA, et al. Perioperative Influenza Vaccination Reduces Postoperative Metastatic Disease by Reversing Surgery-Induced Dysfunction in Natural Killer Cells. *Clin Cancer Res* (2013) 19:5104–15. doi: 10.1158/1078-0432.CCR-13-0246
59. Mafune K, Tanaka Y. Influence of Multimodality Therapy on the Cellular Immunity of Patients With Esophageal Cancer. *Ann Surg Oncol* (2000) 7:609–16. doi: 10.1007/BF02725341
60. Cata JP, Bauer M, Sokari T, Ramirez MF, Mason D, Plautz G, et al. Effects of Surgery, General Anesthesia, and Perioperative Epidural Analgesia on the Immune Function of Patients With Non-Small Cell Lung Cancer. *J Clin Anesth* (2013) 25:255–62. doi: 10.1016/j.jclinane.2012.12.007
61. Lim J-A, Oh C-S, Yoon T-G, Lee JY, Lee S-H, Yoo Y-B, et al. The Effect of Propofol and Sevoflurane on Cancer Cell, Natural Killer Cell, and Cytotoxic T Lymphocyte Function in Patients Undergoing Breast Cancer Surgery: an. *Vitro analysis BMC Cancer* (2018) 18:159. doi: 10.1186/s12885-018-4064-8
62. Saito J, Masters J, Hirota K, Ma D. Anesthesia and Brain Tumor Surgery. *Curr Opin Anaesthesiol* (2019) 32:553–62. doi: 10.1097/ACO.0000000000000749
63. Neeman E, Ben-Eliyahu S. Surgery and Stress Promote Cancer Metastasis: New Outlooks on Perioperative Mediating Mechanisms and Immune Involvement. *Brain Behav Immun* (2013) 30:S32–40. doi: 10.1016/j.bbi.2012.03.006
64. Neeman E, Zmora O, Ben-Eliyahu S. A New Approach to Reducing Postsurgical Cancer Recurrence: Perioperative Targeting of Catecholamines and Prostaglandins. *Clin Cancer Res* (2012) 18:4895–902. doi: 10.1158/1078-0432.CCR-12-1087

65. Howe LR. Inflammation and Breast Cancer. Cyclooxygenase/prostaglandin Signaling and Breast Cancer. *Breast Cancer Res* (2007) 9:210. doi: 10.1186/bcr1678
66. Buggy DJ, Borgeat A, Cata J, Doherty DG, Doornebal CW, Forget P, et al. Consensus Statement From the BJA Workshop on Cancer and Anaesthesia. *Br J Anaesth* (2015) 114:2–3. doi: 10.1093/bja/aeu262
67. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJS, Bevan C, et al. Prostate Cancer Cell Malignancy *via* Modulation of HIF-1α Pathway With Isoflurane and Propofol Alone and in Combination. *Br J Cancer* (2014) 111:1338–49. doi: 10.1038/bjc.2014.426
68. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of Anaesthetic Technique on the Natural Killer Cell Anti-Tumour Activity of Serum From Women Undergoing Breast Cancer Surgery: A Pilot Study. *Br J Anaesth* (2014) 113: i56–62. doi: 10.1093/bja/aeu200
69. Luo X, Zhao H, Hennah L, Ning J, Liu J, Tu H, et al. Impact of Isoflurane on Malignant Capability of Ovarian Cancer *In Vitro* ‡. *Br J Anaesth* (2015) 114:831–9. doi: 10.1093/bja/aeu408
70. Zhu M, Li M, Zhou Y, Dangelmajer S, Kahlert UD, Xie R, et al. Isoflurane Enhances the Malignant Potential of Glioblastoma Stem Cells by Promoting Their Viability, Mobility *In Vitro* and Migratory Capacity *In Vivo*. *Br J Anaesth* (2016) 116:870–7. doi: 10.1093/bja/aew124
71. Qian J, Shen S, Chen W, Chen N. Propofol Reversed Hypoxia-Induced Docetaxel Resistance in Prostate Cancer Cells by Preventing Epithelial–Mesenchymal Transition by Inhibiting Hypoxia-Inducible Factor 1 α. *BioMed Res Int* (2018) 2018:1–9. doi: 10.1155/2018/4174232
72. Cui X, Feng J, Wu J, Zhang X, Ding M. Propofol Postpones Colorectal Cancer Development Through Circ_0026344/miR-645/Akt/mTOR Signal Pathway. *Open Med* (2021) 16:570–80. doi: 10.1515/med-2021-0254
73. Li G, Zhang X, Guo X, Li Y, Li C. Propofol Inhibits the Proliferation, Migration, and Stem-Like Properties of Bladder Cancer Mainly by Suppressing the Hedgehog Pathway. *Cell Transplant* (2021) 30:96368972098511. doi: 10.1177/0963689720985113
74. Le Gac G, Angenard G, Clément B, Laviolle B, Coulouarn C, Beloeil H. Local Anesthetics Inhibit the Growth of Human Hepatocellular Carcinoma Cells. *Anesth Analg* (2017) 125:1600–9. doi: 10.1213/ANE.0000000000002429
75. Xing W, Chen D-T, Pan J-H, Chen Y-H, Yan Y, Li Q, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells *In Vitro* and in a Xenograft Model *In Vivo*. *Anesthesiology* (2017) 126:868–81. doi: 10.1097/ALN.0000000000001528
76. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. *Anticancer Res* (2018) 38:5599–606. doi: 10.21873/anticanres.12894
77. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Ketamine-Xylazine Anaesthesia for Breast Tumour Resection in a Murine Model. *Br J Anaesth* (2018) 121:76–85. doi: 10.1016/j.bja.2017.12.043
78. Elajnaf T, Baptista-Hon DT, Hales TG. Potent Inactivation-Dependent Inhibition of Adult and Neonatal NaV1.5 Channels by Lidocaine and Levobupivacaine. *Anesth Analg* (2018) 127:650–60. doi: 10.1213/ANE.0000000000003597
79. Luo Q, Wu T, Wu W, Chen G, Luo X, Jiang L, et al. The Functional Role of Voltage-Gated Sodium Channel Nav1.5 in Metastatic Breast Cancer. *Front Pharmacol* (2020) 11:1111. doi: 10.3389/fphar.2020.01111
80. Baptista-Hon DT, Robertson FM, Robertson GB, Owen SJ, Rogers GW, Lydon EL, et al. Potent Inhibition by Ropivacaine of Metastatic Colon Cancer SW620 Cell Invasion and Na V 1.5 Channel Function. *Br J Anaesth* (2014) 113:i39–48. doi: 10.1093/bja/aeu104
81. Soltanizadeh S, Degett TH, Gögenur I. Outcomes of Cancer Surgery After Inhalational and Intravenous Anesthesia: A Systematic Review. *J Clin Anesth* (2017) 42:19–25. doi: 10.1016/j.jclinane.2017.08.001
82. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anesth Can d'anesthésie* (2019) 66:546–61. doi: 10.1007/s12630-019-01330-x
83. Chang C-Y, Wu M-Y, Chien Y-J, Su I-M, Wang S-C, Kao M-C. Anesthesia and Long-Term Oncological Outcomes: A Systematic Review and Meta-Analysis. *Anesth Analg* (2021) 132:623–34. doi: 10.1213/ANE.0000000000005237
84. Wigmore TJ, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery. *Anesthesiology* (2016) 124:69–79. doi: 10.1097/ALN.0000000000000936
85. Ash SA, Valchev GI, Looney M, Ni Mhathuna A, Crowley PD, Gallagher HC, et al. Xenon Decreases Cell Migration and Secretion of a Pro-Angiogenesis Factor in Breast Adenocarcinoma Cells: Comparison With Sevoflurane. *Br J Anaesth* (2014) 113:i14–21. doi: 10.1093/bja/aeu191
86. Lai H-C, Lee M-S, Liu Y-T, Lin K-T, Hung K-C, Chen J-Y, et al. Propofol-Based Intravenous Anesthesia Is Associated With Better Survival Than Desflurane Anesthesia in Pancreatic Cancer Surgery. *PloS One* (2020) 15: e0233598. doi: 10.1371/journal.pone.0233598
87. Wu Z-F, Lee M-S, Wong C-S, Lu C-H, Huang Y-S, Lin K-T, et al. Propofol-Based Total Intravenous Anesthesia Is Associated With Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology* (2018) 129:932–41. doi: 10.1097/ALN.0000000000002357
88. Jang D, Lim CS, Shin YS, Ko YK, Il PS, SH S, et al. A Comparison of Regional and General Anesthesia Effects on 5 Year Survival and Cancer Recurrence After Transurethral Resection of the Bladder Tumor: A Retrospective Analysis. *BMC Anesthesiol* (2015) 16:16. doi: 10.1186/s12871-016-0181-6
89. Huang Y-H, Lee M-S, Lou Y-S, Lai H-C, Yu J-C, Lu C-H, et al. Propofol-Based Total Intravenous Anesthesia did Not Improve Survival Compared to Desflurane Anesthesia in Breast Cancer Surgery. *PloS One* (2019) 14: e0224728. doi: 10.1371/journal.pone.0224728
90. Chipollini J, Alford B, Boulware DC, Forget P, Gilbert SM, Lockhart JL, et al. Epidural Anesthesia and Cancer Outcomes in Bladder Cancer Patients: Is it the Technique or the Medication? A Matched-Cohort Analysis From a Tertiary Referral Center. *BMC Anesthesiol* (2018) 18:157. doi: 10.1186/s12871-018-0622-5
91. Hasselager RP, Hallas J, Gögenur I. Inhalation or Total Intravenous Anaesthesia and Recurrence After Colorectal Cancer Surgery: A Propensity Score Matched Danish Registry-Based Study. *Br J Anaesth* (2021) 126:921–30. doi: 10.1016/j.bja.2020.11.019
92. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394:1807–15. doi: 10.1016/S0140-6736(19)32313-X
93. Hovaguimian F, Braun J, Z'graggen BR, Schläpfer M, Dumrese C, Ewald C, et al. Anesthesia and Circulating Tumor Cells in Primary Breast Cancer Patients. *Anesthesiology* (2020) 133:548–58. doi: 10.1097/ALN.0000000000003409
94. Oh C-S, Lee J, Yoon T-G, Seo E-H, Park H-J, Piao L, et al. Effect of Equipotent Doses of Propofol Versus Sevoflurane Anesthesia on Regulatory T Cells After Breast Cancer Surgery. *Anesthesiology* (2018) 129:921–31. doi: 10.1097/ALN.0000000000002382
95. Woo JH, Baik HJ, Kim CH, Chung RK, Kim DY, Lee GY, et al. Effect of Propofol and Desflurane on Immune Cell Populations in Breast Cancer Patients: A Randomized Trial. *J Korean Med Sci* (2015) 30:1503–38. doi: 10.3346/jkms.2015.30.10.1503
96. Zhu J, Zhang X-R, Yang H. Effects of Combined Epidural and General Anesthesia on Intraoperative Hemodynamic Responses, Postoperative Cellular Immunity, and Prognosis in Patients With Gallbladder Cancer. *Med (Baltimore)* (2017) 96:e6137. doi: 10.1097/MD.0000000000006137
97. Aghamelu O, Buggy P, Smith G, Inzitari R, Wall T, Buggy DJ. Serum NETosis Expression and Recurrence Risk After Regional or Volatile Anaesthesia During Breast Cancer Surgery: A Pilot, Prospective, Randomised Single-Blind Clinical Trial. *Acta Anaesthesiol Scand* (2021) 65:313–9. doi: 10.1111/aas.13745
98. Galoș EV, Tat T-F, Popa R, Efrimescu C-I, Finnerty D, Buggy DJ, et al. Neutrophil Extracellular Trapping and Angiogenesis Biomarkers After Intravenous or Inhalation Anaesthesia With or Without Intravenous Lidocaine for Breast Cancer Surgery: A Prospective, Randomised Trial. *Br J Anaesth* (2020) 125:712–21. doi: 10.1016/j.bja.2020.05.003
99. Tsui BCH, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, et al. Epidural Anesthesia and Cancer Recurrence Rates After Radical Prostatectomy. *Can J Anesth Can d'anesthésie* (2010) 57:107–12. doi: 10.1007/s12630-009-9214-7
100. MacFater WS, Xia W, Barazanchi AWH, MacFater HS, Lightfoot N, Svirskis D, et al. Association Between Perioperative Intraperitoneal Local Anaesthetic

Infusion and Long-Term Survival and Cancer Recurrence After Colectomy: Follow-Up Analysis of a Previous Randomized Controlled Trial. *ANZ J Surg* (2020) 90:802–6. doi: 10.1111/ans.15753

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Solid Tumor Opioid Receptor Expression and Oncologic Outcomes: Analysis of the Cancer Genome Atlas and Genotype Tissue Expression Project

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Background: Opioid receptors are expressed not only by neural cells in the central nervous system, but also by many solid tumor cancer cells. Whether perioperative opioids given for analgesia after tumor resection surgery might inadvertently activate tumor cells, promoting recurrence or metastasis, remains controversial. We analysed large public gene repositories of solid tumors to investigate differences in opioid receptor expression between normal and tumor tissues and their association with long–term oncologic outcomes.

Methods: We investigated the normalized gene expression of μ, κ, δ opioid receptors (MOR, KOR, DOR), Opioid Growth Factor (OGFR), and Toll-Like 4 (TLR4) receptors in normal and tumor samples from twelve solid tumor types. We carried out mixed multivariable logistic and Cox regression analysis on whether there was an association between these receptors' gene expression and the tissue where found, i.e., tumor or normal tissue. We also evaluated the association between tumor opioid receptor gene expression and patient disease–free interval (DFI) and overall survival (OS).

Results: We retrieved 8,780 tissue samples, 5,852 from tumor and 2,928 from normal tissue, of which 2,252 were from the Genotype Tissue Expression Project (GTEx) and 672 from the Cancer Genome Atlas (TCGA) repository. The Odds Ratio (OR) [95%CI] for gene expression of the specific opioid receptors in the examined tumors varied: MOR: 0.74 [0.63–0.87], KOR: 1.27 [1.17–1.37], DOR: 1.66 [1.48–1.87], TLR4: 0.29 [0.26–0.32], OGFR: 2.39 [2.05–2.78]. After controlling all confounding variables, including age and cancer stage, there was no association between tumor opioid receptor expression and long–term oncologic outcomes.

Conclusion: Opioid receptor gene expression varies between different solid tumor types. There was no association between tumor opioid receptor expression and recurrence. Understanding the significance of opioid receptor expression on tumor cells remains elusive.

Keywords: opioid receptors, perioperative opioid, cancer, surgery, neoplasm, tumor, immunohistochemistry

INTRODUCTION

Surgery remains a primary treatment for 70% of solid tumors (1) but analgesia after resection is challenging. Pain and nociceptive transmission involve neuronal networks with various receptor types that elicit either activation or suppression of the stimuli (2). Opioids are still the mainstay of postoperative pain management. Their primary site of action is the μ opioid receptor (MOR) which is expressed at various central nervous system (CNS) locations along the pain pathway. Opioid drugs activate MORs to suppress ascending nociception and enhance descending pain inhibition (3, 4). However, one-dimensional reliance on opioid medication has disadvantages. First, MOR is expressed in other tissues such as the brain stem and bowel, leading to undesired side effects such as respiratory depression, nausea, and ileus. Second, repeated, prolonged opioid administration results in hyperalgesia and has been linked to the ongoing problem of opioid dependence (5–8). Third, opioids suppress cell–mediated immunity and directly activate tumor angiogenesis, thereby potentially facilitating residual tumor cell spread (9).

Opioid drugs act as agonists not only at MOR but also at δ–opioid receptors (DOR), and both can be expressed by tumor cells (10). Cancer metastasis and proliferation may be associated with the activation of these opioid receptors through different pathways (11). However, MOR, DOR, and κ opioid receptors (KOR), in addition to opioid growth factor receptor (OGFR) and Toll–like receptor 4 (TLR4), have been shown to promote tumor cell migration (12–14). Previous studies aiming to elucidate the role of these receptors in cancer differ widely in their methodology, e.g., immunohistochemistry (IHC) or nucleic acid polymerase chain reaction (PCR) amplification, as well as in the studied samples, e.g., tissue or cell lines, and in targeted receptors (**eTable 1** in the **Supplementary Digital Content**) (15–24).

The evolution of genetic sequencing technologies and the drive to unravel the mechanisms underlying many human diseases has led to the appearance of large repositories of genetic data such as the Genotype Tissue Expression Project (GTEx) and the Cancer Genome Atlas (TCGA). The TCGA is a National Institute of Health (NIH) sponsored project that aims to discover significant cancer-causing genome alterations in large cohorts of tumors through large-scale genome sequencing (25, 26).

Our study objective was to analyse opioid receptor gene expression in tumors compared to normal tissue and to evaluate the association between this and long-term oncologic outcome, defined as overall survival (OS) and disease-free interval (DFI). Gene expression data was obtained from GTEx and TCGA.

MATERIALS AND METHODS

In this analysis we followed the recommendations on reporting results from observational studies (STROBE guidelines. https://www.equator-network.org/reporting-guidelines/strobe/).

Population

We analyzed data from normal and tumor tissues from bladder, breast, colon, liver, salivary gland, esophagus, prostate, stomach, thyroid, lung, and kidney tumors.

Data Collection

Unified GTEx and TCGA gene expression data for MOR, DOR, KOR, TLR4, and OGFR genes were obtained using an established technique (27) (Data record 3) for each tissue type. This dataset includes a strict selection of high-quality RNA-Seq samples processed with the same analysis pipeline and corrected for unwanted non-biological variation that affects comparative analyses. In addition, gene expression values were reported in Fragments per Kilobase Million (FPKM) units.

TCGA survival data were downloaded from the TCGA TARGET GTEx dataset deposited in Xenabrowser (https://xenabrowser.net/). We collected DFI and OS. The remaining clinical data for TCGA samples were obtained from TCGABiolinks (28). Information for GTEx individuals was directly downloaded from the GTEx project website (GTEx Analysis Release V8). Clinical information from the different sources and gene expression data in log2 (FPKM+1) scale were formatted and merged.

Definitions

OS is the length of time from either the date of cancer diagnosis or the start of treatment and death from any cause. DFI is the length of time between primary cancer treatment and any signs or symptoms reappearance (29).

Statistical Analysis

We used data of all available patients without formal sample size calculation. Also, as the purpose was to explore a pathophysiological hypothesis, we did not specify any *a priori* effect size. We reported continuous variables as median and 25^{th}–75^{th} percentiles and categorical variables as numbers and percentages. Distribution was assessed by inspecting quantile–quantile plots, and log-transformation was carried out if the variable distribution violated the normality assumption. Finally, descriptive analyses were performed to summarize patient characteristics.

To assess the association between opioid receptor gene expression and type of tissue, i.e., control *versus* tumor, we fitted mixed logistic models introducing MOR, KOR, DOR, OGFR, and

TLR4 genes as covariables, and primary tumor site as a random effect to consider the variability between different tumor sites. This model was fitted for tumors with data available for every receptor included in the analysis. We fitted a logistic model with all the receptor data available for each tumor type as a sensitivity analysis.

To assess the association between opioid receptor gene expression and DFI and OS, we fitted a mixed Cox model introducing MOR, KOR, DOR, OGFR, and TLR4 genes, age at diagnosis, and cancer stage as covariables. Primary site of tumor was a random effect to consider the variability between different tumor sites.

Statistical significance was set for two–tailed test at $P<0.05$. No missing values imputation and no correction for multiple comparisons was prespecified: thus, all the findings should be viewed as exploratory. All analyses were performed with R 4.0.3 (The R Foundation for Statistical Computing, www.r-project.org)

RESULTS

We retrieved 8,780 tissue samples: 5,852 from tumor and 2,924 from normal control tissues, of which 2,252 and 672 were from the GTEx and TCGA repository, respectively. Sample characteristics are shown in **Table 1**. OGFR gene expression was highest while MOR gene expression was lowest, with comparable values between control and tumor samples on every overall gene expression. Median and percentiles values and violin and density plots (**Figure 1**) show considerable overlap. Opioid receptor expression by tumor primary site is reported in **Figure 2**.

The logistic model's estimates are reported in **Table 2**. Opioid receptors were significantly associated with tumor samples, albeit differently, as some genes associated positively and others negatively. The estimated standard deviation among tumors, i.e. 3.06, is bigger than the largest estimate among the fixed effects, i.e. OGFR estimate 2.39, suggesting considerable effect differences among tumors (**Figure 3**). Logistic models estimated for each tumor are reported in **Figure 4** and show considerable variability among opioid receptor estimates across tumor types.

Mixed Cox models estimates for DFI and OS are reported in **Table 3**. After controlling for age and cancer stage, we found no association overall between opioid receptor expression and long-term outcomes except a weak effect for KOR on OS. The cancer stage is by far the predominant effect in both DFI and OS models as was expected.

DISCUSSION

This study's' main findings can be summarized as follows: Firstly, higher or lower opioid receptor gene expression within tumors is variable depending on the specific tumor type; Secondly, single gene expression also varies depending on tumor type; Thirdly,

TABLE 1 | Clinical and tumor characteristics.

	Overall (N= 8780)	GTEx Normal (N= 2256)	TCGA Normal (N= 672)	TCGA Tumor (N= 5852)
Tissue type (tumor) % (N)	66.7 (5852/8780)			100 (5852/8780)
MOR gene	0 [0 – 0]	0 [0 – 0.3]	0 [0 – 0.3]	0 [0 – 0]
KOR gene	0.3 [0 –1.1]	0.4 [0 – 1.0]	0.4 [0 – 1.1]	0.2 [0 – 1.2]
DOR gene	0 [0 – 0.4]	0 [0 – 0]	0 [0 – 0]	0 [0 – 0.5]
TLR4 gene	6.7 [6.5 – 7.1]	6.8 [6.5 – 7.0]	6.7 [6.5 – 7.0]	6.8 [6.5 – 7.1]
OGFR gene	4.7 [4.1 – 5.3]	4.7 [4.2 – 5.3]	4.7 [4.2 – 5.3]	4.5 [3.9 – 5.2]
Disease free time (days)			975 [538 – 1677]	724 [410 – 1340]
Relapse (yes) % (N)			16.5 (56/340)	16.8 (531/3167)
Overall survival time (days)			925 [491 – 1813]	738 [402 – 1409]
Death (yes) % (N)			37.4 (235/629)	25.9 (1412/5443)
AJCC stage % (N)				
I			198 (34.9)	1660 (34.3)
II			178 (31.3)	1452 (30.0)
III			123 (21.7)	1118 (23.1)
IV			69 (12.1)	616 (12.7)
Age at diagnosis	62 [53 – 71]		63 [52 – 72]	62 [53 – 71]
Gender (Male) % (N)	53.7 (4484/8780)	59.8 (1348/2256)	48.6 (306/629)	51.8 (2830/5467)
Primary site % (N)				
Bladder	4.4 (390/8780)	0.5 (11/2256)	2.5 (17/672)	6.2 (362/5852)
Breast	13.5 (1181/8780)	3.9 (89/2256)	16.4 (110/672)	16.8 (982/5852)
Colon	8.7 (762/8780)	15.0 (339/2256)	7.6 (51/672)	6.4 (372/5852)
Esophagus	9.7 (853/8780)	29.2 (659/2256)	1.6 (11/672)	3.1 (183/5852)
Kidney	10.6 (929/8780)	1.4 (32/2256)	18.8 (126/672)	13.2 (771/5852)
Liver	5.2 (458/8780)	5.1 (115/2256)	7.1 (48/672)	5.0 (295/5852)
Lung	16.1 (1415/8780)	13.9 (313/2256)	16.4 (110/672)	17.0 (992/5852)
Prostate	6.6 (580/8780)	4.7 (106/2256)	7.1 (48/672)	7.3 (426/5852)
Salivary Gland	5.7 (502/8780)	0 (0/2256)	6.2 (42/672)	7.9 (460/5852)
Stomach	6.9 (605/8780)	8.5 (192/2256)	4.9 (33/672)	6.5 (380/5852)
Thyroid	9.2% (812)	14.1 (318/2256)	7.9 (53/672)	7.5 (441/5852)
Uterus	3.3% (293)	3.6 (82/2256)	3.4 (23/672)	3.2 (188/5852)

Data are reported as median [25^{th} – 75^{th} percentile] or % (N). MOR, μ opioid receptor; KOR, κ opioid receptor; DOR, δ opioid receptor; TLR4, toll–like receptor 4; OGFR, opioid growth factor receptor; Age for GTEx samples is not reported because is recorded as a categorical variable with 10 years strata and not as a continuous variable.

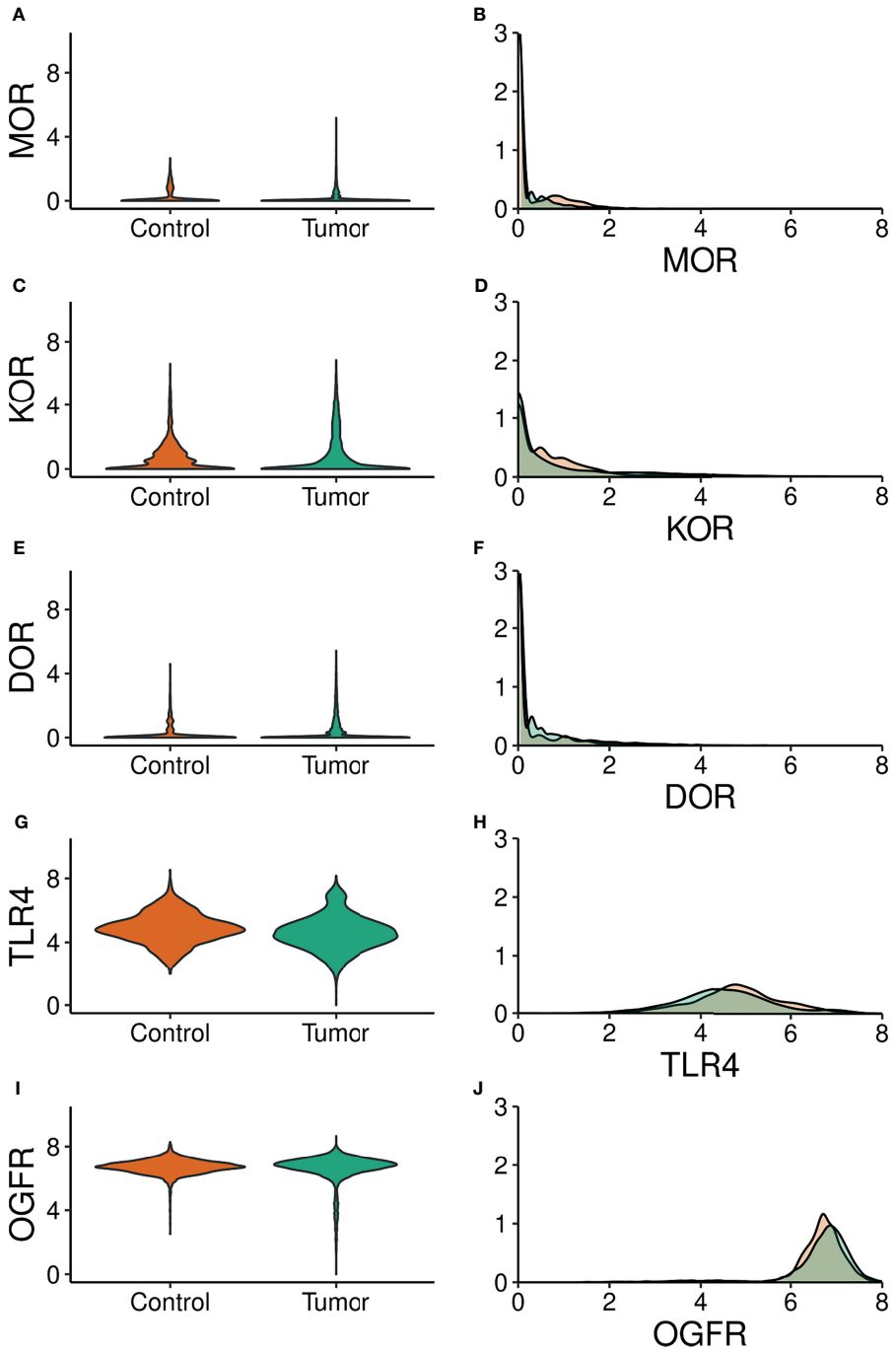

FIGURE 1 | Violin (Left panels) and density (Right panels) plots of the expression of opioid receptor genes. Green: tumor samples. Orange: control samples. MOR, μ opioid receptor; KOR, κ opioid receptor; DOR, δ opioid receptor; TLR4, toll–like receptor; OGFR, opioid growth factor receptor. **(A, C, E, G, I)** Gene expression (Log scale) is on the y axis. **(B, D, F, H, J)** Gene expression (Log scale) s on the x axis.

there was no association between opioid gene receptor expression and DFI or OS after controlling for age and tumor stage.

This analysis has several strengths. First, to our knowledge, this is the first analysis of large public genetic databases focusing specifically on tumor opioid receptor expression and their link to cancer outcome. Secondly, we selected normalized data through a previously published meticulous procedure that consistently removes the batch effect from samples. Thirdly, we controlled for confounding bias by performing a time–to–event analysis, including potential confounders such as age and tumor stage.

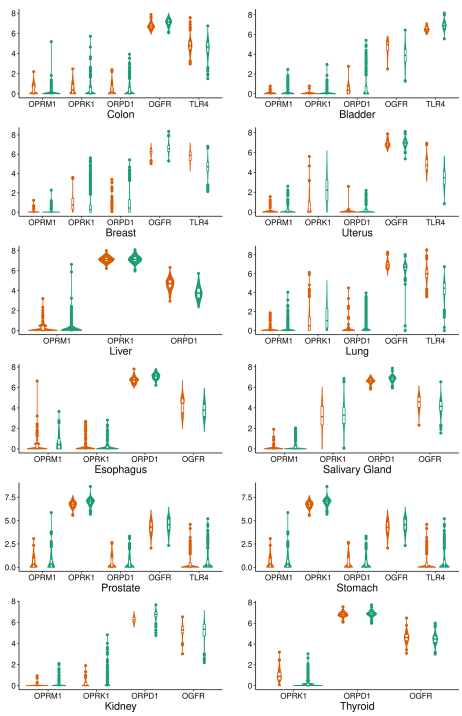

FIGURE 2 | Violin and box plot graphs of the expression of opioid receptors genes by tumor type. Green: tumor samples. Orange: control samples. MOR, μ opioid receptor; KOR, κ opioid receptor; DOR, δ opioid receptor; TLR4, toll–like receptor; OGFR, opioid growth factor receptor.

We also assessed the effect of specific cancer types by adding a random effect to the multivariable model to account for the hierarchical structure of the data. Fourthly, we included all previously studied opioid receptors known to be involved in perioperative opioid drug binding in our analysis.

The role of tumor opioid receptor expression on tumor growth and metastasis has generated considerable interest among researchers involved in surgical oncology (1). Because of the pivotal role of opioid analgesics in the perioperative process, it has been speculated that activation of these receptors could cause cancer cells to proliferate, migrate and escape immune control. Our findings add further to previous studies assessing opioid receptor expression in different tumors. Higher MOR expression was found on prostate cancer samples compared to unpaired control tissue (22). Likewise, in a study that compared human lung cancer samples with non-tumor adjacent tissue samples, MOR expression was significantly increased in tumor tissue from patients with metastatic lung cancer had an approximately twofold increase in MOR expression (21).

Higher expression of MOR was associated with tumor tissue in gastric cancer, hepatocellular carcinoma, and colorectal cancer samples (17–20, 24). In contrast, this association of MOR-1 with oncological results was not observed in other tumors. For instance, in esophageal squamous cell carcinoma (ESCC), MOR expression in the cytoplasm was associated with lymph node metastases. However, no link was found between MOR expression and the OS of patients with ESCC (18).

In a retrospective analysis among breast cancer patients, which analyzed the effect of anesthetic technique on MOR expression, the authors found that general anesthesia with opioid analgesia increased MOR expression in the resected tumor compared to anesthetic technique with locoregional analgesia (30), These results support the hypothesis that the opioid receptor genetic footprint varies with tumor type. This is consistent with recent data from a triple-negative breast tumor databank, which analyzed the same receptors as us and found that MOR, OPRD, and OPRK were overexpressed, while TLR4 was downregulated. Furthermore, these authors found that higher doses of intraoperative opioids were associated with somewhat worse oncologic outcomes than patients receiving lower doses during surgery (16). A thorough mapping of different receptors' expression is important because opposing effects have been described, with some receptor activation having protumor effects while others have potentially tumor suppressing effects. This is even more important since both exogenous and endogenous opioid receptor agonists may play a different role depending on the specific profile of receptor expression, while opioid receptor antagonists such as methylnaltrexone have found to be associated with longer median survival in an unplanned posthoc analysis of two clinical trials (31).

We found no association between opioid receptor expression and long-term outcomes such as DFI and OS. Existing data on this matter are diverging. For example, while some studies found an association between MOR expression in particular and cancer

TABLE 2 | The association between opioid receptor gene expression and tumor type.

Gene expression (Log scale)	Odds Ratio [Lower–Upper 95%CI]	P– value
MOR	0.74 [0.63 – 0.87]	< 0.001
KOR	1.27 [1.17 – 1.37]	< 0.001
DOR	1.66 [1.48 – 1.87]	< 0.001
TLR4	0.29 [0.26 – 0.32]	< 0.001
OGFR	2.39 [2.05 – 2.78]	< 0.001
Random effect parameter (Tumor type): Standard deviation: 3.06		
ICC (Tumor_type): 0.74		

Primary site random effect Standard deviation for multivariable model: 1.34. MOR, μ opioid receptor; KOR, κopioid receptor; DOR, δopioid receptor; TLR4, toll–like receptor; OGFR, opioid growth factor receptor; CI, Confidence Interval; ICC, Intraclass correlation coefficient. The model has been estimated with all tumor types with available data for all receptors.

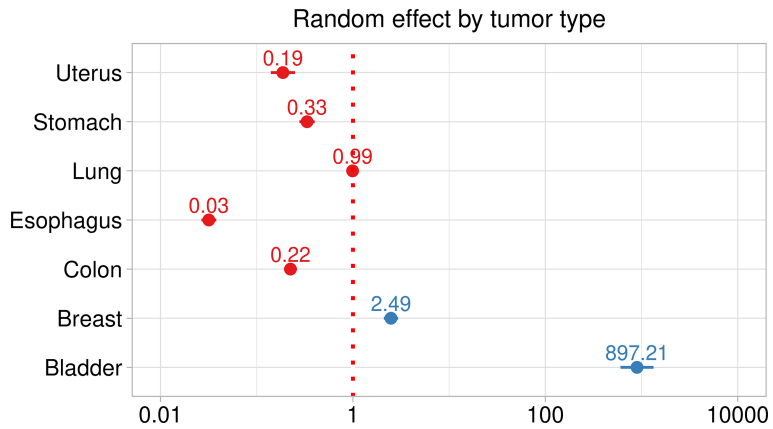

FIGURE 3 | Random effect plot of the mixed logistic model assessing the association between opioid receptors expression and type of tissue. Red dotted line, significance threshold. Dots effect estimates and bar 95% Confidence intervals.

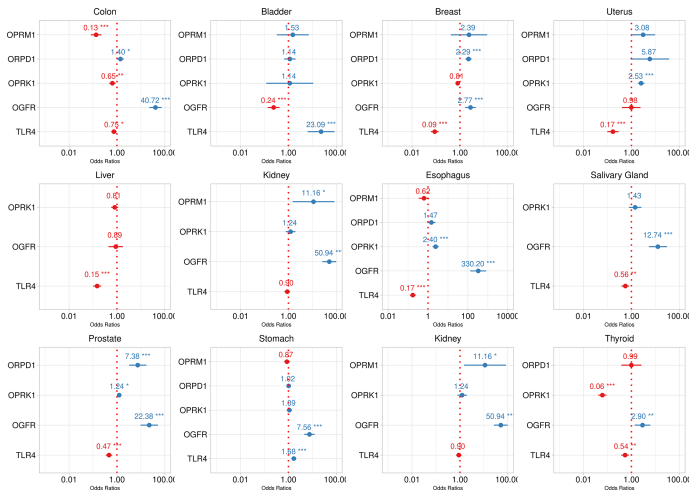

FIGURE 4 | Logistic model fit of opioid receprotrs association with tumor tissue by tumor type. Dotted red line represents no effect. Estimates are reported as red or blue when the odds ratio point estimate is lower or greater than one respectively. Dots are point estimates and bars 95% confidence intervals. Statistical significance is reported as * < 0.05, ** < 0.001, *** < 0.001.

recurrence (18, 19, 22), others did not (16, 24). Indeed, available research on this topic seems to point out that there is no one-size-fits-all explanation to this question. Further investigations on the specific receptor profile of each cancer strain should lay the foundation on whether opioid receptors can be included as oncologic prognostic markers.

Studies that assess opioid receptor expression in cancer rely on immunohistochemistry assay, while quantitative methods such as quantitative real-time polymerase chain reaction (qRT–PCR) are seldom reported, and with different procedures and primers (**eTable 1 Supplementary Material**) (15, 19, 20). Since there are no consensus guidelines on how to perform these assays (32), we consider that availing of large and validated databases such as the TCGA and GTEx is a powerful tool to draw a genetic footprint of opioid receptors in tumor cells. Furthermore, as our present results suggest, the impact of opioid receptors on cancer cells does not seem to be based on a simple pathway involving an individual receptor overexpression and is probably a more integrated mechanism involving several receptor targets with different effects that can vary depending on specific tumor type.

Furthermore, genetic content within tumors is variable and opioid receptors can present single nucleotide polymorphisms (SNPs). This type of polymorphisms on known oncogenes such as p53 and X-Ray Repair Cross Complementing 3 (XRRCC3) genes have been studied to elucidate their effect on cancer

TABLE 3 | Opioid gene expression association with long term oncologic outcomes.

Disease Free interval		
Gene expression (Log scale)	**Hazard Ratio [Lower–Upper 95%CI]**	**P value**
MOR	1.17 [0.89– 1.68]	0.203
KOR	1.07 [0.97 –1.18]	0.156
DOR	1.06 [0.91 – 1.24]	0.417
TLR4	1.01 [0.88 – 1.14]	0.929
OGFR	1.02 [0.85 – 1.23]	0.765
Age at diagnosis	0.99 [0.98 – 1.00]	0.203
AJCC Stage (Ref Stage I)*		
II	1.32 [0.99 – 1.77]	0.057
III	1.96 [1.43 – 2.69]	> 0.001
Random effect parameter (Tumor type): Standard deviation: 0.64		
Overall Survival		
Gene expression (Log scale)	**Hazard Ratio [Lower–Upper 95%CI]**	**P value**
MOR	1.17 [0.97 – 1.41]	0.087
KOR	1.10 [1.01 – 1.21]	0.021
DOR	1.00 [0.94 – 1.07]	0.794
TLR4	0.98 [0.90 – 1.07]	0.731
OGFR	1.00 [0.90 – 1.11]	0.937
Age at diagnosis	1.02 [1.01 – 1.03]	< 0.001
AJCC Stage (Ref: Stage I)		
II	1.49 [1.22 – 1.82]	< 0.001
III	2.57 [2.10 – 3.14]	< 0.001
IV	4.69 [3.66 – 6.01]	< 0.001
Random effect parameter (Tumor type): Standard deviation: 0.62		

MOR, μ opioid receptor; KOR, κ opioid receptor; DOR, δ opioid receptor; TLR4, toll–like receptor; OGFR, opioid growth factor receptor; CI, Confidence Interval; AJCC, American Joint Committee on Cancer.

**AJCC stage IV data were not available for Disease free interval.*

susceptibility with conflicting results to date (33–35). For instance, particular SNPs such as the A118G have been linked to reduced sensitivity to opioid medication in the patient suffering from chronic pain (36, 37) and cancer (19) and even cancer recurrence in specific tumor types and populations (38, 39), Also, TLR4 gene polymorphisms have also been studied and may play a role in proliferation and differentiation and multiple isoforms of receptor subtype resulting from alternative splicing of the pre-mRNA transcript have been identified albeit their functional role has yet to be clarified (40). Investigators are beginning to expand the horizon outside the genetic profile of opioid receptors and to include specific genetic alterations such as Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) mutations (41), although the influence that specific influence of individual receptor isoforms is still a matter of debate (42).

Several limitations must be acknowledged. For instance, differences in baseline characteristics from GTEx and TCGA repositories may be present. Also, although we controlled for age and cancer stage, the effect of other confounding factors not included in the analysis, such as type of surgery or pathologic stage or opioid agonists or antagonists administration, cannot be ruled out. These parameters could have a modifying effect on the association between opioid receptor expression and long-term cancer outcomes. Furthermore, we also acknowledge that while we assessed all the most common opioid receptor genes, other molecular pathways can be involved in the effect of opioids on cancer growth. Finally, because of the hypothesis-generating purpose of this study, we did not set any *a priori* effect threshold or multiple comparisons correction; hence some results' statistical significance and the potential hypothesis derived from them should be confirmed in future trials.

In conclusion, the most common solid tumors express higher opioid receptor genes than normal tissue, but variably depending on the primary tumor analyzed. No association was found between disease-free and overall survival and opioid gene expression after controlling for age and tumor stage. Further studies are warranted to elucidate the specific genetic footprint of opioid receptors in each cancer type and the potential role of gene polymorphisms.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.nature.com/articles/sdata201861#ref-CR22.

AUTHORS CONTRIBUTIONS

AB: This author conceived the idea, helped with data acquisition, critical review of the content, and manuscript preparation. SZ: This author coded the data acquisition from the repositories, provided a critical review of the content, and helped with manuscript preparation. IG-C: This author provided a critical

review of the content, and helped with manuscript preparation. PE: This author provided a critical review of the content, and helped with manuscript preparation. MA: This author provided a critical review of the content, and helped with manuscript preparation. DB: This author provided a critical review of the content, and helped with manuscript preparation. OD-C: This author provided a critical review of the content, and helped with manuscript preparation. GM: This author conceived the idea, helped with data acquisition, critical review of the content, and manuscript preparation. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.801411/full#supplementary-material

REFERENCES

1. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global Cancer Surgery: Delivering Safe, Affordable, and Timely Cancer Surgery. *Lancet Oncol* (2015) 16:1193–224. doi: 10.1016/S1470-2045(15)00223-5
2. Peirs C, Seal RP. Neural Circuits of Pain: Recent Advances and Current Perspectives. *Science* (2016) 354:578–84. doi: 10.1126/science.aaf8933
3. Stein C. The Control of Pain in Peripheral Tissue by Opioids. *N Engl J Med* (1995) 332(25):1685–90. doi: 10.1056/NEJM199506223322506
4. Waldhoer M, Bartlett SE, Whistler JL. Opioid Receptors. *Annu Rev Biochem* (2004) 73:953–90. doi: 10.1146/annurev.biochem.73.011303.073940
5. Hollmann MW, Rathmell JP, Lirk P. Optimal Postoperative Pain Management: Redefining the Role for Opioids. *Lancet* (2019) 393(10180):1483–5. doi: 10.1016/S0140-6736(19)30854-2
6. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, et al. Postsurgical Prescriptions for Opioid Naive Patients and Association With Overdose and Misuse: Retrospective Cohort Study. *BMJ* (2018) 360:j5790. doi: 10.1136/bmj.j5790
7. Neuman MD, Bateman BT, Wunsch H. Inappropriate Opioid Prescription After Surgery. *Lancet* (2019) 393:1547–57. doi: 10.1016/S0140-6736(19)30428-3
8. Makary MA, Overton HN, Wang P. Overprescribing is Major Contributor to Opioid Crisis. *BMJ* (2017) 359:j4792. doi: 10.1136/bmj.j4792
9. Boland JW, McWilliams K, Ahmedzai SH, Pockley AG. Effects of Opioids on Immunologic Parameters That are Relevant to Anti-Tumour Immune Potential in Patients With Cancer: A Systematic Literature Review. *Br J Cancer* (2014) 111:866–73. doi: 10.1038/bjc.2014.384
10. Wigmore T, Farquhar-Smith P. Opioids and Cancer: Friend or Foe? *Curr Opin Support Palliat Care* (2016) 10:109–18. doi: 10.1097/SPC.0000000000000208
11. Sekandarzad MW, Van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression. *Anesth Analg* (2017) 124:1697–708. doi: 10.1213/ANE.0000000000001652
12. Kim JY, Ahn HJ, Kim JK, Kim J, Lee SH, Chae HB. Morphine Suppresses Lung Cancer Cell Proliferation Through the Interaction With Opioid Growth Factor Receptor: An *In Vitro* and Human Lung Tissue Study. *Anesth Analg* (2016) 123:1429–36. doi: 10.1213/ANE.0000000000001293
13. Liao SJ, Zhou YH, Yuan Y, Li D, Wu FH, Wang Q, et al. Triggering of Toll-Like Receptor 4 on Metastatic Breast Cancer Cells Promotes αvβ3-Mediated Adhesion and Invasive Migration. *Breast Cancer Res Treat* (2012) 133:853–63. doi: 10.1007/s10549-011-1844-0
14. Matzner P, Sorski L, Shaashua L, Elbaz E, Lavon H, Melamed R, et al. Perioperative Treatment With the New Synthetic TLR-4 Agonist GLA-SE Reduces Cancer Metastasis Without Adverse Effects. *Int J Cancer* (2016) 138:1754–64. doi: 10.1002/ijc.29885
15. Jorand R, Biswas S, Wakefield DL, Tobin SJ, Golfetto O, Hilton K, et al. Molecular Signatures of Mu Opioid Receptor and Somatostatin Receptor 2 in Pancreatic Cancer. *Mol Biol Cell* (2016) 27:3659–72. doi: 10.1091/mbc.E16-06-0427
16. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative Opioids are Associated With Improved Recurrence-Free Survival in Triple-Negative Breast Cancer. *Br J Anaesth* (2021) 126:367–76. doi: 10.1016/j.bja.2020.10.021
17. Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional Expression of μ-Opioid Receptors in the Human Colon Cancer Cell Line, HT-29, and Their Localization in Human Colon. *Dig Dis Sci* (2008) 53:461–6. doi: 10.1007/s10620-007-9897-y
18. Zhang YF, Xu QX, Liao LD, Xu XE, Wu JY, Wu ZY, et al. Association of Mu-Opioid Receptor Expression With Lymph Node Metastasis in Esophageal Squamous Cell Carcinoma. *Dis Esophagus* (2015) 28:196–203. doi: 10.1111/dote.12165
19. Yao YS, Yao RY, Zhuang LK, Qi WW, Lv J, Zhou F, et al. MOR1 Expression in Gastric Cancer: A Biomarker Associated With Poor Outcome. *Clin Transl Sci* (2015) 8:137–42. doi: 10.1111/cts.12246
20. Chen DT, Pan JH, Chen YH, Xing W, Yan Y, Yuan YF, et al. The Mu-Opioid Receptor is a Molecular Marker for Poor Prognosis in Hepatocellular Carcinoma and Represents a Potential Therapeutic Target. *Br J Anaesth* (2019) 122:e157–67. doi: 10.1016/j.bja.2018.09.030
21. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-Opioid Receptor Expression in Metastatic Lung Cancer. *Br J Anaesth* (2014) 113:i103–8. doi: 10.1093/bja/aeu165
22. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid Requirement, Opioid Receptor Expression, and Clinical Outcomes in Patients With Advanced Prostate Cancer. *Cancer* (2013) 119:4103–10. doi: 10.1002/cncr.28345
23. Zhang H, Sun M, Zhou D, Gorur A, Sun Z, Zeng W, et al. Increased Mu-Opioid Receptor Expression is Associated With Reduced Disease-Free and Overall Survival in Laryngeal Squamous Cell Carcinoma. *Br J Anaesth* (2020) 125:722–9. doi: 10.1016/j.bja.2020.07.051
24. Díaz-Cambronero O, Mazzinari G, Giner F, Belltall A, Ruiz-Boluda L, Marqués-Marí A, et al. Mu Opioid Receptor 1 (MOR-1) Expression in Colorectal Cancer and Oncological Long-Term Outcomes: A Five-Year Retrospective Longitudinal Cohort Study. *Cancers (Basel)* (2020) 12(1):134. doi: 10.3390/cancers12010134
25. Grossman RL, Heath AP, Ferretti V, Varmus HE, Lowy DR, Kibbe WA, et al. Toward a Shared Vision for Cancer Genomic Data. *N Engl J Med* (2016) 375:1109–12. doi: 10.1056/nejmp1607591
26. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): An Immeasurable Source of Knowledge. *Contemp Oncol (Pozn)* (2015) 19:A68–77. doi: 10.5114/wo.2014.47136
27. Wang Q, Armenia J, Zhang C, Penson AV, Reznik E, Zhang L, et al. Data Descriptor: Unifying Cancer and Normal RNA Sequencing Data From Different Sources. *Sci Data* (2018) 5:180061. doi: 10.1038/sdata.2018.61
28. Colaprico A, Silva TC, Olsen C, Garofano L, Cava C, Garolini D, et al. TCGAbiolinks: An R/Bioconductor Package for Integrative Analysis of TCGA Data. *Nucleic Acids Res* (2016) 44:e71. doi: 10.1093/nar/gkv1507
29. Buggy DJ, Freeman J, Johnson MZ, Leslie K, Riedel B, Sessler DI, et al. Systematic Review and Consensus Definitions for Standardised Endpoints in Perioperative Medicine: Postoperative Cancer Outcomes. *Br J Anaesth* (2018) 121:38–44. doi: 10.1016/j.bja.2018.03.020
30. Levins KJ, Prendeville S, Conlon S, Buggy DJ. The Effect of Anesthetic Technique on μ-Opioid Receptor Expression and Immune Cell Infiltration in Breast Cancer. *J Anesth* (2018) 32:792–6. doi: 10.1007/s00540-018-2554-031
31. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment With Methylnaltrexone is Associated With Increased Survival in Patients With Advanced Cancer. *Ann Oncol* (2016) 27:2032–8. doi: 10.1093/annonc/mdw317

32. Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, et al. Effects of Intraoperative Opioid Use on Recurrence-Free and Overall Survival in Patients With Esophageal Adenocarcinoma and Squamous Cell Carcinoma. *Anesth Analg* (2018) 127:210–6. doi: 10.1213/ANE.0000000000003428
33. Kuang J, Yan X, Genders AJ, Granata C, Bishop DJ. An Overview of Technical Considerations When Using Quantitative Real-Time PCR Analysis of Gene Expression in Human Exercise Research. *PloS One* (2018) 13(5):1–27. doi: 10.1371/journal.pone.0196438
34. Manuguerra M, Saletta F, Karagas MR, Berwick M, Veglia F, Vineis P, et al. XRCC3 and XPD/ERCC2 Single Nucleotide Polymorphisms and the Risk of Cancer: A HuGE Review. *Am J Epidemiol* (2006) 164:297–302. doi: 10.1093/aje/kwj189
35. Chen X, Liu F, Li B, Wei YG, Yan LN, Wen TF. P53 Codon 72 Polymorphism and Liver Cancer Susceptibility: A Meta-Analysis of Epidemiologic Studies. *World J Gastroenterol* (2011) 17:1211–8. doi: 10.3748/wjg.v17.i9.1211
36. Kasai S, Ikda K. Pharmacogenomics of the Human μ-Opioid Receptor Pharmacogenomics. *Pharmacogenomics* (2011) 12:1305–20. doi: 10.2217/pgs.11.68
37. Janicki PK, Schuler G, Francis D, Bohr A, Gordin V, Jarzembowski T, et al. A Genetic Association Study of the Functional A118G Polymorphism of the Human μ-Opioid Receptor Gene in Patients With Acute and Chronic Pain. *Anesth Analg* (2006) 103:1011–7. doi: 10.1213/01.ane.0000231634.20341.88
38. Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, Mclean SA. μ-Opioid Receptor Gene A118G Polymorphism Predicts Survival in Patients With Breast Cancer. *Anesthesiology* (2012) 116:896–902. doi: 10.1097/ALN.0b013e31824b96a1
39. Wang S, Li Y, Liu XD, Zhao CX, Yang KQ. Polymorphism of A118G in μ-Opioid Receptor Gene is Associated With Risk of Esophageal Squamous Cell Carcinoma in a Chinese Population. *Int J Clin Oncol* (2013) 18:666–9. doi: 10.1007/s10147-012-0441-5
40. Regan PM, Langford D, Khalili K. Regulation and Functional Implications of Opioid Receptor Splicing in Opioid Pharmacology and HIV Pathogenesis. *J Cell Physiol* (2016) 231(5):976–85. doi: 10.1002/jcp.25237
41. Connolly JG, Tan KS, Mastrogiacomo B, Dycoco J, Caso R, Jones GD, et al. Intraoperative Opioid Exposure, Tumour Genomic Alterations, and Survival Differences in People With Lung Adenocarcinoma. *Br J Anaesth* (2021) 127:75–84. doi: 10.1016/j.bja.2021.03.030
42. Scroope CA, Singleton Z, Hollmann MW, Parat MO. Opioid Receptor-Mediated and Non-Opioid Receptor-Mediated Roles of Opioids in Tumour Growth and Metastasis. *Front Oncol* (2021) 11:792290:792290. doi: 10.3389/fonc.2021.792290

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REVIEW
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Anesthesia and Oncology: Friend or Foe?

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Cancer is a leading cause of death, and surgery is an important treatment modality. Laboratory research and retrospective studies have raised the suspicion that the choice of anesthetics for cancer surgery might affect the course of cancerous disease. The aim of this review is to provide a critical overview of the current state of knowledge. Inhalational anesthesia with volatiles or total intravenous anesthesia (TIVA) with propofol are the two most commonly used anesthetic techniques. Most data comparing volatile anesthetics with TIVA is from either *in vitro* or retrospective studies. Although conflicting, data shows a trend towards favoring propofol. Opioids are commonly used in anesthesia. Data on potential effects of opioids on growth and recurrence of cancer are scarce and conflicting. Preclinical studies have shown that opioids stimulate cancer growth through the μ-opioid receptor. Opioids also act as immunosuppressants and, therefore, have the potential to facilitate metastatic spread. However, the finding of an adverse effect of opioids on tumor growth and cancer recurrence by some retrospective studies has not been confirmed by prospective studies. Regional anesthesia has not been found to have a beneficial effect on the outcome of surgically treated cancer patients, but prospective studies are scarce. Local anesthetics might have a beneficial effect, as observed in animal and *in vitro* studies. However, prospective clinical studies strongly question such an effect. Blood products, which may be needed during extensive cancer surgery suppress the immune system, and data strongly suggest a negative impact on cancer recurrence. The potential effects of other commonly used anesthetic agents on the outcome of cancer patients have not been sufficiently studied for drawing valid conclusions. In conclusion, laboratory data and most retrospective studies suggest a potential advantage of TIVA over inhalational anesthesia on the outcome of surgical cancer patients, but prospective, randomized studies are missing. Given the state of weak scientific evidence, TIVA may be used as the preferred type of anesthesia unless there is an individual contraindication against it. Studies on the effects of other drugs frequently used in anesthesia are limited in number and quality, and have found conflicting results.

Keywords: anesthesia, cancer, cancer recurrence, propofol, volatile anesthesia

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INTRODUCTION

According to estimates from the World Health Organization, cancer is the first or second leading cause of death in over half of the countries worldwide and is expected to take over the lead in all countries during the course of the 21st century (1). Most solid organ tumors are amenable to surgery. Sixty percent of cancer patients undergo surgical tumor resection, and 80% receive

anesthesia at some point for either diagnostic, therapeutic, or palliative procedures (2–4). Despite advances in cancer treatment, cancer recurrence and metastasis remain common and lead to significant morbidity and mortality. Alarmingly, there is an increasing body of evidence that surgery and other perioperative interventions such as anesthesia create an environment conducive to the growth and spread of residual cancer cells.

For cancer recurrence to occur, two requirements need to be met. There need to be residual cancer cells that act as seeds for the recurrent cancer, and these cancer cells need to escape recognition by the host's immune system. Seeding of tumor cells after initial surgical removal of the primary tumor can occur through four pathways (5): local recurrence from residual tumor cells at the resection site; lymph node metastasis from tumor cells released into the lymphatic system; distant organ metastasis from tumor cells released into the circulation; and seeding within a body cavity. To protect the body against tumor growth and recurrence, the body has two lines of defense: the innate immune system, which eliminates cancer cells without prior sensitization, and the adaptive immune system, which is antigen specific. The innate immune system consists primarily of myeloid cells (mononuclear and polymorphonuclear phagocytes) and to a lesser degree of natural killer (NK) cells (6). The cells of the innate immune system initiate the adaptive immune response by activating CD4+ T cells, CD8+ T cells, and B cells. Together, the innate and the adaptive immune systems fight to eliminate tumor cells. However, immune escape is common and eventually leads to cancer progression. If tumor cells survive the elimination phase by the innate and adaptive immune response, they enter the so-called equilibrium phase. In this phase, the adaptive immune response no longer manages to eliminate the tumor cells, rather they are kept in a state of dormancy. Eventually, the tumor cells manage to overcome the equilibrium phase and enter the escape phase where tumor growth occurs. In this phase, the tumor cells produce various cytokines such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), which lead to further promotion of tumor growth (7). However, much of this knowledge is derived from preclinical studies. The processes in the human body are highly complex, and findings from preclinical studies cannot be directly translated to humans. Effects of the stress response to surgery as well as effects from therapies such as chemo- and radiotherapy and other drugs all modulate the response of the human body to cancer treatment.

After surgery, local and systemic reactions lead to an initial pro-inflammatory state, followed by a phase of immunosuppression during which the body's ability to clear cancer cells is reduced. Locally, tumor resection causes tissue injury with a resulting inflammatory process. The inflammatory process is characterized by the release of prostaglandins, cytokines, tumor necrosis factor α (TNF-α), and chemokines. These humoral factors attract macrophages, neutrophils, and fibroblasts necessary for wound healing, but they also promote the viability and proliferation of residual cancer cells (5, 8, 9). In addition, surgery can lead to disrupted perfusion resulting in local hypoxia. Hypoxia causes the expression of hypoxia-inducible factor-1-α (HIF-1-α) and VEGF. HIF-1-α promotes tissue repair but also proliferation of residual cancer cells. VEGF causes angiogenesis as well as lymphatic dilatation, which facilitates escape of cancer cells *via* the hematologic and lymphatic pathway. It has been shown that postoperative wound complications were strongly associated with increased tumor recurrence in breast cancer patients (10). On a systemic level, surgical stress activates the hypothalamic-pituitary-adrenal axis. This activation occurs from the time of surgery until 3-4 days postoperatively. It leads to a secretion of ACTH and cortisol, which increases the production of glucocorticoids, catecholamines, and cytokines and results in immunosuppression (8, 9). In addition, the activation of the sympathetic nervous system causes an immunosuppressive effect *via* sympathetically-innervated lymphoid organs (9).

The aim of this narrative review is to provide a critical overview of the current state of knowledge of the effects of commonly used anesthetic agents on cancer growth and patient survival.

VOLATILE ANESTHETICS

It is increasingly recognized that volatile anesthetics have an effect not only on the central nervous system, but also on other organ systems including the immune system. Volatile anesthetics modulate the innate as well as the adaptive immune response (11, 12). They suppress innate immunity mainly through suppression of neutrophils, dendritic cells, NK cells, and resident tissue macrophages. The adaptive immune system is suppressed by a decrease in proliferation of lymphocytes and an increase in lymphocyte apoptosis. In addition to its effects on the innate and adaptive immune system, volatile anesthetics also affect the immune system indirectly through their impact on stress hormone levels. Surgery leads to the stimulation of the hypothalamic-pituitary-adrenal axis and to the release of glucocorticoids and catecholamines, which can alter the immune response systemically. This effect was found to be more pronounced after anesthesia with volatile versus intravenous agents (13). The suppression of the immune system by volatile anesthetics can be beneficial in cases of sterile inflammation such as ischemia-reperfusion, but in cancer surgery it has the potential to promote tumor recurrence and metastasis (11).

Numerous *in vitro* studies have investigated the effect of volatile anesthetics on human cancer cell lines. Benzonana et al. exposed renal cell carcinoma cells for 2h to different clinical concentrations of the volatile anesthetic isoflurane (0.5-2%) (14). They measured levels of VEGF and hypoxia-inducible factors (HIFs), high levels of which are associated with poor prognosis. In addition, they looked at cell migration. Cultures exposed to isoflurane showed higher levels of HIFs and VEGFs, they contained more cells, more actively proliferating cells, and the cells exhibited greater migration. Iwasaki et al. exposed human ovarian carcinoma cells to high levels of isoflurane (3%), sevoflurane (3.6%), or desflurane (10.3%) for 2h and studied metastasis related gene expression profiles (15). All three volatile anesthetics altered expression of 70 out of 81 metastasis-related genes. Desflurane had the greatest effect, followed by sevoflurane and isoflurane. Luo et al. also studied the

effect of isoflurane on ovarian cancer cells (16). They exposed the cells for 2h to 2% isoflurane and studied the expression of markers involved in cell proliferation, angiogenesis, and migration. Isoflurane exposure increased the expression of insulin-like growth factors, VEGFs, and angiopoietin. Cell cycle progression and cell proliferation were also increased. Ciechanowicz et al. exposed non-small cell lung adenocarcinoma (NSCLC) cells and renal cell carcinoma cells to 3.6% sevoflurane for 2h (17). In NSCLC cells, sevoflurane reduced cell viability and enhanced chemosensitivity to cisplatin, but had no effect on cell migration. In renal carcinoma cells, however, sevoflurane enhanced cell viability, chemoresistance to cisplatin, and cell migration.

Taken together, most *in vitro* studies have found that exposure of cancer cell lines to volatile anesthetics reduced apoptosis of the cancer cells and favored their proliferation, migration, and chemoresistance.

Clinical studies often compare volatile anesthesia to total intravenous anesthesia with propofol. These studies are discussed in the comparative chapter following the next section on propofol.

PROPOFOL

In vitro cancer cell studies have found that propofol may have specific effects on cancer cell apoptosis and proliferation. Propofol exerts an anti-tumor effect mainly but not exclusively by a down-regulation of matrix metalloproteinases (MMPs) (18). This downregulation leads to a decrease in cancer cell proliferation and invasion and an increase in cancer cell apoptosis. Such an effect has been shown for *in vitro* cell cultures of pancreatic cancer cells (19), ovarian cancer cells (20, 21), hepatocellular carcinoma cells (22, 23), gastric cancer cells (24), glioma cells (25), osteosarcoma cells (26), lung adenocarcinoma cells (27), colon carcinoma cells (28) and breast cancer cells (28). Besides downregulating MMPs, propofol has been found to also exert an anti-tumor effect by other pathways. In non-small-cell lung cancer cells, propofol reduced the aggressiveness of cancer cells by reducing the upregulation of HIF-1α (29). In esophageal cancer cell cultures, propofol reduced proliferation, invasion, and angiogenesis by reducing extracellular signal-regulated kinases, which lead to a reduced expression of VEGF and MMP-9 (29). In osteosarcoma cells, propofol decreased sarcoma cell proliferation and invasion, and increased apoptosis by downregulating transforming growth factor β-1 (TGF-β-1), an immunosuppressing cytokine (30). In breast cancer cells, propofol reduced migration by reducing neuroepithelial cell transforming gene 1 (NET1), a gene associated with promoting migration in adenocarcinoma cells (31).

However, propofol has not only been associated with potentially beneficial anti-tumor effects in tumor cell studies. In a breast cancer cell model, Garib et al. found an increase in the percentage of migrating cells after exposing breast cancer cells to propofol (32). The same group also reported that propofol increased the migration of breast cancer cells *via* the activation of the γ-aminobutyric acid-A (GABA-A) receptor (33). Similarly, Meng et al. observed an increase in proliferation and migration in a human breast cancer cell lines after treatment with propofol (34).

Cancer cell studies have found that propofol may also alter the sensitivity of cancer cells to chemotherapeutic agents. Chen et al. reported that propofol enhances paclitaxel-induced apoptosis in ovarian cancer cells through the suppression of the transcription factor slug (35). In pancreatic cancer cells, propofol has been shown to increase gemcitabine sensitivity by inhibition of NF-kB activity (36), and in cervical cancer cells propofol enhanced cisplatin-induced apoptosis (37). In glioma cells, however, propofol was found to depress cisplatin cytotoxicity by reducing gap junctions between the cells (38).

Animal studies provide additional information on the effects of propofol on tumor growth. Cui et al. injected lung cancer cells into the axilla of mice, and once the tumor had reached a size of 3-5 mm, the mice were divided into three groups (39): one receiving no treatment, one receiving saline, and one receiving propofol. After 30 days, mice in the propofol group had significantly decreased tumor size and weight. Kushida et al. injected thymoma cells subcutaneously into mice (40). The cytotoxic activity of T cells collected from the spleen was then measured. The cytotoxicity of the T cells was significantly greater in mice treated with propofol than those treated with intralipid or saline. Further, tumor growth was significantly suppressed.

Taken together, most *in vitro* and animal studies suggest a beneficial effect of propofol on cancer cell apoptosis and proliferation. Few cancer cell studies have also reported that propofol might alter the sensitivity of cancer cells to chemotherapeutic agents.

VOLATILE ANESTHESIA VERSUS TOTAL INTRAVENOUS ANESTHESIA

The effects of volatile versus intravenous anesthetics have been studied in some *in vitro* and animal studies comparing their effects on cancer cell growth, and in a large number of retrospective analyses on the outcome of cancer patients.

In vitro, Huang et al. exposed prostate cancer cell lines either to isoflurane or to propofol and assessed the malignant potential by evaluating expression levels of HIFs and the downstream effects (41). Isoflurane induced an upregulation of HIFs and, thus, an increase in proliferation, migration, and chemoresistance of cancer cells. In contrast, propofol inhibited expression of HIFs. Jaura et al. collected serum from women who had undergone surgery for breast cancer either with propofol anesthesia combined with a paravertebral block or with sevoflurane anesthesia in combination with opioids (42). Estrogen receptor negative breast cancer cells were exposed to serum from either the propofol-paravertebral block group or to serum from the sevoflurane-opioid group. Apoptosis of the cancer cells was significantly reduced in the cell culture exposed to the serum from the sevoflurane-opioid group. In another *in vitro* study with serum from women undergoing breast cancer surgery, Buckley et al. compared effects of serum from a propofol-paravertebral block group and a sevoflurane-opioid group on human NK cell cultures (43). The serum of women from the propofol-paravertebral block group led to a greater cytotoxicity of the NK cells than the serum of women from the sevoflurane-opioid group. Lim et al. studied breast cancer cells co-cultured with NK

cells and cytotoxic T lymphocytes (CTL) (44). They exposed these cultures to serum collected from women who had undergone breast cancer surgery either with propofol-based anesthesia or sevoflurane-based anesthesia. In contrast to the other laboratory studies, propofol was not superior to sevoflurane in this study, as no difference in NK cell count, CTL count, or apoptosis rate was detected between the groups. In an animal study, Melamed et al. injected breast cancer cells into rats and anesthetized the animals for one hour with ketamine, thiopental, halothane, or propofol (45). All anesthetics except propofol significantly reduced NK cell activity and increased lung tumor retention and the occurrence of lung metastasis.

A large number of retrospective clinical studies compare the effects of volatile versus intravenous anesthesia on the outcome of cancer patients. Better overall survival after anesthesia with propofol compared to anesthesia with volatile agents has been reported for gastric cancer (46), colon cancer (47), breast cancer (48), esophageal cancer (49), and hepatocellular carcinoma (50). Wigmore et al. retrospectively analyzed patients with different types of solid organ cancers undergoing resective surgery and found that mortality was approximately 50% higher with volatile anesthesia than with intravenous anesthesia (51). Lee et al. found no difference in overall survival after propofol anesthesia compared to sevoflurane anesthesia in patients undergoing mastectomy for breast cancer, but they found a lower recurrence rate after propofol anesthesia (52). Similarly, Hasselager et al. found a weak association between colorectal cancer recurrence and exposure to inhalational anesthesia when compared to total intravenous anesthesia, but no association between all-cause mortality or disease-free survival (53). Jun et al. similarly found worse recurrence-free survival after anesthesia with volatile agents compared to propofol in patients with esophageal cancer (49). In contrast, no difference in overall patient survival and recurrence-free survival between total intravenous anesthesia and volatile anesthesia was reported for non-small cell lung cancer (54) and breast cancer (55, 56). Enlund et al. looked at patients after radical cancer surgery for breast, colon, or rectal cancer and compared 1- and 5-year overall survival rates between propofol and sevoflurane anesthesia. They found an apparent advantage of propofol over sevoflurane, which disappeared after adjustment for several confounders (57).

One of the very few prospective, randomized trials was published by Oh et al. who studied whether propofol is less immunosuppressive than sevoflurane (58). Indicators of a potential immunosuppressive effect of the anesthetics analyzed in this study were clusters of differentiation 39 and 73. These clusters are expressed on the surface of regulatory T cells that promote cancer recurrence and metastasis by suppressing immune cells. In blood samples collected from women undergoing breast cancer surgery who were randomized to either propofol or sevoflurane anesthesia, changes in cluster differentiation 39 and 73 expression did not differ between the two groups (58). In line with these findings are the conclusions drawn by a recent meta-analysis of 23 randomized controlled trials examining perioperative inflammation after general anesthesia using propofol compared to sevoflurane (59). The authors of the meta-analysis found an increase in the mean inflammatory biomarker levels of IL-6, IL-10, TNF-α, and C-reactive protein (CRP) after surgery but no difference between propofol and sevoflurane.

Finally, a meta-analysis from 2019 included ten studies to compare the potential effects of intravenous versus volatile anesthesia on recurrence-free survival and overall survival in cancer patients (60). Based on six of these studies, the meta-analysis came to the conclusion that the use of TIVA was associated with improved recurrence-free survival in breast, esophageal, and non-small-cell lung cancer. Further, based on eight studies with a total of 18,778 patients, the meta-analysis found that overall survival was also improved with the use of TIVA. It must be noted, however, that nine of the ten studies were retrospective in design, and that the prospective study was much too small to reliably analyze patient outcomes. The authors conclude that their findings suggest a beneficial effect of propofol-based anesthesia on cancer outcomes but indicate the need for prospective studies before reliable conclusions can be drawn.

Taken together, laboratory studies and most retrospective studies suggest a potential beneficial effect of propofol-based TIVA on the outcome of cancer patients undergoing surgery. Data from randomized-controlled trials is scarce and did not confirm the beneficial effects of propofol seen in laboratory and retrospective studies. Results of further ongoing prospective, randomized studies are needed before final conclusions can be drawn. Meanwhile, TIVA may be used as the preferred type of anesthesia in patients with cancerous disease unless there is an individual contraindication against it.

OPIOIDS

Pain and stress have been shown to favor cancer dissemination in rodents (61). Therefore, any drug used to treat pain has the potential to alter this response. Opioids are used widely in cancer patients to treat perioperative and cancer-related pain in the palliative setting. Research regarding the role of opioids in cancer dissemination is conflicting, and there is evidence that not all opioids exert the same effect on the immune system. Morphine seems to have positive and negative effects on the immune system. Fentanyl and codeine seem to have mainly immunosuppressive effects. Tramadol has mainly immunostimulating effects. Buprenorphine, oxycodone, and hydromorphone appear to be neutral (7). It is believed that opioids exert their influence on tumor growth and progression mainly through activation of the μ-opioid receptor. This belief is strengthened by the observation that patients with advanced cancer who were treated with the μ-opioid-receptor antagonist methylnaltrexone had higher disease-free survival (62). Reduced cancer cell growth in lung carcinoma cells after treatment with methylnaltrexone was also seen *in vitro* (63). It further could be shown that naloxone inhibited cell proliferation and increased cell death in human estrogen-receptor negative breast cancer cells *in vitro* and lead to reduced cancer growth in mice (64).

In vitro and mouse studies found that morphine decreases tumor growth in breast (65), colon (66), and melanoma (67) cancer cells. Morphine was also shown to decrease transendothelial migration of leukocytes and reduce angiogenesis in lung cancer cells (68). In a mouse model of

breast cancer, morphine lead to a reduction in tumor growth and to a reduction in circulating levels of MMP-9 and urokinase-like plasminogen activator (69). Harimaya et al. observed that morphine also reduced the adhesion, invasion, and metastasis of colon cancer cells *in vitro* by the regulation of MMPs (66). In contrast, morphine increased tumor growth in breast (70), sarcoma, and leukemia (71) cancer cells *in vitro* and in mouse models. In breast (72) and lung cancer (73), it promoted invasion and migration of cancer cells *via* the upregulation of MMPs and in colon cancer *via* the upregulation of urokinase plasminogen activator (74). A meta-analysis of experimental animal studies on the effect of treatment with analgesics was published in 2015. The authors came to the conclusion that there is no evidence that treatment with any analgesics including opioids increases the occurrence of metastases (75).

Clinical studies have also failed to provide clear evidence on potential effects of opioids on tumor growth and cancer recurrence. One reason is that most studies are retrospective in design, which limits the reliability of their findings. In addition, drawing conclusions from several studies performed in patients with the same type of cancer is limited by the large heterogeneity of the studies. Furthermore, many studies compared general anesthesia combined with regional anesthesia to general anesthesia combined with opioids. It is, therefore, not clear if observed effects, if any, are due to regional anesthesia or to opioids.

There is one large prospective Danish cohort study of more than 34,000 women with newly diagnosed breast cancer (76). After a mean follow-up of more than 8 years, the authors failed to detect any correlation between opioid prescription and breast cancer recurrence, regardless of opioid type, chronicity of use, or cumulative dose. This finding is in agreement with those of two recently published prospective trials comparing general anesthesia with regional analgesia versus general anesthesia plus opioids (77, 78). Sessler et al. compared patients who underwent breast cancer resection and who received general anesthesia either with propofol plus a paravertebral block or with sevoflurane and postoperative opioids. Recurrence of cancer was similar in the two patient groups during a median follow-up period of 36 months (77). In the second prospective study in patients with colorectal cancer, disease-free survival after 5 years was not affected by the use of thoracic epidural analgesia vs. patient-controlled opioid analgesia at the time of surgery (78). There is also a recent systematic review of published data on the effect of perioperative opioids on colorectal cancer recurrence. However, the authors were unable to perform a quantitative analysis because of the great heterogeneity of the studies (79).

Finally, there are many retrospective studies focusing on different types of cancer with quite conflicting results. Differences between these studies include study design and specific focus, size, quality, and complexity of data. One retrospective analysis of almost 500 patients with stage IV prostate cancer found that higher opioid requirements were associated with shorter progression-free and overall survival (80). However, effects of tumor volume on pain and, consequently, opioid use are potential confounders of this finding as the authors of the study indicate in the limitations section. Another retrospective study of 901 patients with NSCLC analyzed the association between intraoperative fentanyl dose and cancer recurrence (81). In stage I patients, the authors found a trend towards increased risk for recurrence and decreased overall survival with higher fentanyl doses. However, no effect was found in stage II and III patients. In patients with lung adenocarcinoma stage I to III, another retrospective study reported an association between intraoperative opioid exposure and worse overall survival (82). Another retrospective study by Biki et al. in patients who had undergone open radical prostatectomy reported an estimated 57% lower risk of cancer recurrence in patients who had received general anesthesia with epidural analgesia compared to patients with general anesthesia and postoperative opioid analgesia (83).

Taken together, the few prospective studies all failed to detect a negative effect of perioperatively-administered opioids on tumor growth and cancer recurrence. This fact questions the findings of previous retrospective studies. Confounding effects (e.g. of tumor volume on pain and thus opioid use) might be reasons for the association between opioid use and outcome found in those earlier studies. The current state of knowledge based on prospective studies strongly suggests to continue using opioids as strong analgesics in cancer patients who frequently suffer from intense pain. Nevertheless, further prospective studies are needed to definitively clarify potential effects of opioids on growth and recurrence of different types of malignant tumors.

REGIONAL ANESTHESIA

Regional anesthesia, used either alone or in combination with general anesthesia reduces the perioperative stress response, perioperative pain, and therefore, the perioperative opioid requirements as well. Whether regional anesthesia has a direct influence on cancer recurrence is less clear.

In vitro studies of serum from patients who underwent cancer surgery showed a potential benefit of regional anesthesia. Xu et al. collected serum from patients undergoing colon cancer surgery with general anesthesia either by propofol and epidural analgesia or by sevoflurane and opioid analgesia (84). *In vitro*, serum from patients of the propofol-epidural group showed inhibited proliferation and invasion of colon cancer cells and induced apoptosis more often than serum from patients of the sevoflurane-opioid group. The previously mentioned *in vitro* studies of Buckley (43) and Jaura (42) showed similar beneficial effects.

Clinical data show controversial results. Prospective studies in patients with colorectal (85), abdominal (86), breast (87), and prostate (88) cancer found no beneficial effect of regional anesthesia. A Cochrane database systematic review published in 2014 analyzed whether regional anesthesia influences long-term prognosis for individuals with malignant tumors (89). The authors searched for controlled trials on general anesthesia alone versus general anesthesia combined with epidural analgesia in cancer patients. They identified four secondary analyses of

controlled, prospective randomized trials with a total of 746 patients with abdominal (two studies), colon, and prostate cancer. The systematic review revealed no difference between the groups without vs. with additional epidural analgesia, and the authors concluded that evidence for the benefit of regional anesthesia techniques on tumor recurrence is inadequate. Similarly, another meta-analysis from 2017, which included 28 studies with an array of cancers also looked at the potential benefit of regional anesthesia (90). This meta-analysis also found no benefit of regional anesthesia on overall survival, recurrence-free survival, or biochemical recurrence-free survival. Finally, a number of retrospective studies in patients with colon (91), abdominal (92), and breast (93) cancer also found no beneficial effect of regional anesthesia. In contrast, a meta-analysis of 21 studies published in 2016 found that the use of neuraxial anesthesia was associated with improved overall survival in patients undergoing cancer surgery, particularly in those with colorectal cancer (94). It also reported a potential association between neuraxial anesthesia and reduced risk of cancer recurrence. It must be noted, however, that only 5 of the 21 studies were prospective trials, and that only one of them found an association between neuraxial anesthesia and improved survival. The retrospective study by Biki et al., which also found an association between epidural anesthesia and reduced cancer recurrence, has already been mentioned (83).

Taken together, there is no adequate scientific evidence for a beneficial effect of regional anesthesia on the outcome of surgically treated cancer patients. Retrospective studies have found conflicting results, and nearly all prospective studies have failed to detect any beneficial effect of regional anesthesia. Therefore, complementing general anesthesia with regional techniques may be reasonable for optimizing patient comfort, but it does not seem to improve patient outcome.

LOCAL ANESTHETICS

The effect of local anesthetics on tumor growth has been studied in several *in vitro* and animal studies, but clinical studies are missing. The clinical administration of intravenous lidocaine during anesthesia has been promoted by the observation that it is associated with a lower use of opioids, a lower incidence of nausea and vomiting, and faster recovery from postoperative ileus (95–97). Furthermore, lidocaine has potent anti-inflammatory activity *via* the modulation of IL-6, IL-8, leukotrienes, and polymorphonuclear leukocytes (9).

Several *in vitro* studies and trials in mice have demonstrated the anti-cancer potential of lidocaine and other local anesthetics. After incubating two breast cancer cell lines with high concentrations of lidocaine, bupivacaine, and four other local anesthetics, Li et al. observed significantly inhibited cell viability and induced cytotoxicity (98). At concentrations reached by regional anesthesia, however, none of the local anesthetics affected cell viability or migration in the included patients. Xuan et al. exposed ovarian and prostate carcinoma cells *in vitro* with bupivacaine at clinically relevant concentrations and observed reduced cell viability and inhibited cellular proliferation in both cell lines (99). Another *in vitro* study found that the growth of human hepatocellular carcinoma cells was inhibited in a dose- and time-dependent manner by lidocaine (100). When human hepatocellular carcinoma cells were transferred into mice, intraperitoneal injection of lidocaine markedly suppressed tumor growth. Chamaraux-Tran et al. exposed normal breast epithelial cells and three tumor breast epithelial cell lines to clinically relevant concentrations of lidocaine and investigated cell viability and migration (101). Lidocaine reduced the viability of all three malignant cell lines and inhibited migration but had no effect on the normal breast epithelial cells. When they injected breast cancer cells intraperitoneally into mice, addition of intraperitoneal lidocaine improved survival of the mice. Also in a murine breast cancer model, other investigators found that addition of lidocaine during anesthesia with sevoflurane for tumor resection reduced cancer progress with pulmonary metastasis but had no effect when ketamine and xylazine had been used for anesthesia (102).

Taken together, some *in vitro* and animal studies suggest a potential beneficial, possibly dose-dependent, effect of local anesthetics on tumor growth and metastatic disease. The prospective clinical studies reported in the section on regional anesthesia strongly question such an effect at plasma levels induced by epidural anesthesia. Whether potentially higher plasma levels of lidocaine, when perioperatively infused as a component of multimodal analgesia (103), have an effect on outcome of cancer patients needs to be investigated in prospective trials.

BLOOD TRANSFUSION

Cancer surgery can be extensive, and therefore, blood transfusion can be lifesaving. However, transfusion of allogenic blood involves specific immunologic risks. Even after leucocyte reduction, the few remaining leucocytes in packed red blood cells (pRBC) have the ability to modulate the immune response of the recipient. In addition to residual leucocytes, there are also biologically active cytokines, non-polar lipids, and a mixture of pro-inflammatory lysophosphatidylcholines in pRBC. Lysophosphatidylcholines activate NK cells, T lymphocytes, and dendritic cells and stimulate the production of pro-inflammatory cytokines. The overall effect of these biological substances is immunosuppression and tumor-promotion (104). Atzil et al. studied the effect of blood transfusion on cancer progression in a mammary adenocarcinoma and a leukemia rat model (105). Blood transfusion was found to be an independent and significant risk factor for tumor progression in both models, regardless whether allogenic or autogenic blood was used. Duration of blood storage was the critical determinant of this effect and, surprisingly, aged erythrocytes rather than leukocytes mediated it. Hod et al. could demonstrate in a murine model that the transfusion of stored red blood cells increased plasma non-transferrin-bound iron, increased acute tissue iron deposition, and initiated inflammation (106).

Available data from clinical studies has been summarized in several meta-analyses. A Cochrane review from 2006 including 36 studies with more than 12,000 patients analyzed the role of perioperative blood transfusion on colorectal cancer recurrence

(107). The effect of perioperative blood transfusion on cancer recurrence yielded an odds ratio (OR) of 1.42 (95% CI: 1.2 to 1.67) against transfused patients. The fact that 26 of the 36 studies in this Cochrane review had been performed retrospectively might question the validity of this finding. However, a separate analysis of the studies with higher quality, and of the ten prospective studies yielded similarly significant ORs. Li et al. performed a meta-analysis to look at the association between allogenic or autologous blood transfusion and survival in patients after radical prostatectomy (108). Data from 26,000 patients in ten studies was included. They found that allogenic blood transfusion was significantly associated with worse recurrence-free survival, overall survival, and cancer-specific survival. In patients with autologous blood transfusion, this effect was not seen. Agnes et al. did a meta-analysis on the association between allogenic perioperative blood transfusion and recurrence of cancer in patients who had undergone curative gastrectomy for gastric cancer (109). Perioperative blood transfusion was associated with worse overall survival, disease-free survival, and disease-specific survival and an increased number of postoperative complications. Similar findings for bladder cancer were found in a meta-analysis by Cata et al. (110). It must be noted, however, that the meta-analyses by Li, Agnes, and Cata all rely on retrospective studies, which require cautious interpretation of the results.

Taken together, there is meta-analytic evidence of an association between allogenic blood transfusion and increased number of postoperative complications, cancer recurrence, and worse patient survival. These findings fit to laboratory evidence of immunosuppression induced by transfused blood. Therefore, using a restrictive transfusion threshold in cancer patients and in general is mandatory, although more aggressive forms of cancer may have contributed to worse outcome in transfused patients by necessitating more blood transfusions.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Cyclooxygenase-2 (COX-2) is a key enzyme in the synthesis of prostaglandins (PG) and has been demonstrated to play an important role in the development, growth, and invasion of several cancer types (111, 112). NSAIDs, selective COX-2-inhibitors, and aspirin, thus, have a potential role in the treatment and prevention of malignant tumors through different pathways. Kashiwagi et al. demonstrated that aspirin downregulates androgen receptors and prostate-specific antigens in prostate cancer cells *in vitro* (113). They also found that aspirin upregulates the prostaglandin receptor EP3. Activation of EP3 receptors leads to a decrease in androgen receptors. Aspirin and EP3 receptor agonists, therefore, have the potential to modulate prostate cancer growth. Evidence for the role of COX-2 and PGs in the development of colorectal cancer could be gained from a murine model of adenomatous polyposis (114). In a mouse model of hepatocarcinoma, the selective COX-2-inhibitor celecoxib delayed growth of the tumor (115).

A Finnish population-based study revealed NSAID use to be associated with an increased risk of prostate cancer, while aspirin use was associated with a decreased risk (116). Another database study looked at prostate cancer patients treated with either surgery or radiotherapy (117). They compared prostate cancer-specific mortality between patients receiving anticoagulant treatment and patients with no anticoagulant treatment and found that prostate cancer-specific mortality was lower in both patients treated with surgery and radiotherapy if they received anticoagulation treatment. A subgroup analysis revealed that the reduced mortality in patients receiving anticoagulation was mainly due to the effect of aspirin. Evidence from a prospective observational study in humans found that the chronic use of NSAIDs reduced the risk of developing gastrointestinal cancer (118). Moreover, the largest body of evidence supports the beneficial effects of NSAIDs in colorectal cancer prevention and adjuvant treatment (119). The adenoma prevention with celecoxib trial examined the efficacy and safety of celecoxib for colorectal adenoma prevention in patients with an increased risk of colorectal cancer. It found that celecoxib had a long-term protective effect on the prevention of colorectal adenoma progression but increased the risk of renal and hypertensive events and cardiac disorders (120, 121). In line with this, Ng et al. found in a prospective observational study that aspirin and COX-2 inhibitors may be associated with improved outcomes in stage III colon cancer (122). Overall, it can be said that the use of NSAIDs and COX-2 inhibitors is associated with a reduced risk of occurrence and progression of colorectal cancer (119). This beneficial effect, however, is offset by the increased risk of cardiovascular events and gastrointestinal toxicity. The risk-benefit analysis, therefore, prevents their widespread use in prevention and adjuvant use in colorectal cancer. Among NSAIDs, aspirin in low doses is the only agent with a potential overall benefit in chemoprevention and adjuvant therapy in colorectal cancer due to its protective nature against cardiovascular events and its low gastrointestinal toxicity. In breast cancer, however, a Danish registry study indicated that post-diagnostic use of aspirin, NSAIDs, or selective COX-2-inhibitors was not associated with a reduced rate of recurrence. However, pre-diagnostic use was associated with a reduced rate of recurrence (123). In contrast to these findings, Huang et al. found in a meta-analysis of 16 studies published in 2015 that NSAID and aspirin use after, but not before diagnosis was associated with improved breast cancer survival including breast cancer-specific mortality, all-cause mortality, relapse, and metastasis (124). These conflicting findings clearly indicate the lack of reliable evidence in the absence of adequate prospective trials.

When it comes to perioperative administration of NSAIDs and cancer recurrence, data is even more sparse. In breast cancer, retrospective data showed an association between the intraoperative administration of ketorolac and reduced recurrence rate in patients undergoing surgery (125–127). In patients with ovarian cancer, a retrospective study found the perioperative use of ketorolac to be associated with a decreased cancer-specific mortality six years after surgery. In patients with prostate cancer undergoing retropubic prostatectomies and NSCLC, there was no association between perioperative NSAIDs and cancer recurrence (128, 129).

To summarize the existing evidence on the effect of NSAIDs on cancer recurrence, we would like to mention a systematic review from 2017 (130). The authors found 16 trials but did not

perform a meta-analysis because of the high heterogeneity and low quality of the available studies. This fact clearly indicates that we lack adequate scientific evidence to make any recommendation on the use of NSAIDs, aspirin, and COX-2-inhibitors based on outcome aspects in cancer patients.

KETAMINE

There has been a revival in the use of ketamine in recent years. Ketamine is a NMDA-receptor antagonist and has agonistic properties on the μ- and δ-opioid receptors. It has a strong analgesic effect and, therefore, can reduce the amount of preoperatively-used opioids (9). Its effect on the immune system and cancer recurrence is less clear.

The murine study by Melamed et al. has already been mentioned (45). They anesthetized rats with either thiopental, ketamine, halothane, or propofol for one hour and then injected them with breast cancer cells. All anesthetics except propofol decreased NK cell activity and increased cancer cell retention and lung metastasis. Ketamine increased lung metastasis most potently (45). Forget et al. looked at the influence of ketamine on NK cell activity and occurrence of lung metastasis in rats injected with breast cancer cells (131). Ketamine only led to a reduction of NK cell activity in unoperated rats. However, ketamine reduced the number of metastasis in operated animals, a finding that is in full contrast to the study by Melamed et al. (45).

Clinical studies are scarce and partially conflicting. In a prospective and randomized study of patients with colorectal cancer, Cho et al. found that the administration of intraoperative low-dose ketamine did not have a favorable impact on overall postoperative NK cell activity, inflammatory response, and prognosis (132). In a small randomized trial in patients undergoing minimally invasive prostatectomy for prostate cancer, Kawaguchi et al. also failed to detect an immunomodulatory effect by ketamine (131). In a retrospective study, Forget et al. also found no beneficial effect of ketamine on cancer recurrence in patients who had undergone mastectomy for breast cancer (127). In another retrospective study, Connolly et al. made the contrary finding of improved recurrence-specific survival in patients with early-stage lung adenocarcinoma who had received ketamine intraoperatively (82).

In summary, there is no adequate scientific evidence to advocate the perioperative use of ketamine for improving outcome in cancer patients.

A2-AGONISTS

The centrally acting α2-agonists clonidine and dexmedetomindine reduce the release of noradrenaline and, therefore, dampen the sympathetic stress response. They have a sedative effect and are used perioperatively to reduce the need for opioids. There is little data available on their effect on the immune system and cancer recurrence.

Cheng et al. could demonstrate *in vitro* that dexmedetomidine inhibited the maturation of dendritic cells, which are important players in the immune response (133). Wang et al. demonstrated *in vitro* that dexmedetomidine promoted cell proliferation and migration and upregulated anti-apoptotic proteins in human lung carcinoma cells and human neuroglioma cells (134). In a murine model of lung carcinoma, dexmedetomidine did not alter tumor growth (134). In contrast, dexmedetomidine and clonidine increased tumor growth and metastasis in murine breast cancer models (135, 136). Other investigators found that dexmedetomidine increased tumor cell retention and growth of metastases in different animal models of breast, lung, and colon carcinoma (137), and that it had a tumor promoting effect through the increasing production of VEGF in a murine lung cancer model (138). In surgical lung cancer patients, these investigators found that dexmedetomidine induced the proliferation of M-MDSC cells, which have a potent proangiogenic ability (138).

Prospective outcome studies in patients have not been published, and retrospective studies are scarce and inconsistent. In lung cancer patients undergoing surgery, Connolly et al. did not find an association between the administration of dexmedetomindine and overall survival and recurrence-specific survival (82), while Cata et al. found that dexmedetomidine was associated with reduced overall survival but not with recurrence-free survival (139).

Taken together, the effects of α2-agonists on the outcome of cancer patients, if any, are unknown.

STEROIDS

Steroids inhibit cyclooxygenase and lipoxygenase pathways and, thereby, reduce postoperative pain. Further, they have an antiemetic effect. For these reasons, steroids are often administered perioperatively to cancer patients. While they are part of the treatment in hematologic malignancies, their role in solid organ tumors is less clear.

In a xenograft mouse model of prostate cancer, dexamethasone led to a decrease in tumor growth and microvessel density through the downregulation of VEGF and IL-8 (140). As this effect was not seen *in vitro*, the investigators hypothesized that dexamethasone might decrease tumor growth by inhibition of tumor-associated angiogenesis. In a xenograft model of prostate cancer, Nishimura et al. also found that dexamethasone inhibited the NF-kB and IL-6 pathway and lead to reduced cancer growth (141). *In vitro* as well as in a xenograft model, Arai et al. also observed that dexamethasone inhibited growth of renal cancer cells through the inhibition of the NF-kappa-B pathway and its downstream products IL-6, IL-8, and VEGF (142). In contrast to these findings, dexamethasone mediated tumor progression in pancreatic cancer cell lines and in a pancreatic cancer cell xenograft model (143).

In one published outcome study in patients with colon cancer, based on the follow up of a previous randomized trial (144), the authors found that preoperative dexamethasone was associated with a higher rate of distant metastases five years after colectomy. However, they point out that the very small sample size (20 vs. 23 in the dexamethasone vs. placebo group, respectively) prohibits reliable conclusions. Another observational study by McSorley et al. in patients undergoing either open or laparoscopic surgery for colonic cancer looked at the effect of surgical approach and intraoperatively administered dexamethasone (145). They found a significant trend towards a lower postoperative systemic inflammatory response with the

use of laparoscopic surgery and higher doses of dexamethasone. The combination of laparoscopic surgery and higher doses of dexamethasone was also associated with fewer postoperative complications. The authors also found that the use of dexamethasone was not significantly associated with either improved or poorer cancer-specific or overall survival. In another retrospective study, the same group found that preoperatively administered dexamethasone in patients undergoing surgery for colorectal cancer was associated with a lower postoperative systemic inflammatory response as evidenced by a lower CRP level (146). A systematic review and meta-analysis in patients undergoing surgery for gastrointestinal cancer found that preoperatively administered corticosteroids were associated with a reduced postoperative systemic inflammatory response and fewer postoperative complications (147). In a cohort study, patients were followed up for 5-10 years after breast cancer surgery (148). A single dose of perioperatively administered dexamethasone was not associated with increased recurrence or mortality after curative breast cancer surgery. Finally, retrospective analysis of data from a prospectively maintained database of patients undergoing pancreaticoduodenectomies for pancreatic cancer revealed that intraoperatively administered dexamethasone did not increase morbidity, was associated with a decrease in infectious complications, and an increase in overall survival (149).

More data from prospective human studies is necessary before valid conclusions on the effects of perioperatively administered steroids on the outcome of cancer patients can be made.

DISCUSSION

Numerous laboratory, animal, and clinical retrospective studies have investigated the impact of commonly used anesthetic agents on cancer outcome. Good high quality prospective randomized trials, however, are scarce.

Based on this insufficient scientific evidence, no firm conclusions can be drawn and no sound recommendations be made at this juncture. Findings from *in vitro* and animal studies must not be extrapolated to cancer patients undergoing surgery. Reasons are that there are multiple differences between the complex clinical situation in surgical cancer patients and the situation in artefactual cell culture studies or animal studies. Highly cultured tumor cell lines with optimal cell culture conditions are artefactual and have only limited relevance to the much more complex *in vivo* situation. It is also unclear if or to what degree anesthetic dosage and duration of exposure to such agents as used in cancer cell line studies are representative of the *in vivo* situation.

Well-controlled animal studies also differ in multiple aspects from the much more complex situation of surgical cancer patients, and it is unclear to what degree their findings can be extrapolated to humans. Differences include effects of the stress response to surgery, interaction with other drugs, or the effects of potential chemotherapy and radiotherapy in patients, conditions that are generally absent in animal models. Fever or cold are two of many additional factors that may differ between animal studies and the clinical situation in surgical patients. Fever stimulates the innate as well as the adaptive immune system. Pyrogenic cytokines produced during the induction of fever also activate the immune system (150). Cold stress, however, leads to an increased release of norepinephrine and has been associated with accelerated tumor growth in murine models, suppression of endogenous immune responses, and therapeutic resistance of tumors (150, 151). Laboratory mice are generally kept at sub-thermoneutral housing temperatures. This characteristic might potentially lead to biased outcomes in murine cancer models (151). Xenograft studies have the specific limitation that they are performed in mice with immunocompromised immune systems, which again questions their generalizability to humans.

Finally, retrospective clinical studies have inherent limitations, which limit the validity of their findings (152).

Taken together, scientific evidence is quite limited. The fundamental differences between laboratory conditions and the clinical situation as well as the limitations of retrospective clinical studies must be considered when their meaningfulness for clinical decisions in cancer patients is appraised.

Laboratory, animal, and retrospective clinical studies suggest a potential advantage of propofol-based total intravenous anesthesia over inhalational anesthesia. The few prospective clinical trials available, however, have failed to prove a benefit of propofol. In addition, the few prospective studies available have often compared propofol plus regional anesthesia with inhalational anesthesia plus opioids, making it even more difficult to isolate the effects of propofol and inhalational anesthesia. Until large prospective clinical trials are available, it is certainly not wrong to favor propofol over volatiles for maintenance of anesthesia during cancer surgery.

With regard to opioids, the evidence is conflicting. There are retrospective studies that have found higher perioperatively administered opioid doses to be associated with worse cancer outcome. However, the few available prospective studies have failed to detect a negative effect of perioperatively administered opioids on tumor growth and cancer recurrence. As many cancer patients suffer from intense pain, it would be unethical to withhold opioids based on the current evidence. In addition, it must be mentioned that opioid requirements are affected by multiple factors. More severe disease and postoperative complications are both associated with higher opioid requirements. However, both factors are also independent risk factors for cancer recurrence.

Prospective studies on the effect of regional anesthesia on cancer outcome have failed to show an advantage of regional analgesia over opioid analgesia. While using regional anesthesia to optimize patient comfort may be reasonable, there is no evidence that this approach improves patient outcome. Laboratory studies might hypothesize that higher plasma concentrations of lidocaine, which can be reached by perioperative intravenous infusion as a component of multimodal analgesia, might have an effect on outcome of cancer patients, but again large randomized controlled trials are missing.

TABLE 1 | Summary of anesthetic effects on cancerous disease.

Drug or Method	Basic Research		Human Research		Conclusion, Recommendation
	In vitro	Animal	Retrospective	Prospective	
Volatile Anesthetics	↓		*	*	*
Propofol	Mostly ↑ Breast Cancer ↔ Glioma ↓		*	*	*
Volatile vs. Propofol	Propofol (↑)	Propofol ↑	Propofol (↑)	≈	Use propofol unless individually contraindicated
Opioids	↔	↔	(↓)	×	Use as clinically indicated
Regional Anesthesia	(↑)	—	↔	×	Use as clinically indicated
Local Anesthetics	Mostly ↑	Mostly ↑	—	—	Insufficient scientific data
Blood Transfusion		↓	↓	↓	Apply restrictive transfusion threshold
NSAIDs	↑	↑	↔	↔	Use as clinically indicated
Ketamine	—	↔	↔	×	Use as clinically indicated
α2-agonists	(↓)	↓	↔		Insufficient scientific data
Steroids	↔	↔	—	—	Insufficient scientific data

*↓, unfavorable; *, see studies on volatile anesthetics vs. propofol; ↑, advantageous; (↑), advantageous in majority of studies; ≈, no difference between the two drugs; ↔, conflicting results; (↓), unfavorable in majority of studies; —, no studies available; ×, no evidence of positive or negative treatment effect.*

There is evidence from meta-analyses that allogenic blood transfusions are associated with worse cancer outcomes. In general, a restrictive transfusion protocol should, therefore, be applied in cancer surgery.

Concerning other perioperatively administered drugs such as ketamine, α-2-agonists, and steroids, evidence is at best scarce regarding their impact on cancer outcome. Their use should be guided by the patient's needs and not by the potential effect of these agents on cancer outcome.

Table 1 summarizes the current evidence of the commonly used anesthetic agents on cancer progression.

AUTHOR CONTRIBUTIONS

BB and MS performed the literature search and the manuscript preparation together. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68 (6):394–424. doi: 10.3322/caac.21492
2. Dubowitz JA, Sloan EK, Riedel BJ. Implicating Anaesthesia and the Perioperative Period in Cancer Recurrence and Metastasis. *Clin Exp Metastasis* (2018) 35(4):347–58. doi: 10.1007/s10585-017-9862-x
3. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global Cancer Surgery: Delivering Safe, Affordable, and Timely Cancer Surgery. *Lancet Oncol* (2015) 16(11):1193–224. doi: 10.1016/S1470-2045 (15)00223-5
4. Alkire BC, Raykar NP, Shrime MG, Weiser TG, Bickler SW, Rose JA, et al. Global Access to Surgical Care: A Modelling Study. *Lancet Global Health* (2015) 3(6):e316–23. doi: 10.1016/S2214-109X(15)70115-4
5. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of Perioperative Anaesthetic and Analgesic Interventions on Oncological Outcomes: A Narrative Review. *Br J Anaesth* (2019) 123(2):135–50. doi: 10.1016/j.bja.2019.04.062
6. Beutler B. Innate Immunity: An Overview. *Mol Immunol* (2004) 40 (12):845–59. doi: 10.1016/j.molimm.2003.10.005
7. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression. *Anesth Analg* (2017) 124(5):1697–708. doi: 10.1213/ANE.0000000000001652
8. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative Events Influence Cancer Recurrence Risk After Surgery. *Nat Rev Clin Oncol* (2018) 15 (4):205–18. doi: 10.1038/nrclinonc.2017.194
9. Malo-Manso A, Raigon-Ponferrada A, Diaz-Crespo J, Escalona-Belmonte JJ, Cruz-Manas J, Guerrero-Orriach JL. Opioid Free Anaesthesia and Cancer. *Curr Pharm Des* (2019) 25:3011–9. doi: 10.2174/1381612825666190705183754
10. Murthy BL, Thomson CS, Dodwell D, Shenoy H, Mikeljevic JS, Forman D, et al. Postoperative Wound Complications and Systemic Recurrence in Breast Cancer. *Br J Cancer* (2007) 97(9):1211–7. doi: 10.1038/sj.bjc.6604004
11. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune Modulation by Volatile Anesthetics. *Anesthesiology* (2016) 125(2):399–411. doi: 10.1097/ALN.0000000000001195
12. Yuki K, Eckenhoff RG. Mechanisms of the Immunological Effects of Volatile Anesthetics: A Review. *Anesth Analg* (2016) 123(2):326–35. doi: 10.1213/ANE.0000000000001403
13. Schneemilch CE, Ittenson A, Ansorge S, Hachenberg T, Bank U. Effect of 2 Anesthetic Techniques on the Postoperative Proinflammatory and Anti-Inflammatory Cytokine Response and Cellular Immune Function to Minor Surgery. *J Clin Anesth* (2005) 17:517–27. doi: 10.1016/j.jclinane.2004.12.017
14. Benzonana LL, Perry NJS, Watts HR, Yang B, Perry IA, Coombes C, et al. Isofluarane, a Commonly Used Volatile Anesthetic, Enhances Renal Cancer Growth and Malignant Potential *via* the Hypoxia-Inducible Factor Cellular Signaling Pathway *in Vitro*. *Anesthesiology* (2013) 119:593–605. doi: 10.1097/ALN.0b013e31829e47fd
15. Iwaskai M, Zhao H, Jaffer T, Unwith S, Benzonana LL, Lian Q, et al. Volatile Anaesthetics Enahance the Metastasis Related Cellular Signalling Including CXCR2 of Ovarian Cancer Cells. *Oncotarget* (2016) 7(18):26042–56. doi: 10.18632/oncotarget.8304
16. Luo X, Zhao H, Hennah L, Ning J, Liu J, Tu H, et al. Impact of Isoflurane on Malignant Capability of Ovarian Cancer *In Vitro*. *Br J Anaesth* (2015) 114(5):831–9. doi: 10.1093/bja/aeu408
17. Ciechanowicz S, Zhao H, Chen Q, Cui J, Mi E, Mi E, et al. Differential Effects of Sevoflurane on the Metastatic Potential and Chemosensitivity of Non-Small-Cell Lung Adenocarcinoma and Renal Cell Carcinoma *In Vitro*. *Br J Anaesth* (2018) 120(2):368–75. doi: 10.1016/j.bja.2017.11.066

18. Jiang S, Liu Y, Huang L, Zhang F, Kang R. Effects of Propofol on Cancer Development and Chemotherapy: Potential Mechanisms. *Eur J Pharmacol* (2018) 831:46–51. doi: 10.1016/j.ejphar.2018.04.009
19. Wang ZT, Gong HY, Zheng F, Liu DJ, Dong TL. Propofol Suppresses Proliferation and Invasion of Pancreatic Cancer Cells by Upregulating microRNA-133a Expression. *Genet Mol Res* (2015) 14(3):7529–37. doi: 10.4238/2015.July.3.28
20. Su Z, Hou XK, Wen QP. Propofol Induces Apoptosis of Epithelial Ovarian Cancer Cells by Upregulation of microRNS Let-7i Expression. *Eur J Gynaecol Oncol* (2014) 35(6):688–91.
21. Huang X, Teng Y, Yang H, Ma J. Propofol Inhibits Invasion and Growth of Ovarian Cancer Cells *via* Regulating miR-9/NF-kappaB Signal. *Braz J Med Biol Res* (2016) 49(12):e5717. doi: 10.1590/1414-431X20165717
22. Zhang J, Wu GQ, Zhang Y, Feng ZY, Zhu SM. Propofol Induces Apoptosis of Hepatocellular Carcinoma Cells by Upregulation of microRNA-199a Expression. *Cell Biol Int* (2013) 37(3):227–32. doi: 10.1002/cbin.10034
23. Zhang J, Zhang D, Wu G-Q, Feng Z-Y, Zhu S-M. Propofol Inhibits the Adhesion of Hepatocellular Carcinoma Cells by Upregulating microRNA-199a and Downregulating MMP-9 Expression. *Hepatobiliary Pancreatic Dis Int* (2013) 12(3):305–9. doi: 10.1016/S1499-3872(13)60048-X
24. Peng Z, Zhang Y. Propofol Inhibits Proliferation and Accelerates Apoptosis of Human Gastric Cancer Cells by Regulation of microRNA-451 and MMP-2 Expression. *Genet Mol Res* (2016) 15(2):1–9. doi: 10.4238/gmr.15027078
25. Xu J, Xu W, Zhu J. Propofol Suppresses Proliferation and Invasion of Glioma Cells by Upregulating microRNA-218 Expression. *Mol Med Rep* (2015) 12 (4):4815–20. doi: 10.3892/mmr.2015.4014
26. Ye Z, Jingzhong L, Yangbo L, Lei C, Jiandong Y. Propofol Inhibits Proliferation and Invasion of Osteosarcoma Cells by Regulation of microRNA-143 Expression. *Oncol Res* (2013) 21(4):201–7. doi: 10.3727/096504014X13890370410203
27. Wu KC, Yang ST, Hsia TC, Yang JS, Chiou SM, Lu CC, et al. Suppression of Cell Invasion and Migration by Propofol Are Involved in Down-Regulating Matrix Metalloproteinase-2 and P38 MAPK Signaling in A549 Human Lung Adenocarcinoma Epithelial Cells. *Anticancer Res* (2012) 32:4833–42.
28. Miao Y, Zhang Y, Wan H, Chen L, Wang F. GABA-Receptor Agonist, Propofol Inhibits Invasion of Colon Carcinoma Cells. *BioMed Pharmacother* (2010) 64(9):583–8. doi: 10.1016/j.biopha.2010.03.006
29. Xu YB, Du QH, Zhang MY, Yun P, He CY. Propofol Suppresses Proliferation, Invasion and Angiogenesis by Down-Regulating ERK-VEGF/MMP-9 Signaling in Eca-109 Esophageal Squamous Cell Carcinoma Cells. *Eur Rev Med Pharmacol Sci* (2013) 17:2486–94.
30. Xu YB, Jiang W, Zhao FR, Li G, Du QH, Zhang MY, et al. Propofol Suppresses Invasion and Induces Apoptosis of Osteosarcoma Cell *In Vitro via* Downregulation of TGF-β1 Expression. *Eur Rev Med Pharmacol Sci* (2016) 20:1430–5.
31. Ecimovic P, Murray D, Doran P, Buggy DJ. Propofol and Bupivacain in Breast Cancer Cell Function *in Vitro* - Role of the NET1 Gene. *Anticancer Res* (2014) 34:1321–32.
32. Garib V, Niggemann B, Zänker KS, Brandt L, Kubens BS. Influence of non-Volatile Anesthetics on the Migration Behavior of the Human Breast Cancer Cell Line MDA-MB-468. *Acta Anaesthesiol Scand* (2002) 46:836–44. doi: 10.1034/j.1399-6576.2002.460714.x
33. Garib V, Lang K, Niggemann B, Zänker KS, Brandt L, Dittmar T. Propofol-Induced Calcium Signalling and Actin Reorganization Within Breast Carcinoma Cells. *Eur J Anaesthesiol* (2005) 22(8):609–15. doi: 10.1017/S026502150500102X
34. Meng C, Song L, Wang J, Li D, Liu Y, Cui X. Propofol Induces Proliferation Partially *via* Downregulation of P53 Protein and Promotes Migration *via* Activation of the Nrf2 Pathway in Human Breast Cancer Cell Line MDA-MB-231. *Oncol Rep* (2017) 37(2):841–8. doi: 10.3892/or.2016.5332
35. Wang P, Chen J, Mu LH, Du QH, Niu XH, Zhang MY. Propofol Inhibits Invasion and Enhances Paclitaxel-Induced Apoptosis in Ovarian Cancer Cells Through the Suppression of the Transcription Factor Slug. *Eur Rev Med Pharmacol Sci* (2013) 17:1722–9.
36. Du QH, Xu YB, Zhang MY, Yun P, He CY. Propofol Induces Apoptosis and Increases Gemcitabine Sensitivity in Pancreatic Cancer Cells *In Vitro* by Inhibition of Nuclear factor-kappaB Activity. *World J Gastroenterol* (2013) 19(33):5485–92. doi: 10.3748/wjg.v19.i33.5485
37. Li H, Lu Y, Pang Y, Li M, Cheng X, Chen J. Propofol Enhances the Cisplatin-Induced Apoptosis on Cervical Cancer Cells *via* EGFR/JAK2/STAT3 Pathway. *BioMed Pharmacother* (2017) 86:324–33. doi: 10.1016/j.biopha.2016.12.036
38. Zhang Y, Wang X, Wang Q, Ge H, Tao L. Propofol Depresses Cisplatin Cytotoxicity *via* the Inhibition of Gap Junctions. *Mol Med Rep* (2016) 13 (6):4715–20. doi: 10.3892/mmr.2016.5119
39. Cui WY, Liu Y, Zhu YQ, Song T, Wang QS. Propofol Induces Endoplasmic Reticulum (ER) Stress and Apoptosis in Lung Cancer Cell H460. *Tumour Biol* (2014) 35(6):5213–7. doi: 10.1007/s13277-014-1677-7
40. Kushida A, Inada T, Shingu K. Enhancement of Antitumor Immunity After Propofol Treatment in Mice. *Immunopharmacol Immunotoxicol* (2007) 29 (3-4):477–86. doi: 10.1080/08923970701675085
41. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, et al. Prostate Cancer Cell Malignancy *via* Modulation of HIF-1alpha Pathway With Isoflurane and Propofol Alone and in Combination. *Br J Cancer* (2014) 111(7):1338–49. doi: 10.1038/bjc.2014.426
42. Jaura AI, Flood G, Gallagher HC, Buggy DJ. Differential Effects of Serum From Patients Administered Distinct Anaesthetic Techniques on Apoptosis in Breast Cancer Cells *In Vitro*: A Pilot Study. *Br J Anaesth* (2014) 113 Suppl 1:i63–7. doi: 10.1093/bja/aet581
43. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of Anaesthetic Technique on the Natural Killer Cell Anti-Tumour Activity of Serum From Women Undergoing Breast Cancer Surgery: A Pilot Study. *Br J Anaesth* (2014) 113 Suppl 1:i56–62. doi: 10.1093/bja/aeu200
44. Lim JA, Oh CS, Yoon TG, Lee JY, Lee SH, Yoo YB, et al. The Effect of Propofol and Sevoflurane on Cancer Cell, Natural Killer Cell, and Cytotoxic T Lymphocyte Function in Patients Undergoing Breast Cancer Surgery: An *In Vitro* Analysis. *BMC Cancer* (2018) 18(1):159. doi: 10.1186/s12885-018-4064-8
45. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, But Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth Analg* (2003) 97(5):1331–9. doi: 10.1213/01.ANE.0000082995.44040.07
46. Zheng X, Wang Y, Dong L, Zhao S, Wang L, Chen H, et al. Effects of Propofol-Based Total Intravenous Anesthesia on Gastric Cancer: A Retrospective Study. *Onco Targets Ther* (2018) 11:1141–8. doi: 10.2147/OTT.S156792
47. Wu ZF, Lee MS, Wong CS, Lu CH, Huang YS, Lin KT, et al. Propofol-Based Total Intravenous Anesthesia Is Associated With Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology* (2018) 129 (5):932–41. doi: 10.1097/ALN.0000000000002357
48. Enlund M, Berglund A, Ahlstrand R, Wallden J, Lundberg J, Warnberg F, et al. Survival After Primary Breast Cancer Surgery Following Propofol or Sevoflurane General Anesthesia-A Retrospective, Multicenter, Database Analysis of 6305 Swedish Patients. *Acta Anaesthesiol Scand* (2020) 64 (8):1048–54. doi: 10.1111/aas.13644
49. Jun IJ, Jo JY, Kim JI, Chin JH, Kim WJ, Kim HR, et al. Impact of Anesthetic Agents on Overall and Recurrence-Free Survival in Patients Undergoing Esophageal Cancer Surgery: A Retrospective Observational Study. *Sci Rep* (2017) 7(1):14020. doi: 10.1038/s41598-017-14147-9
50. Lai HC, Lee MS, Lin C, Lin KT, Huang YH, Wong CS, et al. Propofol-Based Total Intravenous Anaesthesia is Associated With Better Survival Than Desflurane Anaesthesia in Hepatectomy for Hepatocellular Carcinoma: A Retrospective Cohort Study. *Br J Anaesth* (2019) 123(2):151–60. doi: 10.1016/j.bja.2019.04.057
51. Wigmore TJ, Mohammed K, Jhanji S. Long-Term Survival for Patients Undergoing Volatile Versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* (2016) 124(1):69–79. doi: 10.1097/ALN.0000000000000936
52. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of Propofol-Based Total Intravenous Anesthesia on Recurrence and Overall Survival in Patients After Modified Radical Mastectomy: A Retrospective Study. *Korean J Anesthesiol* (2016) 69(2):126–32. doi: 10.4097/kjae.2016.69.2.126
53. Hasselager RP, Hallas J, Gogenur I. Inhalation or Total Intravenous Anaesthesia and Recurrence After Colorectal Cancer Surgery: A

Propensity Score Matched Danish Registry-Based Study. *Br J Anaesth* (2021) 126(5):921–30. doi: 10.1016/j.bja.2020.11.019
54. Oh TK, Kim K, Jheon S, Lee J, Do SH, Hwang JW, et al. Long-Term Oncologic Outcomes for Patients Undergoing Volatile Versus Intravenous Anesthesia for Non-Small Cell Lung Cancer Surgery: A Retrospective Propensity Matching Analysis. *Cancer Control* (2018) 25 (1):1073274818775360. doi: 10.1177/1073274818775360
55. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, et al. Total Intravenous Anesthesia Versus Inhalation Anesthesia for Breast Cancer Surgery: A Retrospective Cohort Study. *Anesthesiology* (2019) 130(1):31–40. doi: 10.1097/ALN.0000000000002491
56. Kim MH, Kim DW, Kim JH, Lee KY, Park S, Yoo YC. Does the Type of Anesthesia Really Affect the Recurrence-Free Survival After Breast Cancer Surgery? *Oncotarget* (2017) 8(52):90477–87. doi: 10.18632/oncotarget.21014
57. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The Choice of Anaesthetic–Sevoflurane or Propofol–and Outcome From Cancer Surgery: A Retrospective Analysis. *Ups J Med Sci* (2014) 119(3):251–61. doi: 10.3109/03009734.2014.922649
58. Oh CS, Lee J, Yoon TG, Seo EH, Park HJ, Piao L, et al. Effect of Equipotent Doses of Propofol Versus Sevoflurane Anesthesia on Regulatory T Cells After Breast Cancer Surgery. *Anesthesiology* (2018) 129(5):921–31. doi: 10.1097/ALN.0000000000002382
59. O'Bryan LJ, Atkins KJ, Lipszyc A, Scott DA, Silbert BS, Evered LA. Inflammatory Biomarker Levels After Propofol or Sevoflurane Anesthesia: A Meta-Analysis. *Anesth Analg* (2022) 134(1):69–81. doi: 10.1213/ANE.0000000000005671
60. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B, Global Onco-Anesthesia Research Collaboration Group. Anesthetic Technique and Cancer Outcomes: A Meta-Analysis of Total Intravenous Versus Volatile Anesthesia. *Can J Anaesth* (2019) 66(5):546–61. doi: 10.1007/s12630-019-01330-x
61. Page GG, Blakely WP, Ben-Eliyahu S. Evidence That Postoperative Pain is a Mediator of the Tumor-Promoting Effects of Surgery in Rats. *Pain* (2001) 90 (1-2):191–9. doi: 10.1016/S0304-3959(00)00403-6
62. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment With Methylnaltrexone Is Associated With Increased Survival in Patients With Advanced Cancer. *Ann Oncol* (2016) 27(11):2032–8. doi: 10.1093/annonc/mdw317
63. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The Novel Role of the Mu Opioid Receptor in Lung Cancer Progression: A Laboratory Investigation. *Anesth Analg* (2011) 112 (3):558–67. doi: 10.1213/ANE.0b013e31820568af
64. Bimonte S, Barbieri A, Cascella M, Rea D, Palma G, Del Vecchio V, et al. The Effects of Naloxone on Human Breast Cancer Progression: *In Vitro* and *In Vivo* Studies on MDA.MB231 Cells. *Onco Targets Ther* (2018) 11:185–91. doi: 10.2147/OTT.S145780
65. Tegeder I, Grosch S, Schmidtko A, Haussler A, Schmidt H, Niederberger E, et al. G Protein-Independent G1 Cell Cycle Block and Apoptosis With Morphine in Adenocarcinoma Cells: Involvement of P53 Phosphorylation. *Cancer Res* (2003) 63:1846–52.
66. Harimayaa Y, Koizumia K, Andohb T, Nojimab H, Kuraishib Y, Saiki I. Potential Ability of Morphine to Inhibit the Adhesion, Invasion and Metastasis of Metastatic Colon 26-L5 Carcinoma Cells. *Cancer Lett* (2002) 187:121–7. doi: 10.1016/S0304-3835(02)00360-9
67. Sasamura T, Nakamura S, Iida Y, Fujii H, Murata J, Saiki I, et al. Morphine Analgesia Suppresses Tumor Growth and Metastasis in a Mouse Model of Cancer Pain Produced by Orthotopic Tumor Inoculation. *Eur J Pharmacol* (2002) 441:185–91. doi: 10.1016/S0014-2999(02)01450-4
68. Koodie L, Yuan H, Pumper JA, Yu H, Charboneau R, Ramkrishnan S, et al. Morphine Inhibits Migration of Tumor-Infiltrating Leukocytes and Suppresses Angiogenesis Associated With Tumor Growth in Mice. *Am J Pathol* (2014) 184(4):1073–84. doi: 10.1016/j.ajpath.2013.12.019
69. Afsharimani B, Baran J, Watanabe S, Lindner D, Cabot PJ, Parat MO. Morphine and Breast Tumor Metastasis: The Role of Matrix-Degrading Enzymes. *Clin Exp Metastasis* (2014) 31(2):149–58. doi: 10.1007/s10585-013-9616-3
70. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, et al. Morphine Stimulates Angiogenesis by Activating Proangiogenic and Survival-Promoting Signaling and Promotes Breast Tumor Growth. *Cancer Res* (2002) 62:4491–8.
71. Ishikawa M, Tanno K, Kamo A, Takayanagi Y, Sasaki K. Enhancement of Tumor Growth by Morphine and its Possible Mechanism in Mice. *Biol Pharm Bull* (1993) 16(8):762–6. doi: 10.1248/bpb.16.762
72. Gach K, Szemraj J, Wyrebska A, Janecka A. The Influence of Opioids on Matrix Metalloproteinase-2 and -9 Secretion and mRNA Levels in MCF-7 Breast Cancer Cell Line. *Mol Biol Rep* (2011) 38(2):1231–6. doi: 10.1007/s11033-010-0222-z
73. Bimonte S, Barbieri A, Palma G, Arra C. The Role of Morphine in Animal Models of Human Cancer: Does Morphine Promote or Inhibit the Tumor Growth? *BioMed Res Int 2013* (2013) p:258141. doi: 10.1155/2013/258141
74. Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional Expression of Mu-Opioid Receptors in the Human Colon Cancer Cell Line, HT-29, and Their Localization in Human Colon. *Dig Dis Sci* (2008) 53(2):461–6. doi: 10.1007/s10620-007-9897-y
75. Hooijmans CR, Geessink FJ, Ritskes-Hoitinga M, Scheffer GJ. A Systematic Review and Meta-Analysis of the Ability of Analgesic Drugs to Reduce Metastasis in Experimental Cancer Models. *Pain* (2015) 156(10):1835–44. doi: 10.1097/j.pain.0000000000000296
76. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, et al. Opioids and Breast Cancer Recurrence: A Danish Population-Based Cohort Study. *Cancer* (2015) 121(19):3507–14. doi: 10.1002/cncr.29532
77. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. *Lancet* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X
78. Falk W, Magnuson A, Eintrei C, Henningsson R, Myrelid P, Matthiessen P, et al. Comparison Between Epidural and Intravenous Analgesia Effects on Disease-Free Survival After Colorectal Cancer Surgery: A Randomised Multicentre Controlled Trial. *Br J Anaesth* (2021) 127(1):65–74. doi: 10.1016/j.bja.2021.04.002
79. Diaz-Cambronero O, Mazzinari G, Cata JP. Perioperative Opioids and Colorectal Cancer Recurrence: A Systematic Review of the Literature. *Pain Manag* (2018) 8(5):353–61. doi: 10.2217/pmt-2018-0029
80. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid Requirement, Opioid Receptor Expression, and Clinical Outcomes in Patients With Advanced Prostate Cancer. *Cancer* (2013) 119(23):4103–10. doi: 10.1002/cncr.28345
81. Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A Retrospective Analysis of the Effect of Intraoperative Opioid Dose on Cancer Recurrence After Non-Small Cell Lung Cancer Resection. *Cancer Med* (2014) 3(4):900–8. doi: 10.1002/cam4.236
82. Connolly JG, Tan KS, Mastrogiacomo B, Dycoco J, Caso R, Jones GD, et al. Intraoperative Opioid Exposure, Tumour Genomic Alterations, and Survival Differences in People With Lung Adenocarcinoma. *Br J Anaesth* (2021) 127 (1):75–84. doi: 10.1016/j.bja.2021.03.030
83. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence. *Anesthesiology* (2008) 109:180–7. doi: 10.1097/ALN.0b013e31817f5b73
84. Xu YJ, Li SY, Cheng Q, Chen WK, Wang SL, Ren Y, et al. Effects of Anaesthesia on Proliferation, Invasion and Apoptosis of LoVo Colon Cancer Cells *In Vitro*. *Anaesthesia* (2016) 71(2):147–54. doi: 10.1111/anae.13331
85. Siekmann W, Eintrei C, Magnuson A, Sjolander A, Matthiessen P, Myrelid P, et al. Surgical and Not Analgesic Technique Affects Postoperative Inflammation Following Colorectal Cancer Surgery: A Prospective, Randomized Study. *Colorectal Dis* (2017) 19(6):O186–95. doi: 10.1111/codi.13643
86. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI, et al. Perioperative Epidural Analgesia for Major Abdominal Surgery for Cancer and Recurrence-Free Survival: Randomised Trial. *BMJ* (2011) 342:d1491. doi: 10.1136/bmj.d1491
87. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival Analysis of Patients With Breast Cancer Undergoing a Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: A 5-Year Follow-Up of a Randomized Controlled Trial. *Anticancer Res* (2017) 37 (10):5813–20. doi: 10.21873/anticanres.12024
88. Fant F, Tina E, Sandblom D, Andersson SO, Magnuson A, Hultgren-Hornkvist E, et al. Thoracic Epidural Analgesia Inhibits the Neuro-

Hormonal But Not the Acute Inflammatory Stress Response After Radical Retropubic Prostatectomy. *Br J Anaesth* (2013) 110(5):747–57. doi: 10.1093/bja/aes491
89. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic Techniques for Risk of Malignant Tumour Recurrence. *Cochrane Database Syst Rev* (2014) 11:1–61. doi: 10.1002/14651858.CD008877.pub2
90. Grandhi RK, Lee S, Abd-Elsayed A. The Relationship Between Regional Anesthesia and Cancer: A Metaanalysis. *Ochsner J* (2017) 17(4):345–61.
91. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-Term Survival After Colon Cancer Surgery: A Variation Associated With Choice of Anesthesia. *Anesth Analg* (2008) 107(1):325–32. doi: 10.1213/ane.0b013e3181770f55
92. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major Abdominal Surgery for Cancer: Does Epidural Analgesia Have a Long-Term Effect on Recurrence-Free and Overall Survival? *Ann Fr Anesth Reanim* (2013) 32 (5):e81–8. doi: 10.1016/j.annfar.2013.02.027
93. Exadactylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis? *Anesthesiology* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008
94. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The Effect of Neuraxial Anesthesia on Cancer Recurrence and Survival After Cancer Surgery: An Updated Meta-Analysis. *Oncotarget* (2016) 7(12):15262–73. doi: 10.18632/oncotarget.7683
95. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-Analysis of Intravenous Lidocaine and Postoperative Recovery After Abdominal Surgery. *Br J Surg* (2008) 95(11):1331–8. doi: 10.1002/bjs.6375
96. Vigneault L, Turgeon AF, Cote D, Lauzier F, Zarychanski R, Moore L, et al. Perioperative Intravenous Lidocaine Infusion for Postoperative Pain Control: A Meta-Analysis of Randomized Controlled Trials. *Can J Anaesth* (2011) 58(1):22–37. doi: 10.1007/s12630-010-9407-0
97. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Continuous Intravenous Perioperative Lidocaine Infusion for Postoperative Pain and Recovery. *Cochrane Database Syst Rev* (2015) 7: CD009642. doi: 10.1002/14651858.CD009642.pub2
98. Li R, Xiao C, Liu H, Huang Y, Dilger JP, Lin J. Effects of Local Anesthetics on Breast Cancer Cell Viability and Migration. *BMC Cancer* (2018) 18(1):666. doi: 10.1186/s12885-018-4576-2
99. Xuan W, Zhao H, Hankin J, Chen L, Yao S, Ma D. Local Anesthetic Bupivacaine Induced Ovarian and Prostate Cancer Apoptotic Cell Death and Underlying Mechanisms *In Vitro*. *Sci Rep* (2016) 6:26277. doi: 10.1038/srep26277
100. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells *In Vitro* and in a Xenograft Model *In Vivo*. *Anesthesiology* (2017) 126(5):868–81. doi: 10.1097/ALN.0000000000001528
101. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, et al. Antitumor Effects of Lidocaine on Human Breast Cancer Cells: An *In Vitro* and *In Vivo* Experimental Trial. *Anticancer Res* (2018) 38 (1):95–105. doi: 10.21873/anticanres.12196
102. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Ketamine-Xylazine Anaesthesia for Breast Tumour Resection in a Murine Model. *Br J Anaesth* (2018) 121(1):76–85. doi: 10.1016/j.bja.2017.12.043
103. Greenwood E, Nimmo S, Paterson H, Homer N, Foo I. Intravenous Lidocaine Infusion as a Component of Multimodal Analgesia for Colorectal Surgery-Measurement of Plasma Levels. *Perioper Med (Lond)* (2019) 8:1. doi: 10.1186/s13741-019-0112-4
104. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory Response, Immunosuppression, and Cancer Recurrence After Perioperative Blood Transfusions. *Br J Anaesth* (2013) 110(5):690–701. doi: 10.1093/bja/aet068
105. Atzil S, Arad M, Glasner A, Abiri N, Avraham R, Greenfeld K, et al. Blood Transfusion Promotes Cancer Progression: A Critical Role for Aged Erythrocytes. *Anesthesiology* (2008) 109(6):989–97. doi: 10.1097/ALN.0b013e31818ddb72
106. Hod EA, Zhang N, Sokol SA, Wojczyk BS, Francis RO, Ansaldi D, et al. Transfusion of Red Blood Cells After Prolonged Storage Produces Harmful Effects That are Mediated by Iron and Inflammation. *Blood* (2010) 115 (21):4284–92. doi: 10.1182/blood-2009-10-245001
107. Amato A, Pescatori M. Perioperative Blood Transfusions for the Recurrence of Colorectal Cancer. *Cochrane Database Syst Rev* (2006) 1):CD005033. doi: 10.1002/14651858.CD005033.pub2
108. Li SL, Ye Y, Yuan XH. Association Between Allogeneic or Autologous Blood Transfusion and Survival in Patients After Radical Prostatectomy: A Systematic Review and Meta-Analysis. *PloS One* (2017) 12(1):e0171081. doi: 10.1371/journal.pone.0171081
109. Agnes A, Lirosi MC, Panunzi S, Santocchi P, Persiani R, D'Ugo D. The Prognostic Role of Perioperative Allogeneic Blood Transfusions in Gastric Cancer Patients Undergoing Curative Resection: A Systematic Review and Meta-Analysis of non-Randomized, Adjusted Studies. *Eur J Surg Oncol* (2018) 44(4):404–19. doi: 10.1016/j.ejso.2018.01.006
110. Cata JP, Lasala J, Pratt G, Feng L, Shah JB. Association Between Perioperative Blood Transfusions and Clinical Outcomes in Patients Undergoing Bladder Cancer Surgery: A Systematic Review and Meta-Analysis Study. *J Blood Transfus* (2016) 2016:9876394. doi: 10.1155/2016/9876394
111. Yusup G, Akutsu Y, Mutallip M, Qin W, Hu X, Komatsu-Akimoto A, et al. A COX-2 Inhibitor Enhances the Antitumor Effects of Chemotherapy and Radiotherapy for Esophageal Squamous Cell Carcinoma. *Int J Oncol* (2014) 44(4):1146–52. doi: 10.3892/ijo.2014.2300
112. Muraki C, Ohga N, Hida Y, Nishihara H, Kato Y, Tsuchiya K, et al. Cyclooxygenase-2 Inhibition Causes Antiangiogenic Effects on Tumor Endothelial and Vascular Progenitor Cells. *Int J Cancer* (2012) 130(1):59–70. doi: 10.1002/ijc.25976
113. Kashiwagi E, Shiota M, Yokomizo A, Itsumi M, Inokuchi J, Uchiumi T, et al. Prostaglandin Receptor EP3 Mediates Growth Inhibitory Effect of Aspirin Through Androgen Receptor and Contributes to Castration Resistance in Prostate Cancer Cells. *Endocr Relat Cancer* (2013) 20(3):431–41. doi: 10.1530/ERC-12-0344
114. Chang J, Vacher J, Bing Y, Fan X, Zhang B, Harris RC, et al. Prostaglandin E Receptor 4 (EP4) Promotes Colonic Tumorigenesis. *Oncotarget* (2015) 6 (32):33500–11. doi: 10.18632/oncotarget.5589
115. Sui W, Zhang Y, Wang Z, Wang Z, Jia Q, Wu L, et al. Antitumor Effect of a Selective COX-2 Inhibitor, Celecoxib, may be Attributed to Angiogenesis Inhibition Through Modulating the PTEN/PI3K/Akt/HIF-1 Pathway in an H(2)(2) Murine Hepatocarcinoma Model. *Oncol Rep* (2014) 31(5):2252–60. doi: 10.3892/or.2014.3093
116. Veitonmäkia T, Tammelabc TLJ, Auvinena A, Murtola TJ. Use of Aspirin, But Not Other non-Steroidal Anti-Inflammatory Drugs is Associated With Decreased Prostate Cancer Risk at the Population Level. *Eur J Cancer* (2013) 49(4):938–45. doi: 10.1016/j.ejca.2012.09.030
117. Choe KS, Cowan JE, Chan JM, Carroll PR, D'Amico AV, Liauw SL. Aspirin Use and the Risk of Prostate Cancer Mortality in Men Treated With Prostatectomy or Radiotherapy. *J Clin Oncol* (2012) 30(28):3540–4. doi: 10.1200/JCO.2011.41.0308
118. Cathcart MC, O'Byrne KJ, Reynolds JV, O'Sullivan J, Pidgeon GP. COX-Derived Prostanoid Pathways in Gastrointestinal Cancer Development and Progression: Novel Targets for Prevention and Intervention. *Biochim Biophys Acta* (2012) 1825(1):49–63. doi: 10.1016/j.bbcan.2011.09.004
119. Piazuelo E, Lanas A. NSAIDS and Gastrointestinal Cancer. *Prostaglandins Other Lipid Mediat* (2015) 120:91–6. doi: 10.1016/j.prostaglandins.2015.06.001
120. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Breazna A, Kim K, et al. Five-Year Efficacy and Safety Analysis of the Adenoma Prevention With Celecoxib Trial. *Cancer Prev Res (Phila)* (2009) 2(4):310–21. doi: 10.1158/1940-6207.CAPR-08-0206
121. Rigas B, Tsioulias GJ. The Evolving Role of Nonsteroidal Anti-Inflammatory Drugs in Colon Cancer Prevention: A Cause for Optimism. *J Pharmacol Exp Ther* (2015) 353(1):2–8. doi: 10.1124/jpet.114.220806
122. Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, et al. Aspirin and COX-2 Inhibitor Use in Patients With Stage III Colon Cancer. *J Natl Cancer Inst* (2015) 107(1):345. doi: 10.1093/jnci/dju345
123. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen P, Ejlertsen B, et al. Low-Dose Aspirin, Nonsteroidal Anti-Inflammatory Drugs, Selective COX-2 Inhibitors and Breast Cancer Recurrence. *Epidemiology* (2016) 27(4):586–93. doi: 10.1097/EDE.0000000000000480

124. Huang X, Gao P, Sun J, Song Y, Tsai C, Liu J, et al. Aspirin and Nonsteroidal Anti-Inflammatory Drugs After But Not Before Diagnosis are Associated With Improved Breast Cancer Survival: A Meta-Analysis. *Cancer Causes Control* (2015) 26:589–600. doi: 10.1007/s10552-015-0539-y
125. Retsky M, Rogers R, Demicheli R, Hrushesky WJ, Gukas I, Vaidya JS, et al. NSAID Analgesic Ketorolac Used Perioperatively may Suppress Early Breast Cancer Relapse: Particular Relevance to Triple Negative Subgroup. *Breast Cancer Res Treat* (2012) 134(2):881–8. doi: 10.1007/s10549-012-2094-5
126. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative Use of Ketorolac or Diclofenac is Associated With Improved Disease-Free Survival and Overall Survival in Conservative Breast Cancer Surgery. *Br J Anaesth* (2014) 113 Suppl 1:i82–7. doi: 10.1093/bja/aet464
127. Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, et al. Do Intraoperative Analgesics Influence Breast Cancer Recurrence After Mastectomy? A Retrospective Analysis. *Anesth Analg* (2010) 110(6):1630–5. doi: 10.1213/ANE.0b013e3181d2ad07
128. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, et al. Do Intraoperative Analgesics Influence Oncological Outcomes After Radical Prostatectomy for Prostate Cancer? *Eur J Anaesthesiol* (2011) 28(12):830–5. doi: 10.1097/EJA.0b013e32834b7d9a
129. Choi JE, Villarreal J, Lasala J, Gottumukkala V, Mehran RJ, Rice D, et al. Perioperative Neutrophil:Lymphocyte Ratio and Postoperative NSAID Use as Predictors of Survival After Lung Cancer Surgery: A Retrospective Study. *Cancer Med* (2015) 4(6):825–33. doi: 10.1002/cam4.428
130. Cata JP, Guerra CE, Chang GJ, Gottumukkala V, Joshi GP. Non-Steroidal Anti-Inflammatory Drugs in the Oncological Surgical Population: Beneficial or Harmful? A Systematic Review of the Literature. *Br J Anaesth* (2017) 119 (4):750–64. doi: 10.1093/bja/aex225
131. Kawaguchi J, Ota D, Niwa H, Sugo Y, Kushikata T, Hirota K. Immunomodulation by Ketamine as an Adjunct to Total Intravenous Anesthesia in Patients Undergoing Minimally Invasive Radical Prostatectomy: A Randomized Pilot Trial. *Mol Clin Oncol* (2020) 13 (2):203–8. doi: 10.3892/mco.2020.2060
132. Cho JS, Kim NY, Shim JK, Jun JH, Lee S, Kwak YL. The Immunomodulatory Effect of Ketamine in Colorectal Cancer Surgery: A Randomized-Controlled Trial. *Can J Anaesth* (2021) 68(5):683–92. doi: 10.1007/s12630-021-01925-3
133. Chen G, Le Y, Zhou L, Gong L, Li X, Li Y, et al. Dexmedetomidine Inhibits Maturation and Function of Human Cord Blood-Derived Dendritic Cells by Interfering With Synthesis and Secretion of IL-12 and IL-23. *PloS One* (2016) 11(4):e0153288. doi: 10.1371/journal.pone.0153288
134. Wang C, Datoo T, Zhao H, Wu L, Date A, Jiang C, et al. Midazolam and Dexmedetomidine Affect Neuroglioma and Lung Carcinoma Cell Biology *In Vitro* and *In Vivo*. *Anesthesiology* (2018) 129(5):1000–14. doi: 10.1097/ALN.0000000000002401
135. Szpunar MJ, Burke KA, Dawes RP, Brown EB, Madden KS. The Antidepressant Desipramine and Alpha2-Adrenergic Receptor Activation Promote Breast Tumor Progression in Association With Altered Collagen Structure. *Cancer Prev Res (Phila)* (2013) 6(12):1262–72. doi: 10.1158/1940-6207.CAPR-13-0079
136. Bruzzone A, Pinero CP, Castillo LF, Sarappa MG, Rojas P, Lanari C, et al. Alpha2-Adrenoceptor Action on Cell Proliferation and Mammary Tumour Growth in Mice. *Br J Pharmacol* (2008) 155(4):494–504. doi: 10.1038/bjp.2008.278
137. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine Promotes Metastasis in Rodent Models of Breast, Lung, and Colon Cancers. *Br J Anaesth* (2018) 120(1):188–96. doi: 10.1016/j.bja.2017.11.004
138. Su X, Fan Y, Yang L, Huang J, Qiao F, Fang Y, et al. Dexmedetomidine Expands Monocytic Myeloid-Derived Suppressor Cells and Promotes Tumour Metastasis After Lung Cancer Surgery. *J Transl Med* (2018) 16 (1):347. doi: 10.1186/s12967-018-1727-9
139. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, et al. Intraoperative Use of Dexmedetomidine is Associated With Decreased Overall Survival After Lung Cancer Surgery. *J Anaesthesiol Clin Pharmacol* (2017) 33(3):317–23. doi: 10.4103/joacp.JOACP_299_16
140. Yano A, Fujii Y, Iwai A, Kageyama Y, Kihara K. Glucocorticoids Suppress Tumor Angiogenesis and *In Vivo* Growth of Prostate Cancer Cells. *Clin Cancer Res* (2006) 12(10):3003–9. doi: 10.1158/1078-0432.CCR-05-2085
141. Nishimura K, Nonomura N, Satoh E, Harada Y, Nakayama M, Tokizane T, et al. Potential Mechanism for the Effects of Dexamethasone on Growth of Androgen-Independent Prostate Cancer. *J Natl Cancer Inst* (2001) 93 (22):1739–46. doi: 10.1093/jnci/93.22.1739
142. Arai Y, Nonomura N, Nakai Y, Nishimura K, Oka D, Shiba M, et al. The Growth-Inhibitory Effects of Dexamethasone on Renal Cell Carcinoma *In Vivo* and *In Vitro*. *Cancer Invest* (2008) 26(1):35–40. doi: 10.1080/07357900701638418
143. Liu L, Aleksandrowicz E, Schonsiegel F, Groner D, Bauer N, Nwaeburu CC, et al. Dexamethasone Mediates Pancreatic Cancer Progression by Glucocorticoid Receptor, TGFbeta and JNK/AP-1. *Cell Death Dis* (2017) 8 (10):e3064. doi: 10.1038/cddis.2017.455
144. Singh PP, Lemanu DP, Taylor MH, Hill AG. Association Between Preoperative Glucocorticoids and Long-Term Survival and Cancer Recurrence After Colectomy: Follow-Up Analysis of a Previous Randomized Controlled Trial. *Br J Anaesth* (2014) 113 Suppl 1:i68–73. doi: 10.1093/bja/aet577
145. McSorley ST, Dolan RD, Roxburgh CS, Horgan PG, MacKay GJ, McMillan DC. Possible Dose Dependent Effect of Perioperative Dexamethasone and Laparoscopic Surgery on the Postoperative Systemic Inflammatory Response and Complications Following Surgery for Colon Cancer. *Eur J Surg Oncol* (2019) 45(9):1613–8. doi: 10.1016/j.ejso.2019.05.020
146. McSorley ST, Roxburgh CSD, Horgan PG, McMillan DC. The Impact of Preoperative Dexamethasone on the Magnitude of the Postoperative Systemic Inflammatory Response and Complications Following Surgery for Colorectal Cancer. *Ann Surg Oncol* (2017) 24(8):2104–12. doi: 10.1245/s10434-017-5817-3
147. McSorley ST, Horgan PG, McMillan DC. The Impact of Preoperative Corticosteroids on the Systemic Inflammatory Response and Postoperative Complications Following Surgery for Gastrointestinal Cancer: A Systematic Review and Meta-Analysis. *Crit Rev Oncol Hematol* (2016) 101:139–50. doi: 10.1016/j.critrevonc.2016.03.011
148. Kim MH, Kim DW, Park S, Kim JH, Lee KY, Hwang J, et al. Single Dose of Dexamethasone is Not Associated With Postoperative Recurrence and Mortality in Breast Cancer Patients: A Propensity-Matched Cohort Study. *BMC Cancer* (2019) 19(1):251. doi: 10.1186/s12885-019-5451-5
149. Sandini M, Ruscic KJ, Ferrone CR, Warshaw AL, Qadan M, Eikermann M, et al. Intraoperative Dexamethasone Decreases Infectious Complications After Pancreaticoduodenectomy and is Associated With Long-Term Survival in Pancreatic Cancer. *Ann Surg Oncol* (2018) 25:4020–6. doi: 10.1245/s10434-018-6827-5
150. Evans SS, Repasky EA, Fisher DT. Fever and the Thermal Regulation of Immunity: The Immune System Feels the Heat. *Nat Rev Immunol* (2015) 15 (6):335–49. doi: 10.1038/nri3843
151. Hylander BL, Repasky EA. Thermoneutrality, Mice, and Cancer: A Heated Opinion. *Trends Cancer* (2016) 2(4):166–75. doi: 10.1016/j.trecan.2016.03.005
152. Sessler DI, Imrey PB. Clinical Research Methodology 1: Study Designs and Methodologic Sources of Error. *Anesth Analg* (2015) 121(4):1034–42. doi: 10.1213/ANE.0000000000000815

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Exploring Potential Regulatory Anesthetic Drugs Based on RNA Binding Protein and Constructing CESC Prognosis Model: A Study Based on TCGA Database

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Objective: To investigate the differential expression of RBPs in cervical squamous cell carcinoma (CESC), analyze the regulatory effect of narcotic drugs on RBPs, and establish the prognostic risk model of CESC patients.

Methods: RNA-SEQ data and clinical case data of cancer and normal samples from CESC patients were obtained from the Cancer Genome Atlas (TCGA) database and Genotype-Tissue Expression (GTEx) database. Differentially expressed RBPs were screened by R language and enriched. The CMAP database is used to predict the anesthetic drugs that regulate the differential expression of RBPs. The prognostic risk score model was constructed by COX regression analysis. Risk score of each CESC patient was calculated and divided into high-risk group and low-risk group according to the median risk score. The prediction efficiency of prognostic risk model was evaluated by Kaplan-Meier (KM) analysis and receiver operating characteristic (ROC) curve, and the correlation between prognostic risk model and clinical characteristics was analyzed. Immunohistochemistry was used to detect the expression of RNASEH2A and HENMT1 in tissues.

Results: There were 65 differentially expressed RBPs in CESC. Five anesthetics, including benzocaine, procaine, pentoxyverine, and tetracaine were obtained to regulate RBPs. Survival analysis showed that seven genes were related to the prognosis of patients, and the CESC risk score model was constructed by COX regression. The risk score can be used as an independent prognostic factor. RNASEH2A and HENMT1 are up-regulated in tumors, which can effectively distinguish normal tissues from tumor tissues.

Conclusion: It is found that different anesthetic drugs have different regulatory effects on the differential expression of RBPs. Based on the differentially expressed RBPs, the prognostic risk score model of CESC patients was constructed. To provide ideas for the formulation of individualized precise anesthesia scheme and cancer pain analgesia scheme, which is helpful to improve the perioperative survival rate of cancer patients.

Keywords: cervical squamous cell carcinoma (CESC), bioinformatics, narcotic drugs, predictors, risk score

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women in the world, with a high mortality rate among women in developing countries (1). As the most common tissue type of cervical cancer, cervical squamous cell carcinoma (CESC) is a serious threat to women's health, causing about 273,200 death every year (2). In recent years, with the development of cancer screening and various treatment methods such as surgery, radiotherapy and chemotherapy, the clinical prognosis of CESC has been improved to some extent. However, due to the lack of effective diagnostic methods in the early stage of the disease, the risk of metastasis and recurrence of CESC is still high and the prognosis is poor. More and more evidence shows that the abnormal expression of a variety of genes is involved in the occurrence and development of CESC (3–5). In view of the high incidence rate and high mortality rate of CESC, early detection and risk assessment are particularly important for improving the prognosis of CESC patients. Therefore, it is necessary and urgent to find new biomarkers for diagnosis, prognosis and treatment to improve the survival rate of cervical cancer patients. RNA binding proteins (RBPs) are proteins that interact with many types of RNA, including rRNAs, ncRNAs, snrnas, miRNAs, mRNAs, tRNAs and snoRNAs. So far, more than 1,500 RBPs genes have been found in the human genome (6). These RBPs play an important role in maintaining the physiological balance of cells, especially in the process of development and stress response. RBPs can bind to target RNA in a structure or sequence dependent manner to form RNA protein complexes, and regulate mRNA stability, RNA processing, splicing, localization, output and translation at the post transcriptional level (7). In the past decades, many studies have revealed that RBPs are abnormally expressed in tumors, affect the transformation of mRNA to protein, and participate in tumorigenesis (8–10). Among them, only a few RBPs have been deeply studied and found to play a key role in human cancer (11–13). The systematic functional study of RBPs will help us to fully understand its role in tumors.

Narcotic drugs are prescription drugs for the treatment of cancer pain. If they are used continuously, they will cause extreme physical and mental dependence, and can only be used in medical treatment and scientific research. Local anesthetics are commonly used for postoperative analgesia and local anesthesia at the surgical site of cancer patients. Local anesthesia includes intestinal nerve block, local infiltration anesthesia, surface anesthesia and so on. Studies have found that local anesthesia can reduce the stress response after surgery and reduce the inhibitory effect of stress response on the immune system (14). Local anesthesia can reduce the dosage of opinions, reduce the inhibition of opiate analgesics on the immune system, and play a certain role in tumor recurrence and metastasis. At the same time, intestinal nerve block combined with propofol can reduce interleukin (IL) 1 β/ IL-8, increase IL-10. IL-1 β/ IL-8 is considered to be a cytokine promoting tumor formation, and IL-10 is a cytokine inhibiting tumor formation (15). Local

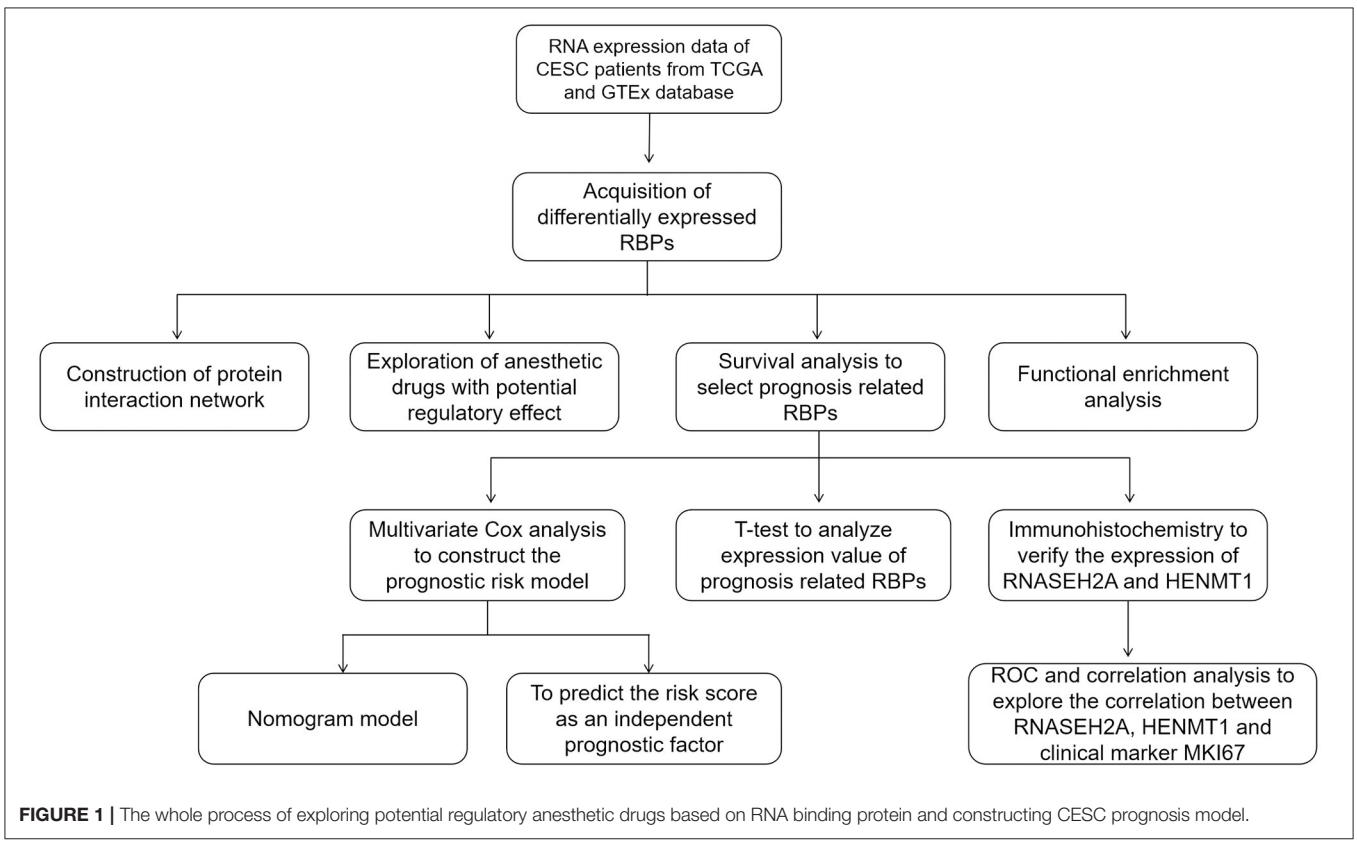

FIGURE 1 | The whole process of exploring potential regulatory anesthetic drugs based on RNA binding protein and constructing CESC prognosis model.

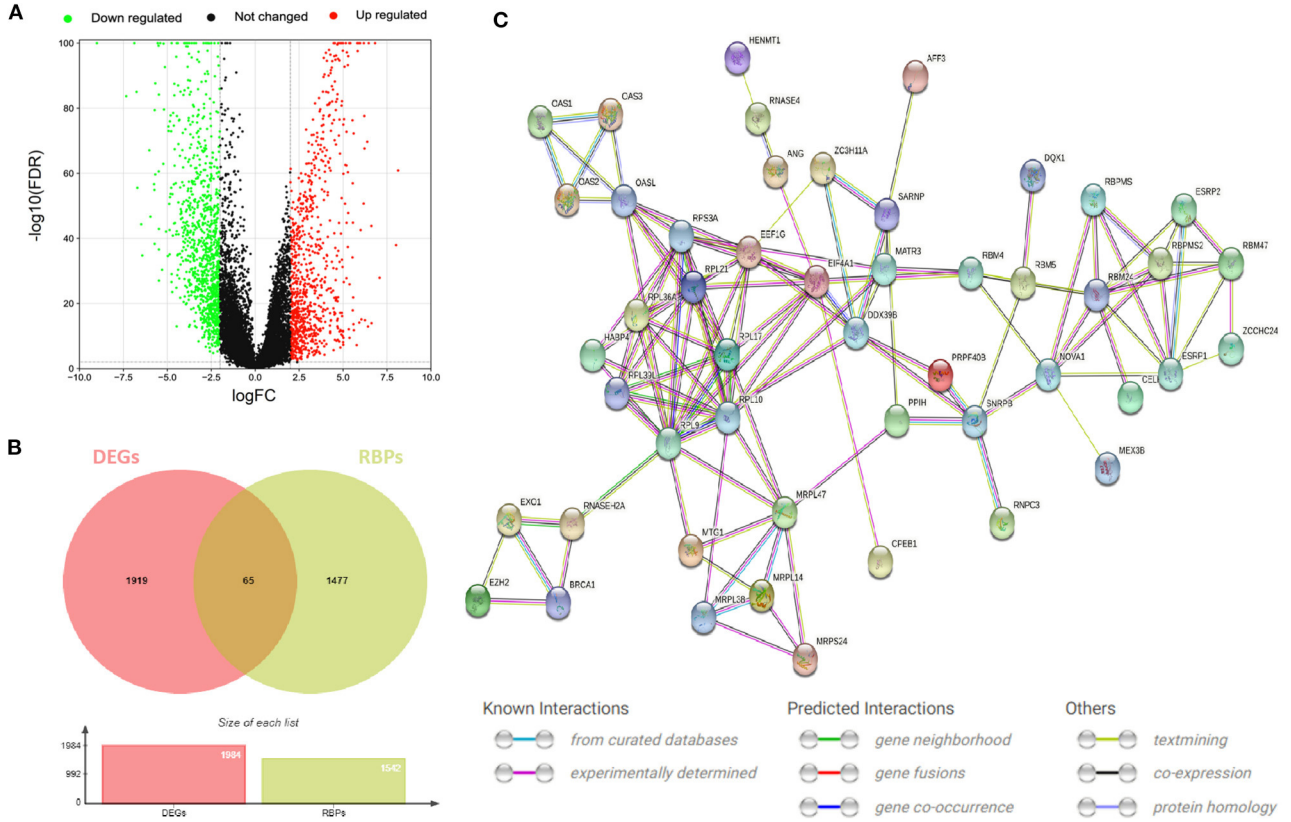

FIGURE 2 | RBPs differentially expressed in CESC. **(A)** Volcano map of DEGs differentially expressed between CESC and normal tissues. The selection criteria were |logFC| > 2 and FDR value <0.01 (red and green represent up-regulated and down-regulated genes, respectively). **(B)** Wayne diagram of differentially expressed RBPs in CESC. **(C)** Protein interaction network differentially expressing RBPs.

anesthetics are commonly used in the clinic. Local anesthesia is also a commonly used anesthesia technology in clinic. Some narcotic drugs inhibit tumor growth, invasion and metastasis. Other narcotic drugs promote tumor growth, invasion and metastasis. Their mechanism may be related to regulating the immune ability of the body to the tumor. So choosing different anesthetic drugs in different preoperative periods may have different effects on tumor recurrence and invasion, and directly affect the prognosis of surgical patients. Therefore, the effects of narcotic drugs on tumors and their related mechanisms need to be further studied and discussed.

Based on the above, the RNA sequencing and clinicopathological data of CESC were downloaded from the Cancer Genome Atlas (TCGA) database and Genotype-Tissue Expression (GTEX) database. Subsequently, abnormally expressed RBPs between CESC and normal cervical tissues were identified by high-throughput bioinformatics analysis, and their potential functions and molecular mechanisms were systematically explored. This study identified some RBPs that may affect the prognosis of CESC and promoted the understanding of the molecular mechanism of CESC progression. These RBPs may provide potential biomarkers for diagnosis and prognosis.

MATERIALS AND METHODS

Data Download and Processing

Three hundred and nine human cervical cancer gene expression samples were downloaded from TCGA database (https://portal.gdc.cancer.gov/), including 3 normal samples and 306 tumor samples, and the corresponding clinical information was provided. The data of the additional 19 normal tissue samples were from GTEx database (https://gtexportal.org/home/datasets). RBPs were collected by Merkley et al. (16) and a total of 1542 RBPs genes were obtained (**Supplementary Table 1**). The original data were preprocessed with limma software package, and the differentially expressed RBPs were included with error detection rate (FDR)< 0.01 and |logFC (foldchange)| > 2. Differentially expressed RBPs were submitted to the STRING database to identify protein-protein interaction information.

GO Enrichment and KEGG Pathway Analysis

The biological functions of these differentially expressed RBPs were comprehensively detected by Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. GO analysis terms include cellular

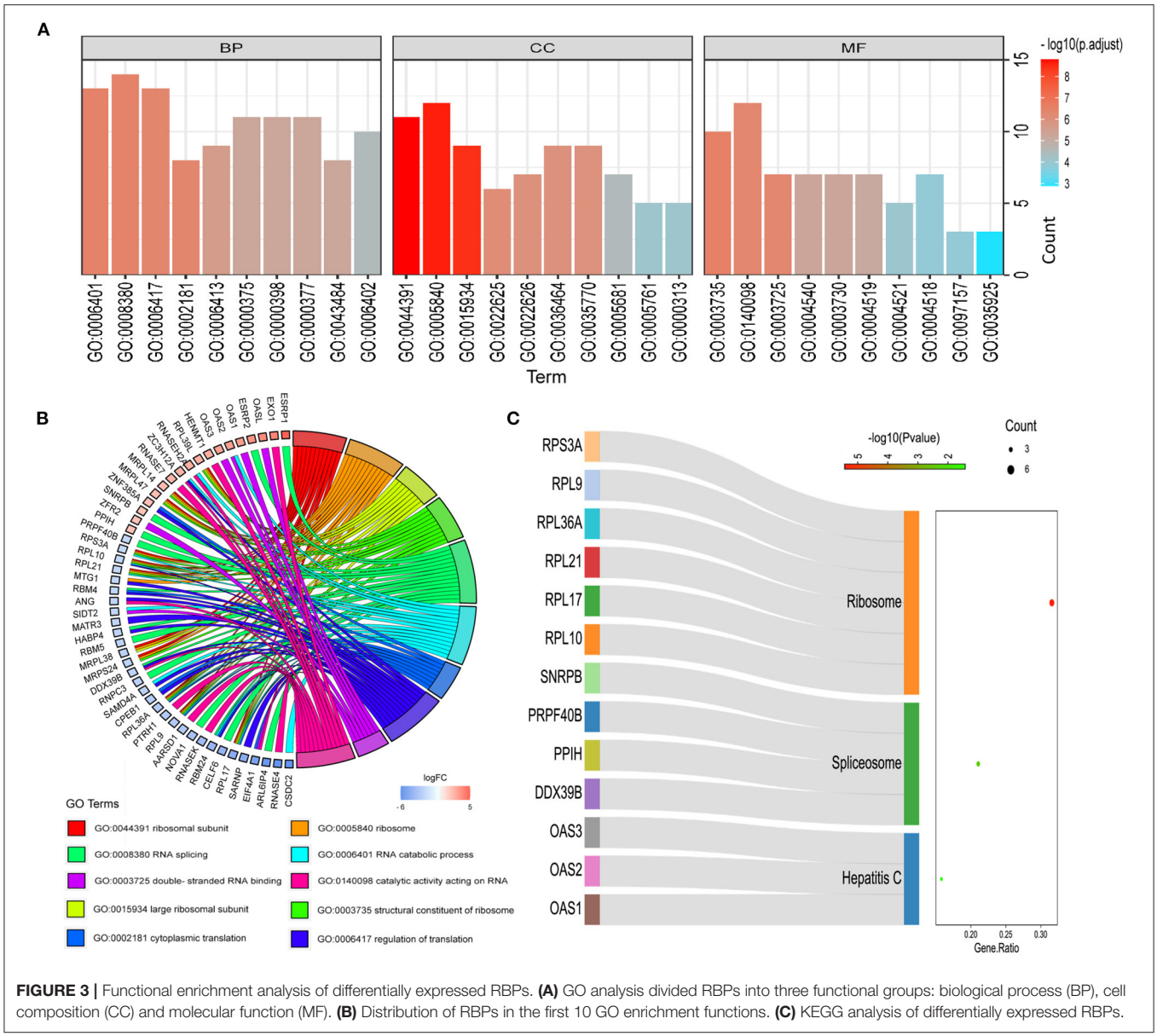

FIGURE 3 | Functional enrichment analysis of differentially expressed RBPs. **(A)** GO analysis divided RBPs into three functional groups: biological process (BP), cell composition (CC) and molecular function (MF). **(B)** Distribution of RBPs in the first 10 GO enrichment functions. **(C)** KEGG analysis of differentially expressed RBPs.

components (CC), molecular functions (MF), and biological processes (BP). R packages such as clusterProfiler and pathview are used for GO and KEGG pathway enrichment analysis. The difference was statistically significant (p.adjust < 0.05).

Exploration of Anesthetic Drugs With Potential Regulatory Effect

Connectivity map (CMAP) database was used to find anesthetic drugs that regulate the differential expression of RBPs. The database can use computer simulation methods to predict potential drugs that may induce or reverse biological states encoded by gene expression characteristics. Differentially expressed RBPs were classified into up-regulated group and down-regulated group and uploaded to CMAP database. The negative correlation score indicates that the drug inhibits the expression of up-regulated genes and promotes the expression of down-regulated genes, which may reverse the cancer process.

Screening of Prognostic Genes of RBPs and Construction of Prognostic Model

According to the amount of single gene expression, the median gene expression was used as the grouping method. Prognostic differences of different groups were analyzed by Kaplan-Meier survival analysis. *P*-value and hazard ratio (HR) with 95% confidence interval (CI) were obtained by log-rank test and univariate COX proportional hazards regression. Then, based on the differentially expressed RBPs related to prognosis, the risk score model was constructed by multivariate COX regression analysis, and the risk score was calculated. Calculation formula of prognosis model: riskscore = b1 × Exp1+ b2 × Exp2+

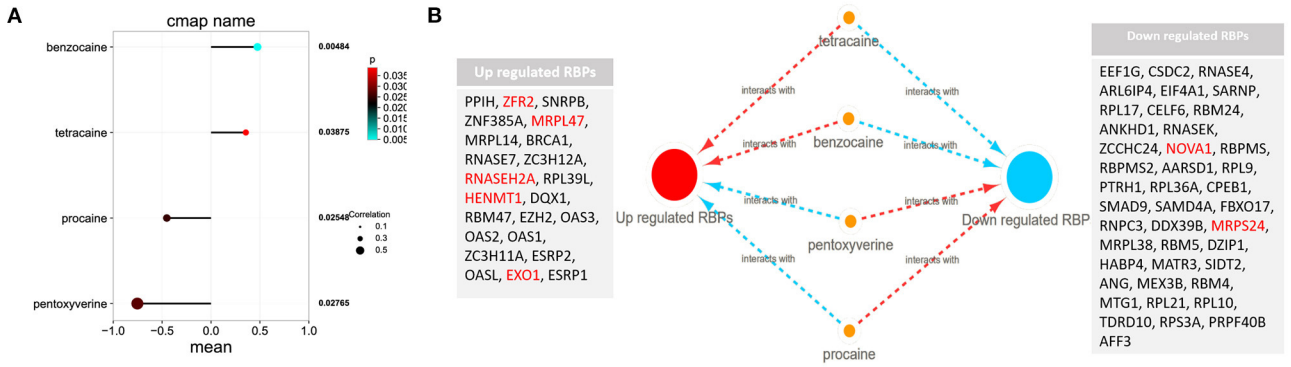

FIGURE 4 | Potential anesthetic drugs that regulate differentially expressed RBPs. **(A)** Regulatory relationship between narcotic drugs and differentially expressed RBPs. Mean indicates the regulatory relationship coefficient (>0 indicates a positive correlation with gene expression) **(B)** the relationship between narcotic drugs and up and down regulated RBPs. The red line represents promoting gene expression and the blue line represents inhibiting gene expression. EXO1, HENMT1, RNASEH2A, MRPL47, ZFR2, MRPS24 and NOVA1 are related to the prognosis of CESC.

bi × Expi. Among them b represents the coefficient value, and Exp represents the gene expression level. In order to verify the prognostic value of RBPs, the risk score of each CESC sample in TCGA-CESC data was calculated based on the formula. In each data set, the samples were divided into high-risk and low-risk groups by setting the median of risk score as the critical standard. Log-rank test was used to compare the difference in overall survival (OS) between the two groups. In addition, ROC curve analysis was performed using "survivalROC" package to evaluate the prediction ability of the above model. Finally, the nomogram was drawn using RMS package to predict the survival time of patients.

Correlation Analysis of Independent Prognosis and Clinical Characteristics of Model

Taking the mean value (46.89) as the boundary value, the age was divided into two groups < 47 years old and ≥47 years old. Age, gender, grade, stage, T stage and N stage were used as clinical classification variables. Chi square test was used to compare the differences between high and low risk groups. The difference was statistically significant ($P < 0.05$). Univariate and multivariate COX regression models were used to evaluate the relationship between clinical variables, risk score and prognosis, so as to judge whether the risk model can be used as an independent prognostic factor.

Expression of Model Genes in the Database

In order to determine the expression of model genes in cervical cancer, we used the expression data of cervical cancer and normal tissues in TCGA and GTEx databases to verify the gene expression. Student's *t*-test and Welch's *t*-test were used to analyze the difference of gene expression between cancer and normal tissues. Pearson test was used to analyze the correlation between genes. $P < 0.001$ was considered as significant correlation.

Immunohistochemistry Staining

With the approval of the hospital ethics committee, paraffin sections of surgically removed tissues of 150 patients with cervical cancer treated from 2017 to 2019 were collected from the pathology department of our hospital, including cervical cancer tissues and corresponding adjacent tissue sections. After paraffin embedding, it was continuously sliced and fixed with formaldehyde. After hydration, it was allowed to stand at 37.5°C for 0.5 h, and 1% Ethylene Diamine Tetraacetic Acid (EDTA) solution was added to block the goat serum. First antibody (1: 300 dilution) and second antibody were added successively, incubated at room temperature, and washed with PBS for 3 times. Add 50 drops per slice μl DAB developer freshly prepared and washed with running water. Counterstain with hematoxylin, dehydrate with alcohol, and seal the film with neutral balsam after drying. Light yellow to brownish yellow is positive. According to the staining intensity, it is divided into (0–1 points) negative, (1–2 points) weak positive, (2–3 points) moderate and (3–4 points) strong positive.

Correlation Analysis Between RNASEH2A, HENMT1 and Clinical Markers of Cervical Cancer

The correlation between RNASEH2A and HENMT1 and cervical cancer tumor marker (MKI67) was analyzed by GEPIA database. Immunohistochemical staining of RNASEH2A and HENMT1 was performed on microarrays constructed from cancer and adjacent tissues of 150 patients with cervical cancer. In the RNASEH2A protein expression microarray, 120 pairs of RNASEH2A expression tissue nodes of cancer and adjacent tissues were complete. In the HENMT1 protein expression microarray, 93 pairs of HENMT1 expression tissue

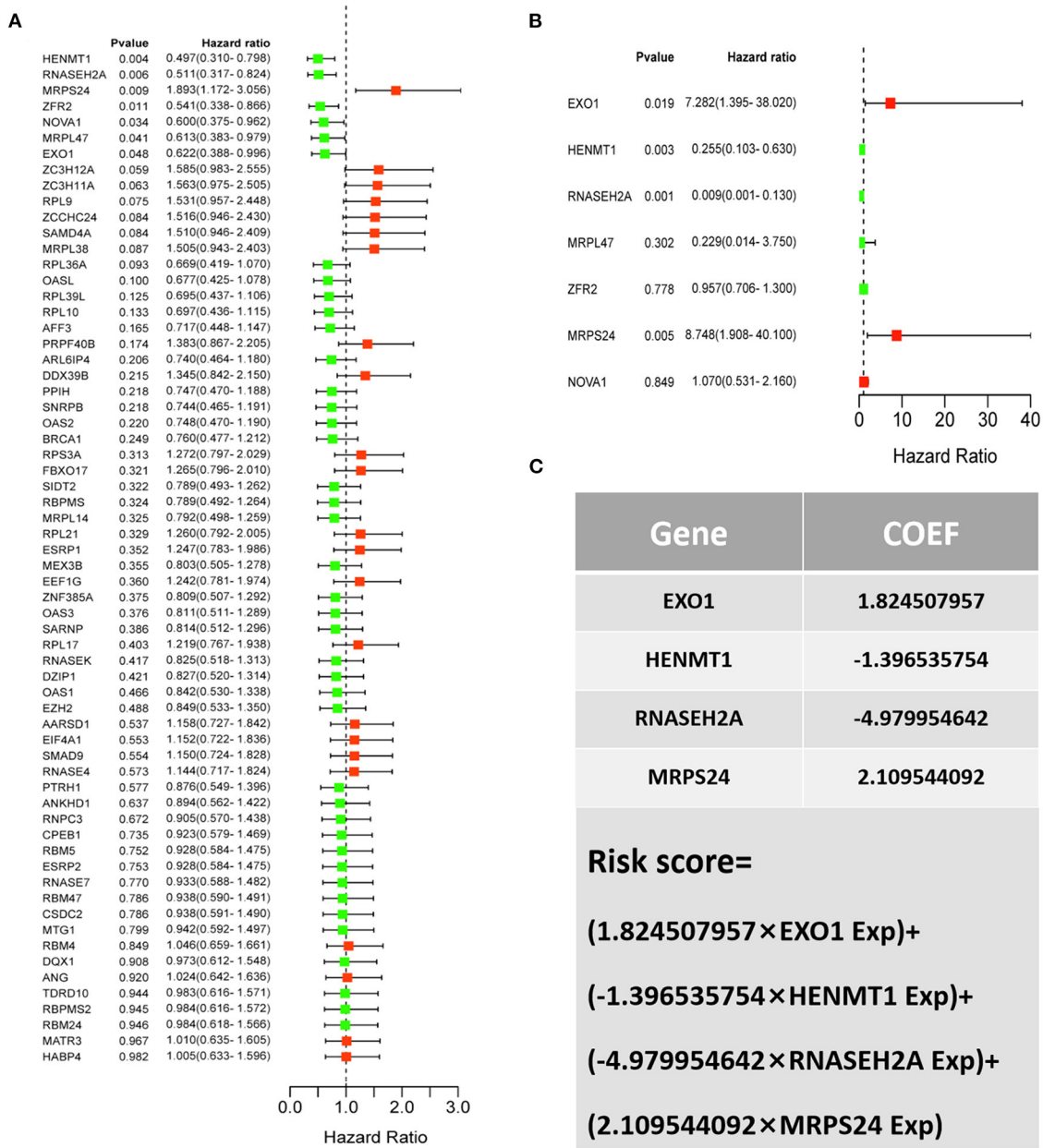

FIGURE 5 | CESC patient risk model based on prognosis related RBPs **(A)** Survival analysis was used to screen prognosis related RBP. **(B)** Multivariate prognostic analysis of seven prognosis related RBPs (EXO1, HENMT1, RNASEH2A, MRPL47, ZFR2, MRPS24 and NOVA1). **(C)** Calculation formula of comprehensive risk score of four genes. Exp stands for gene expression.

nodes of cancer and adjacent tissues were complete. Among 150 patients with cervical cancer, the results of MKI67 immunohistochemistry were collected from 115 patients. *T*-test was used to analyze the difference of gene expression between cancer and adjacent cancer. Correlation test is used to reflect the linear correlation between the expression of two genes. ROC curve was used to analyze the diagnostic effect of gene expression on cervical cancer.

RESULTS

RBPs in Differentially Expressed CESC Tissues Were Screened

The flow of this study is shown in **Figure 1**. The data obtained from TCGA and GTEx databases are processed by Perl and R language, and 1984 DEGs (**Figure 2A**) are obtained by "limma" package analysis, including 65 RBPs (**Figure 2B**). RBPs

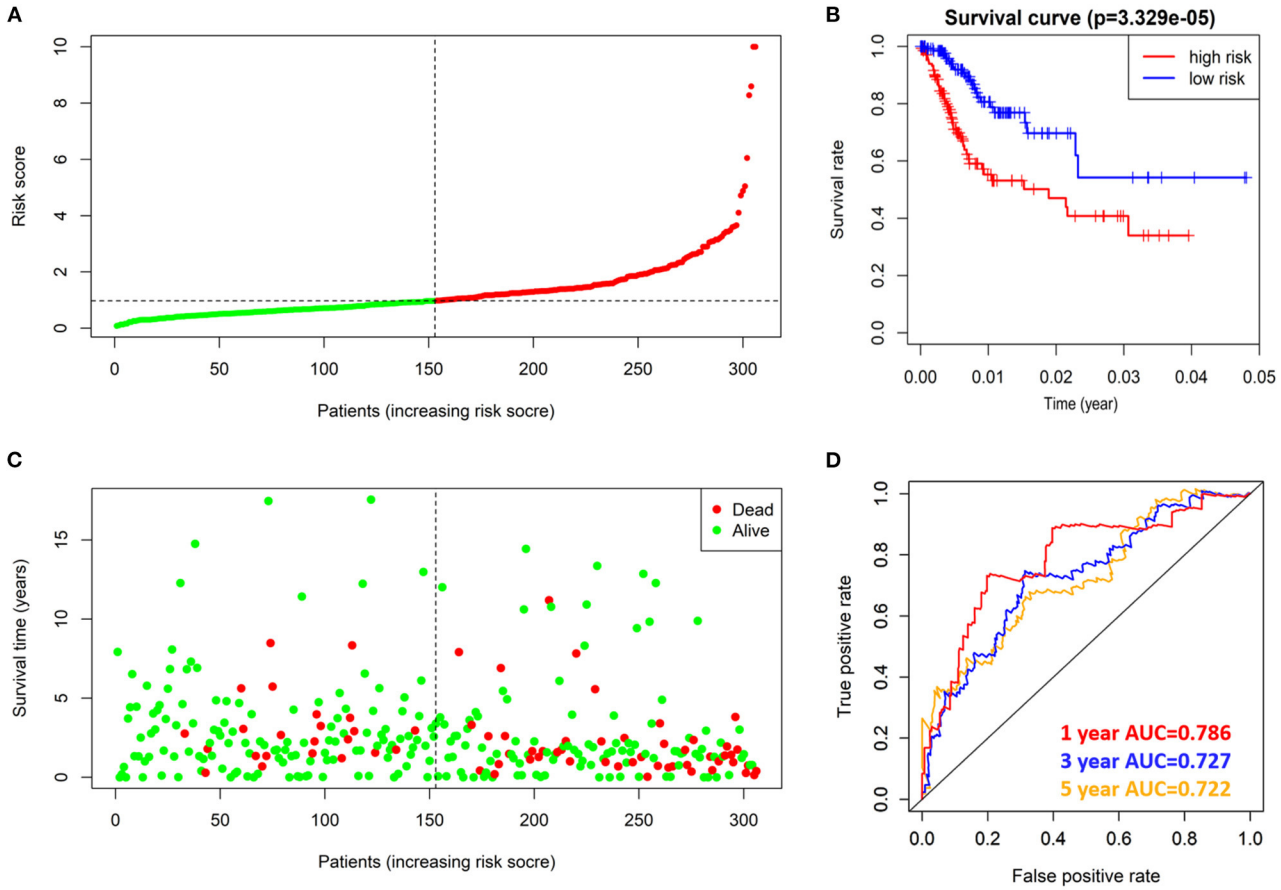

FIGURE 6 | prognostic value of 4 prognostic related RBPs risk models in TCGA dataset. **(A)** Distribution of risk scores in prognosis related RBPs models. **(B)** Kaplan-Meier survival curve of OS in high-risk group and low-risk group. **(C)** Different patterns of survival status and survival time between high-risk group and low-risk group. **(D)** ROC to evaluate the prognostic efficacy of risk score in predicting patients at 1, 3 and 5 years.

were collected by Merkley et al. (16) and a total of 1542 RBPs genes were obtained (**Supplementary Table 1**). STRING database analysis showed that there was a relationship of protein interaction among 49 RBPs (**Figure 2C**).

Expression of Differentially Expressed RBPs and Enrichment Analysis of Go and KEGG Pathways

In order to study the function and mechanism of the identified RBPs, these differentially expressed RBPs were enriched and analyzed. The GO analysis results were included in the analysis with $P < 0.05$ as the standard, and the results were divided into BP, CC and MF groups (**Figure 3A**). The first 10 significant GO analyses showed that RBPs were mainly involved in ribosomal subunit, ribosome, large ribosomal subunit, structural constituent of ribosome, RNA splicing, RNA catabolic process, cytoplasmic translation, regulation of translation, double-stranded RNA binding and catalytic activity acting on RNA (**Figure 3B**). KEGG signaling pathway is mainly enriched in Hepatitis C, Spliceosome and Ribosome (**Figure 3C**).

Potential Small Molecule Drug Screening

Among these highly significantly related molecules, benzocaine, procaine, Pentoxyverine and tetracaine are narcotic drugs (**Figure 4A**). Procaine and Pentoxyverine are negatively correlated with RBPs gene expression and have potential therapeutic effects on CESC (**Figure 4B**).

Construct a Prognostic RBP Prediction Model

For the survival analysis of 65 differentially expressed RBPs, the *P*-value and hazard ratio (HR) with 95% confidence interval (CI) were obtained by logrank test and univariate COX proportional hazards regression (**Figure 5A**). According to the results of survival analysis, seven RBPs (EXO1, HENMT1, RNASEH2A, MRPL47, ZFR2, MRPS24 and NOVA1) were related to the prognosis of patients. Subsequently, seven prognostic RBPs were analyzed by multiple COX regression, in which EXO1, HENMT1, RNASEH2A and MRPS24 can be used as independent predictors of CESC prognosis (**Figure 5B**). Then, the prognostic risk model of CESC was constructed with the

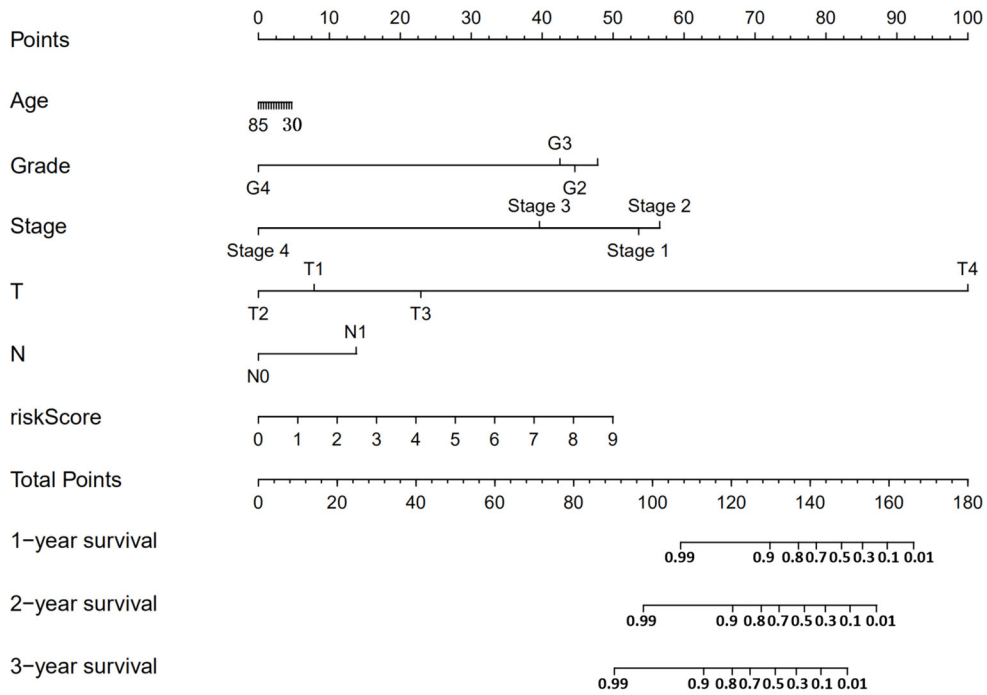

FIGURE 7 | Nomogram can predict the 1,3, and 5 year overall survival of patients with CESC.

above four genes. The risk score of each sample was calculated according to the risk coefficient and the expression of 4 RBPs (**Figure 5C**).

Risk Model Performance Evaluation

According to the risk score formula, the risk score of 306 CESC patients was calculated, and the median score was taken as the cut-off value. The patients were divided into high-risk group and the low-risk group, with 153 cases in each group (**Figure 6A**). The distribution of survival time shows that the number of deaths of CESC patients in the high-risk group is more than that in the low-risk group, and the patients with shorter overall survival (OS) in the high-risk group are more than those in the low-risk group (**Figure 6C**). Kaplan-Meier survival analysis was conducted for patients with high-risk and low-risk groups. The survival rate of low-risk group was significantly higher than that of high-risk group (**Figure 6B**). The results of ROC curve show that the AUC as the prediction efficiency of risk score for 1-year, 3-year and 5-year prognosis of patients are 0.786, 0.727, and 0.722 respectively, indicating that the model has a certain ability to predict the prognosis of CESC patients (**Figure 6D**). The nomogram provides a graphical representation of each factor. The prognostic risk of a single patient can be calculated from the points associated with each risk factor, which can be used to predict the 1, 3, and 5 year overall survival of CESC patients (**Figure 7**).

Correlation Between Risk Score and Clinical Factors

Data of TCGA-CESC data set were used to further study the correlation between patients' risk score and clinical factors in the model. Chi square test showed that there were differences in tumor grade distribution between high-risk group and low-risk group (**Figure 8A**). To assess whether the risk score was independent of other clinical variables, COX univariate and multivariate analyses were performed in 182 patients with complete clinical data. Univariate COX analysis showed that the T, N stages and riskScore of CESC patients were related to the prognosis (**Figure 8B**). Further multivariate COX regression analysis showed that riskScore, T stage and N stage were independent factors affecting OS in patients with CESC (**Figure 8C**).

Validation of Prognostic Genes

The expression data analysis of the database showed that there were significant differences in the expression of seven RBPs between CESC and normal tissues, including the up-regulated expression of five genes (HENMT1, RNASEH2A, EXO1, MRPL47 and ZFR2) and the down-regulated expression of two genes (MRPS24 and NOVA1) (**Figures 9A–G**). In addition, the expression of RNASEH2A was positively correlated with the expression of EXO1, ZFR2, HENMT1, MRPL47, and MRPS24. The expression of HENMT1 was positively correlated with the expression of EOX1 and ZFR2 (**Figure 9H**). Finally, protein expression levels of RNASEH2A and HENMT1

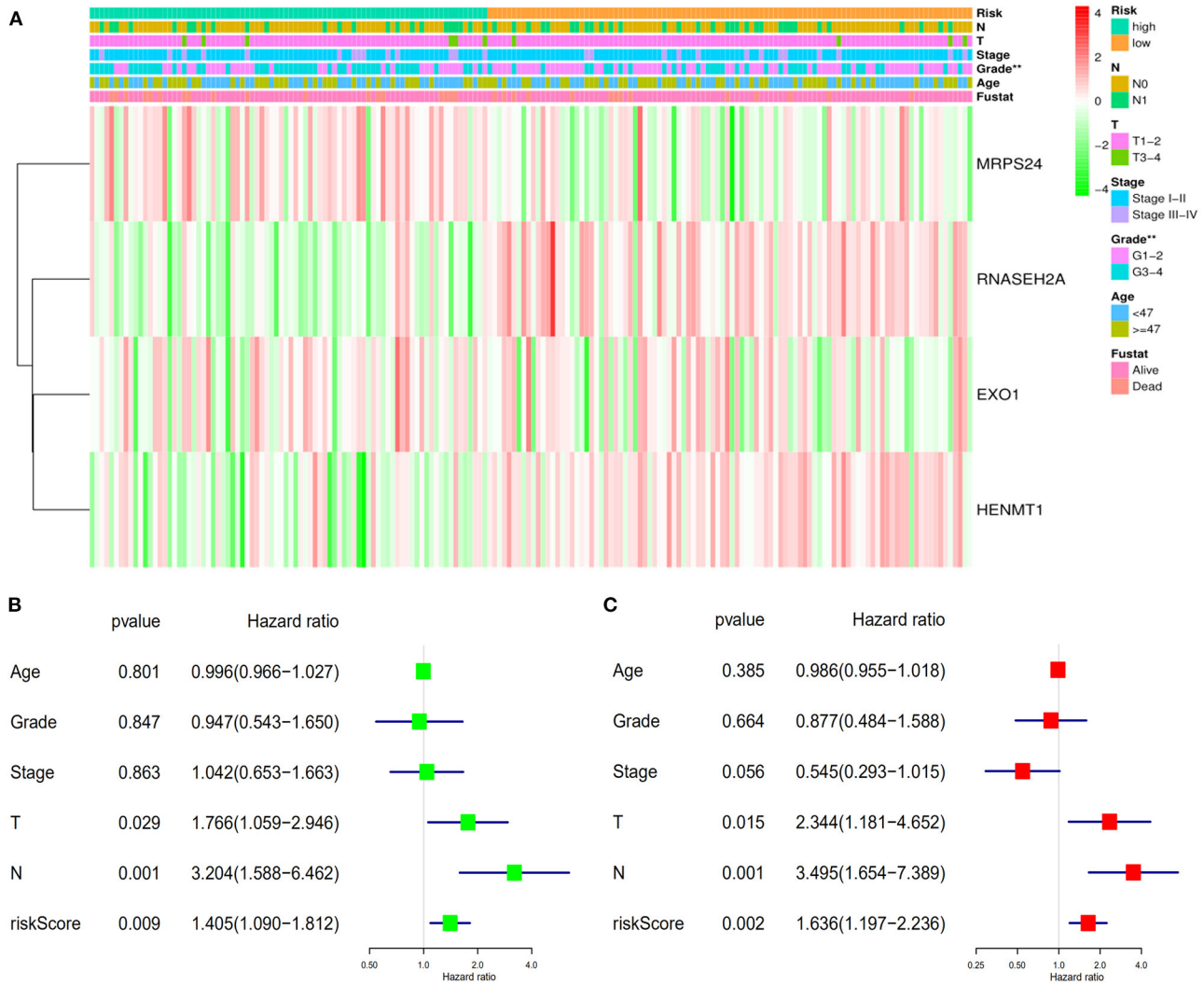

FIGURE 8 | Verifies the accuracy of the prognostic scoring model. **(A)** Differences in the distribution of clinical factors between high and low risk groups. **(B)** Univariate prognostic analysis. **(C)** Multivariate independent prognostic analysis. $^{**}P < 0.01$.

in cervical cancer and adjacent tissues were verified by immunohistochemistry. It can be seen that the expression of RNASEH2A and HENMT1 in tumor tissues is significantly higher than that in adjacent tissues (**Figures 10A,C**). In the RNASEH2A immunohistochemical expression micro array, after deleting the tissue points shed during the experiment, the expression of RNASEH2A in the remaining 120 pairs of cancer and adjacent tissues was statistically analyzed (**Supplementary Figure 1**). Statistical analysis showed that the expression of RNASEH2A in cervical cancer was higher than that in adjacent tissues (**Figure 10B**). In the HENMT1 immunohistochemical expression micro array, after deleting the tissue points shed during the experiment, the expression of HENMT1 in the remaining 93 pairs of cancer and adjacent tissues was statistically analyzed (**Supplementary Figure 2**). Statistical analysis showed that the expression of HENMT1 in cervical cancer was higher than that in adjacent tissues (**Figure 10D**).

Correlation Between RNASEH2A and HENMT1 and Clinical Markers, and Evaluation of Diagnostic Effect

GEPIA database analysis showed that RNASEH2A and HENMT1 were positively correlated with the expression of tumor marker (MKI67) (**Figures 11A,D**). Clinical immunohistochemical data showed that the expression of tumor marker (MKI67) in cancer tissues was stronger than that in normal tissues (**Figures 11B,E**). At the same time, RNASEH2A and HENMT1 were positively correlated with the expression of clinical markers (MKI67) in cancer tissues (**Figures 11C,F**). ROC curve analysis shows that the areas under RNASEH2A, HENMT1 and MKI67 curves are 0.92, 0.946, and 0.925, respectively (**Figures 11G–I**). However, RNASEH2A, HENMT1 combined with clinical markers (MKI67) calculated the largest area under the ROC curve, which was 0.992 (**Figure 11J**).

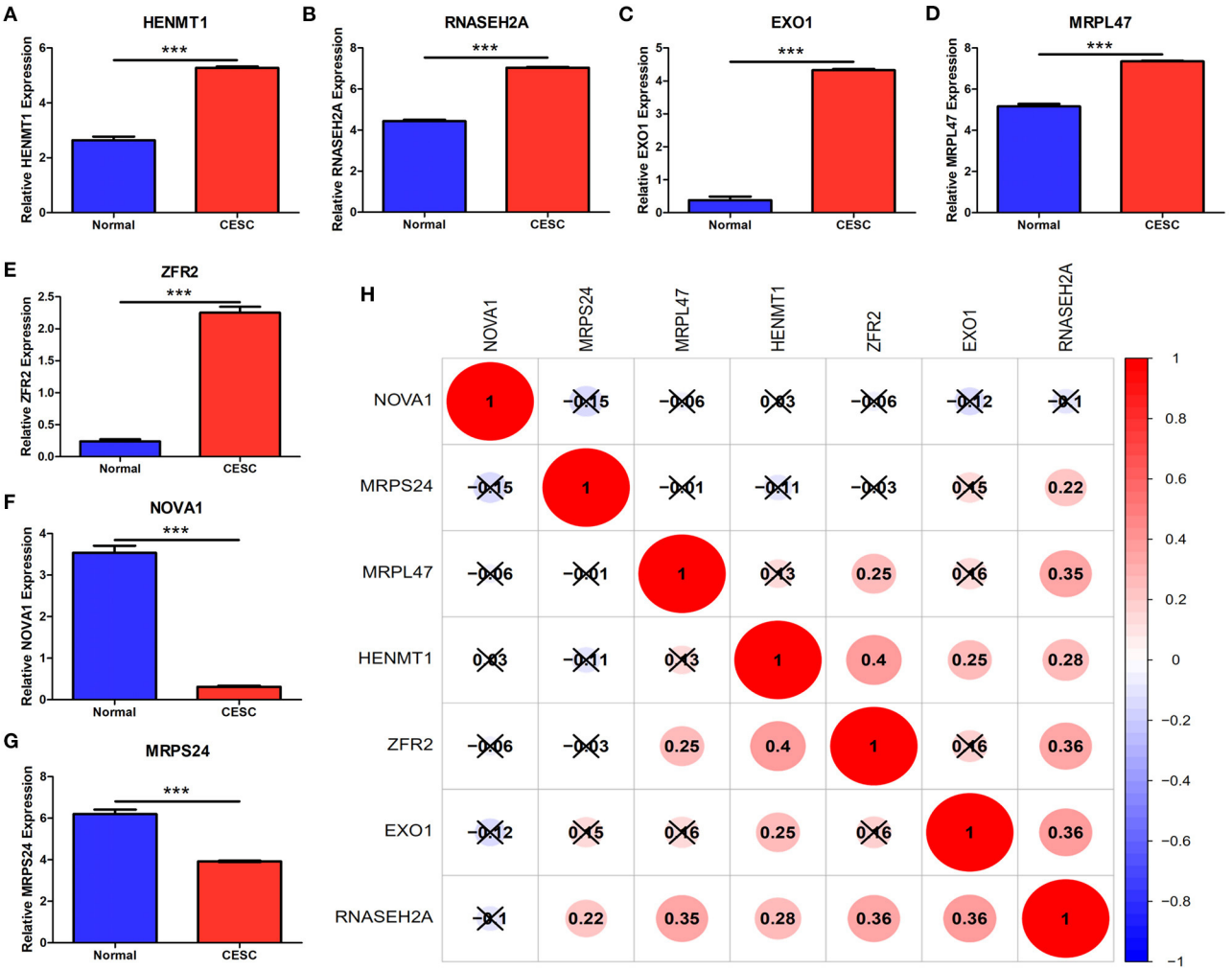

FIGURE 9 | Differences in gene expression of seven RBPs between CESC and normal samples in the database. **(A)** HENMT1. **(B)** RNASEH2A. **(C)** EXO1. **(D)** MRPL47. **(E)** ZFR2. **(F)** NOVA1. **(G)** MRPS24. **(H)** Expression correlation analysis of seven RBPs. ***$P < 0.001$.

DISCUSSION

CESC is one of the most common malignant tumors in women worldwide, and has a high incidence rate (16). The risk of recurrence and metastasis of CESC is high. Early diagnosis and treatment are very important to improve the prognosis of CESC patients. Therefore, it is urgent to explore new potential biomarkers that can be used for early diagnosis, targeted therapy or prognosis evaluation to improve the prognosis of CESC patients. Micro array analysis is a high-throughput technology, which can detect the expression level of thousands of genes at the same time. Nowadays, abnormal gene expression is considered to be one of the factors in the occurrence and development of CESC, and more and more studies show that some deregulated genes in CESC may become candidate biomarkers for diagnosis and prognosis (17). RBPs are proteins that can bind to a variety of RNAs and can be stably expressed in cells. Their main role is RNA processing, such as mRNA splicing and translation regulation. In the past decades, it has been found that RBPs are closely related to the occurrence and development of many tumors (18). At present, narcotic drugs are prescription drugs for the treatment of cancer pain. Some narcotic drugs inhibit tumor growth, invasion and metastasis. Other narcotic drugs promote tumor growth, invasion and metastasis. Their mechanism may be related to regulating the immune ability of the body to the tumor. So choosing different anesthetic drugs in different preoperative periods may have different effects on tumor recurrence and invasion, and directly affect the prognosis of surgical patients. Therefore, this study analyzed the relationship between RBPs and narcotic drugs in CESC.

In this study, the gene expression profile of CESC was analyzed by bioinformatics to explore its molecular mechanism and identify important molecules that may be used as CESC biomarkers and therapeutic targets. In this study, we downloaded the gene expression profile data set of CESC from TCGA database, deeply analyzed it by bioinformatics method, and

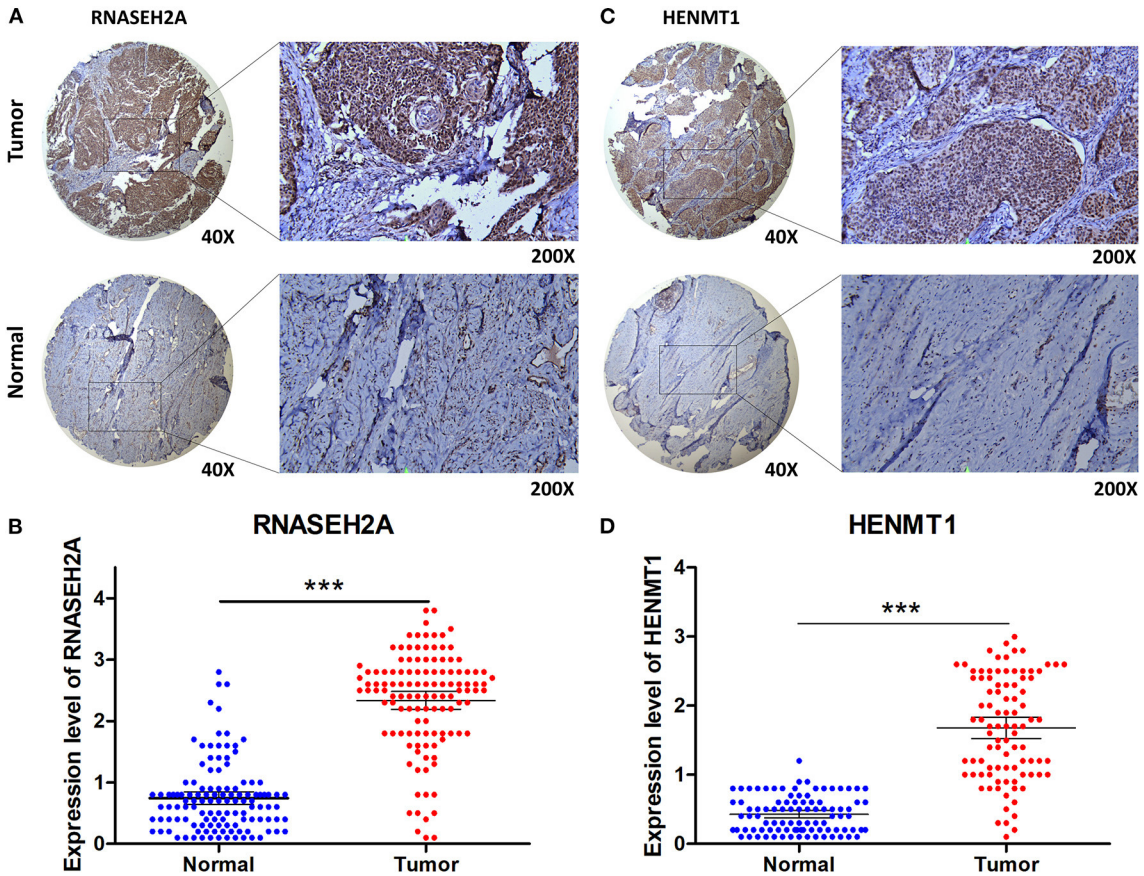

FIGURE 10 | Immunohistochemical verification of RNASEH2A and HENMT1. **(A)** Expression of RNASEH2A protein in cancer and normal samples. **(B)** Differential expression analysis of RNASEH2A in cancer and adjacent tissues in tissue expression microarray. **(C)** Expression of HENMT1 protein in cancer and normal samples. **(D)** Differential expression analysis of HENMT1 in cancer and adjacent tissues in tissue expression microarray. *t-test* was used to compare the differential expression between cancer and adjacent samples. ***$P < 0.001$.

obtained the RBPs between CESC tissue and normal tissue. The results showed that 65 RBPs were identified between CESC and normal tissues. GO functional enrichment analysis showed that DEGs were mainly involved in ribosomal subunit, ribosome, large ribosomal subunit, structural constituent of ribosome, RNA splicing, RNA catabolic process, cytoplasmic translation, regulation of translation, double-stranded RNA binding and catalytic activity acting on RNA. In addition, enrichment results of KEGG pathway showed that the enriched pathways mainly involved Hepatitis C, Spliceosome and Ribosome. Post transcriptional regulation of RNA stability is an important step in the process of gene expression. RBPs can interact with RNA to form RNA protein complexes, so as to increase the stability of target mRNA, promote gene expression and play a key role in the progress of various diseases. The above information shows that our data mining results are consistent with the existing research results. In this study, local anesthetics (benzocaine, procaine, pentoxyverine and tetracaine) with regulatory function to 65 differentially expressed RBPs were analyzed. Among them, the regulation trend of benzocaine and tetracaine on genes is the same as that of RBPs. Although drugs have analgesic effect, they may lead to disease deterioration by promoting cell biological function. Procaine and Pentoxyverine may inhibit tumor progression on the basis of anesthesia and analgesia. Its effect on the tumor and its related mechanism needs to be further studied and discussed.

Survival analysis was used to screen the genes related to the prognosis of CESC patients in 65 differentially expressed RBPs. The results showed that seven RBPs (HENMT1, RNASEH2A, EXO1, MRPL47, ZFR2, NOVA1, and MRPS24) were related to the prognosis of patients. Among them, four genes (HENMT1, RNASEH2A, EXO1, and MRPS24) are independent predictors of the prognosis of CESC patients. Based on the above four genes, a CESC prognostic risk score model was constructed to further improve the reliability of the prediction results.

Hen methyltransferase 1 (HENMT1) is a methyltransferase. It is a kind of RNA composed of 24–30 nucleotides. It is produced by Dicer independent mechanism and mainly comes from transposons and other repeat elements (19, 20). The expression of HENMT1 in ovarian cancer is increased with the increase of tumor grade, which was related to the degree of malignancy (21). In this study, the expression of HENMT1 in cervical cancer

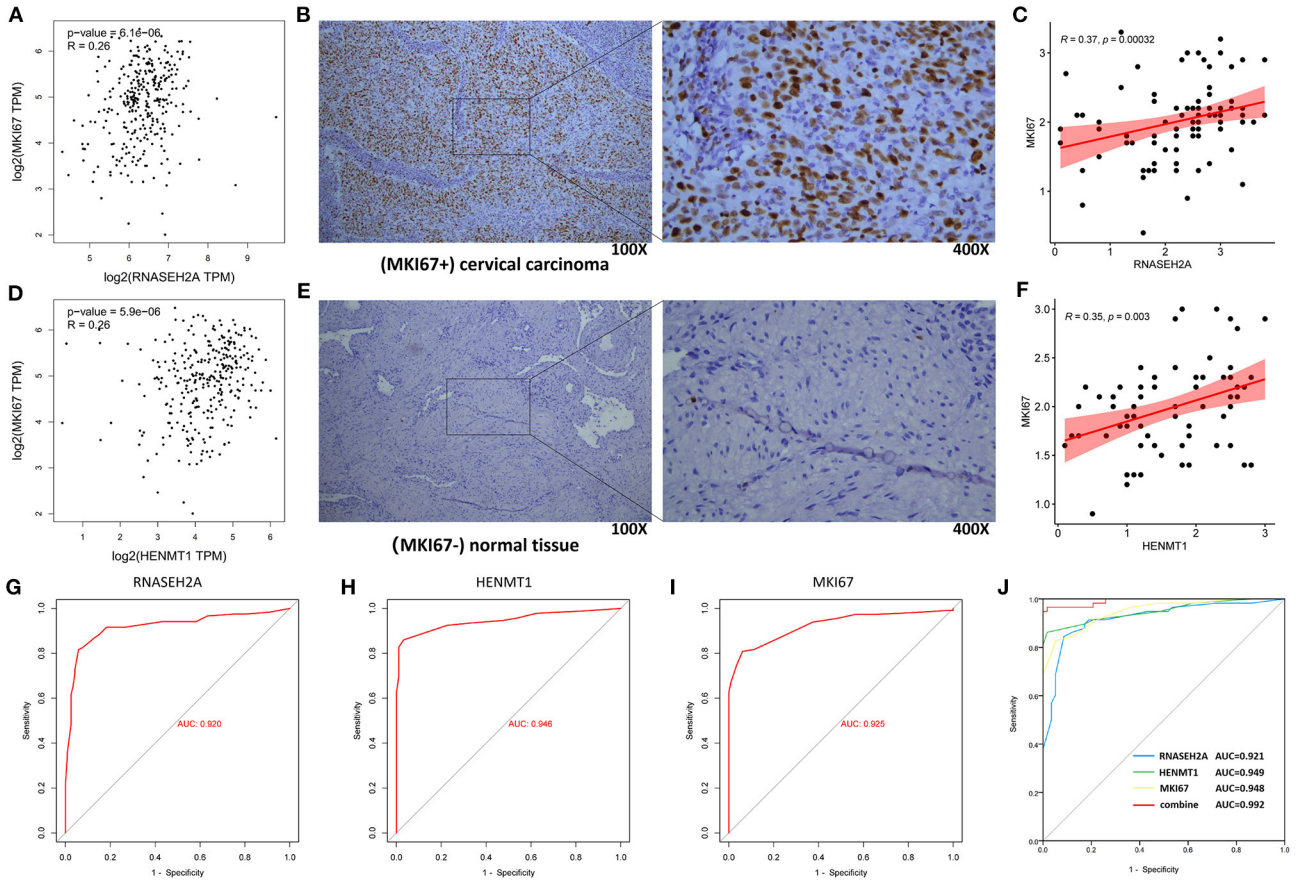

FIGURE 11 | Correlation analysis between RNASEH2A and HENMT1 and clinical marker MKI67, and evaluation of molecular diagnostic effect. **(A,D)** The correlation between RNASEH2A and HENMT1 and clinical markers (MKI67) in CESC was analyzed by GEPIA database. R represents the correlation coefficient. **(B,E)** Expression of clinical marker (MKI67) in cervical cancer and normal tissues. The brown part represents the target protein. **(C)** The correlation between RNASEH2A and clinical marker (MKI67) was analyzed according to the immunohistochemical results. **(F)** The correlation between HENMT1 and clinical marker (MKI67) was analyzed according to the immunohistochemical results. **(G–I)** ROC curve was used to analyze the diagnostic effect of RNASEH2A, HENMT1 and MKI67 on cervical cancer. **(J)** The efficacy of RNASEH2A and HENMT1 combined with clinical marker (MKI67) in the diagnosis of cervical cancer.

patients is up-regulated, and its high expression indicates a better prognosis. As a low-risk gene, HENMT1 may be a marker for predicting the prognosis of cervical cancer patients.

Ribonuclease H2 subunit A (RNASEH2A) is an endonuclease that specifically degrades RNA. It can remove lag strand Okazaki fragment RNA primers by mediating the process of DNA replication. RNASEH2A participates in the occurrence of human glioma by promoting glioma cell proliferation and inhibiting apoptosis (22). Over expression of RNASEH2A is positively correlated with chemoresistance of breast cancer cells (23). RNASEH2A was highly expressed in lung cells, and its knockdown inhibited the proliferation of lung cells and induced apoptosis (24). Similarly, we found that RNASEH2A is highly expressed in cervical cancer and participates in RNA catabolic process, which is expected to become a molecular diagnostic marker and therapeutic target of cervical cancer.

Exonuclease 1 (EXO1) has both 5′-3′ exonuclease and 5′ structure specific endonuclease activities. It plays an important role in base mismatch repair, cross injury synthesis, nucleotide excision repair, DNA double strand break repair, meiotic recombination repair and telomere maintenance (25). It was found that the abnormal expression of EXO1 gene may affect the prognosis, survival and progress of patients with prostate cancer (26). The high expression of EXO1 in breast cancer and lung cancer may promote tumor development (27, 28). We found that EXO1 was highly expressed in cervical cancer and was verified by immunohistochemistry. EXO1 participates in catalytic activity in RNA and is expected to become a molecular diagnostic marker of CESC.

Mitochondrial ribosomal protein L47 (MRPL47) is a member of the MRPs family. Mitochondrial ribosome is composed of a small 28s subunit and a large 39s subunit. MRPL47 encodes a large subunit protein. MRPL47 gene mutation is a new high risk factor of vincristine induced peripheral neuropathy in children with acute lymphoblastic leukemia (29). MRPL47 was reported in square cell carcinoma of head and neck, which was related to the prognosis of patients (30). In this study, compared with normal samples, the expression of MRPL47 in CESC was up-regulated

and involved in the structural components of ribosomes, and its increased expression in CESC showed a good prognosis.

Nova alternative splicing regulator 1 (NOVA1) is an RNA binding protein with a specific sequence. The protein has three KH type domains that can bind to RNA. In recent years, many studies have shown that NOVA1 is involved in regulating the occurrence and development of tumors. Zhang et al. (31) have shown that nova1 plays a carcinogenic role in primary liver cancer. Kim et al. (32) showed that the expression of NOVA1 was significantly down regulated in gastric cancer, and the low expression level of nova1 was closely related to the poor prognosis of patients with gastric cancer. Similarly, NOVA1 expression was down regulated in CESC, and patients with low expression had a poor prognosis. NOVA1 plays a role in RNA splicing and is expected to become a molecular diagnostic marker of CESC.

Mitochondrial ribosomal protein S24 (MRPS24) belongs to the universal ribosomal protein US3 family. At present, the role of MRPS24 in tumorigenesis and development has not been reported. In this study, the expression of MRPS24 was down regulated in CESC, which is the structural component of ribosome and a risk factor for poor prognosis.

Finally, in order to explore the correlation between the markers predicted in this study and clinical tumor markers, the correlation between the experimental results of HENMT1, RNASEH2A and clinical tumor markers was analyzed. It was found that HENMT1 and RNASEH2A were positively correlated with the expression of tumor marker (MKI67). At the same time, compared with the diagnostic efficiency of simple tumor markers, HENMT1 and RNASEH2A combined with clinical markers (MKI67) have higher diagnostic efficiency and reduce the misdiagnosis and missed diagnosis rate of patients to a certain extent.

In conclusion, we used bioinformatics methods to deeply mine the RBPs expression profile data set of CESC. On this basis, we mined narcotic drugs (benzocaine, procaine, pentoxyverine and tetracaine) that regulate RBPs. It was found that procaine and Pentoxyverine are expected to become potential drugs for the treatment of CESC. We screened seven hub genes (HENMT1, RNASEH2A, EXO1, MRPL47, ZFR2, NOVA1 and MRPS24). Among them, the prognostic risk model was constructed based on four independent predictors (HENMT1, RNASEH2A, EXO1 and MRPS24) of the prognosis of CESC patients. The model not only provides new insights into the heterogeneity of CESC, but also has independent predictive value for unconventional clinicopathological factors. It can provide patients with more accurate prognosis evaluation and individualized diagnosis and treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ and JY participated in the study design, drafted the manuscript, and revised the manuscript. YZ and XM statistically analyzed the data. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.823566/full#supplementary-material

Supplementary Table 1 | Information list of 1,542 RBPs genes.

Supplementary Figure 1 | The expression of RNASEH2A in the remaining 120 pairs of cancer and adjacent tissues.

Supplementary Figure 2 | The expression of HENMT1 in the remaining 93 pairs of cancer and adjacent tissues.

REFERENCES

1. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. *Cancer.* (2017) 123:2404–12. doi: 10.1002/cncr.30667
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* (2018) 68:7–30. doi: 10.3322/caac.21442
3. Bahrami A, Hasanzadeh M, Shahidsales S, Farazestanian M, Hassanian SM, Moetamani Ahmadi M, et al. Genetic susceptibility in cervical cancer: From bench to bedside. *J Cell Physiol.* (2018) 233:1929–39. doi: 10.1002/jcp.26019
4. Gu X, Guo XK, Chen BH, Gao XJ, Chen F, Liu Q. Prognostic and clinicopathological value of ZIC1 in patients with cervical squamous cell carcinoma. *Oncol Lett.* (2019) 18:6621–7. doi: 10.3892/ol.2019.11007
5. Zhao D, Qin W, Zhao C, Long J, Li M. CXCR7, a Prognostic Biomarker in Cervical Squamous Cell Carcinoma, May Be a Screening Index for Treatment Options at Stages IB1 and IIA1. *Cancer Manag Res.* (2019) 11:10287–96. doi: 10.2147/CMAR.S228684
6. Gerstberger S, Hafner M, Tuschl T. A census of human RNA-binding proteins. *Nat Rev Genet.* (2014) 15:829–45. doi: 10.1038/nrg3813

7. Masuda K, Kuwano Y. Diverse roles of RNA-binding proteins in cancer traits and their implications in gastrointestinal cancers. *Wiley Interdiscip Rev RNA*. (2019) 10:e1520. doi: 10.1002/wrna.1520
8. Pereira B, Billaud M, Almeida R. RNA-binding proteins in cancer: old players and new actors. *Trends Cancer*. (2017) 3:506–28. doi: 10.1016/j.trecan.2017.05.003
9. Legrand N, Dixon DA, Sobolewski C. AU-rich element-binding proteins in colorectal cancer. *World J Gastrointest Oncol*. (2019) 11:71–90. doi: 10.4251/wjgo.v11.i2.71
10. Chatterji P, Rustgi AK. RNA. Binding proteins in intestinal epithelial biology and colorectal cancer trends. *Mol Med*. (2018) 24:490–506. doi: 10.1016/j.molmed.2018.03.008
11. Zhang H, Wang Y, Dou J, Guo Y, He J, Li L, et al. Acetylation of AGO2 promotes cancer progression by increasing oncogenic miR-19b biogenesis. *Oncogene*. (2019) 38:1410–31. doi: 10.1038/s41388-018-0530-7
12. Jeong HM, Han J, Lee SH, Park HJ, Lee HJ, Choi JS, et al. ESRP1 is overexpressed in ovarian cancer and promotes switching from mesenchymal to epithelial phenotype in ovarian cancer cells. *Oncogenesis*. (2017) 6:e389. doi: 10.1038/oncsis.2017.89
13. Chen H, Liu J, Wang H, Cheng Q, Zhou C, Chen X, et al. Inhibition of RNA-binding protein Musashi-1 suppresses malignant properties and reverses paclitaxel resistance in ovarian carcinoma. *J Cancer*. (2019) 10:1580–92. doi: 10.7150/jca.27352
14. Tønnesen E, Wahlgreen C. Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. *Br J Anaesth*. (1988) 60:500–7. doi: 10.1093/bja/60.5.500
15. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Reg Anesth Pain Med*. (2010) 35:490–5. doi: 10.1097/AAP.0b013e3181ef4d05
16. Merkley MA, Hildebrandt E, Podolsky RH, Arnouk H, Ferris DG, Dynan WS, et al. Large-scale analysis of protein expression changes in human keratinocytes immortalized by human papilloma virus type 16 E6 and E7 oncogenes. *Proteome Sci*. (2009) 7:29. doi: 10.1186/1477-5956-7-29
17. Ouyang F, Liu J, Xia M, Lin C, Wu X, Ye L, et al. GINS2 is a novel prognostic biomarker and promotes tumor progression in early-stage cervical cancer. *Oncol Rep*. (2017) 37:2652–62. doi: 10.3892/or.2017.5573
18. Tang R, Jiang Y, Tan A, Ye J, Xian X, Xie Y, et al. 16S rRNA gene sequencing reveals altered composition of gut microbiota in individuals with kidney stones. *Urolithiasis*. (2018) 46:503–14. doi: 10.1007/s00240-018-1037-y
19. Lim SL, Qu ZP, Kortschak RD, Lawrence DM, Geoghegan J, Hempfling AL, et al. HENMT1 and piRNA stability are required for adult male germ cell transposon repression and to define the spermatogenic program in the mouse. *PLoS Genet*. (2015) 11:e1005620. doi: 10.1371/journal.pgen.1005782
20. Hempfling AL, Lim SL, Adelson DL, Evans J, O'Connor AE, Qu ZP, et al. Expression patterns of HENMT1 and PIWIL1 in human testis: implications for transposon expression. *Reproduction*. (2017) 154:363–74. doi: 10.1530/REP-16-0586
21. Lee E, Lokman NA, Oehler MK, Ricciardelli C, Grutzner F, A. Comprehensive molecular and clinical analysis of the piRNA pathway genes in ovarian cancer. *Cancers (Basel)*. (2020) 13:4. doi: 10.3390/cancers13010004
22. Dai B, Zhang P, Zhang Y, Pan C, Meng G, Xiao X, et al. RNaseH2A is involved in human gliomagenesis through the regulation of cell proliferation and apoptosis. *Oncol Rep*. (2016) 36:173–80. doi: 10.3892/or.2016.4802
23. Shen J, Lin S, Liu L, Wang C. Ribonuclease H2 Subunit A impacts invasiveness and chemoresistance resulting in poor survivability of breast cancer in ER dependent manner. *Am J Transl Res*. (2020) 12:2281–94.
24. Zhang J, Ma D, Kang H, Zhao J, Yang M. Long noncoding RNA LINC01287 promotes proliferation and inhibits apoptosis of lung adenocarcinoma cells via the miR-3529-5p/RNASEH2A axis under the competitive endogenous RNA pattern. *Environ Toxicol*. (2021) 36:2093–104. doi: 10.1002/tox.23325
25. Sertic S, Quadri R, Lazzaro F, Muzi-Falconi M. EXO1: A tightly regulated nuclease. *DNA Repair (Amst)*. (2020) 93:102929. doi: 10.1016/j.dnarep.2020.102929
26. Hua X, Ge S, Chen J, Zhang L, Tai S, Liang C. Effects of RNA binding proteins on the prognosis and malignant progression in prostate cancer. *Front Genet*. (2020) 11:591667. doi: 10.3389/fgene.2020.591667
27. Liu J, Zhang J. Elevated EXO1 expression is associated with breast carcinogenesis and poor prognosis. *Ann Transl Med*. (2021) 9:135. doi: 10.21037/atm-20-7922
28. Zhou CS, Feng MT, Chen X, Gao Y, Chen L, Li LD Li DH, et al. Exonuclease 1 (EXO1) is a potential prognostic biomarker and correlates with immune infiltrates in lung adenocarcinoma. *Onco Targets Ther*. (2021) 14:1033–48. doi: 10.2147/OTT.S286274
29. Abaji R, Ceppi F, Patel S, Gagné V, Xu CJ, Spinella JF, et al. Genetic risk factors for VIPN in childhood acute lymphoblastic leukemia patients identified using whole-exome sequencing. *Pharmacogenomics*. (2018) 19:1181–93. doi: 10.2217/pgs-2018-0093
30. Hu G, Jiang Q, Liu L, Peng H, Wang Y, Li S, et al. Integrated analysis of RNA-binding proteins associated with the prognosis and immunosuppression in squamous cell carcinoma of head and neck. *Front Genet*. (2021) 11:571403. doi: 10.3389/fgene.2020.571403
31. Zhang YA, Liu HN, Zhu JM, Zhang DY, Shen XZ, Liu TT, et al. binding protein Nova1 promotes tumor growth *in vivo* and its potential mechanism as an oncogene may due to its interaction with GABAA Receptor-γ2. *J Biomed Sci*. (2016) 23:71. doi: 10.1186/s12929-016-0288-6
32. Kim EK, Yoon SO, Jung WY, Lee H, Kang Y, Jang YJ, et al. Implications of NOVA1 suppression within the microenvironment of gastric cancer: association with immune cell dysregulation. *Gastric Cancer*. (2017) 20:438–47. doi: 10.1007/s10120-016-0623-3

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Opioid Receptor Expression in Colorectal Cancer: A Nested Matched Case-Control Study

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Background: There is growing interest in the possible effect of perioperative anesthetic management on the growth and spread of cancer. The impact of perioperative use of opioids on cancer recurrence remains controversial and an assessment cannot yet be established based on current publications. This study aimed to assess the differential expression of opioid receptors between healthy and tumor tissues in patients with stage II and III colorectal cancer undergoing elective surgery by immunohistochemistry (IHC).

Methods: Propensity–score matched case–control study nested in a retrospective cohort of patients with stage II or III colorectal. The primary endpoint was the difference in μ–opioid receptor (MOR) expression measured by IHC between tumor and healthy tissue in subject with or without recurrence. Secondary endpoints were to evaluate the differences in Opioid Growth Factor Receptor (OGFR), cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) in the matched sample and from a from samples of colorectal cancer stored in the Cancer Genome Atlas (TCGA) and Genotype Tissue Expression Project (GTEx).

Results: There was a significant difference in MOR receptor (median 3 [intequartile range IQR: 1–3] and 0 [IQR: 0–2], P<0.001) and OGFR receptor (median 6 [IQR: 5–6] and 2 [IQR: 1–2], P<0.001) in tumor and control tissue respectively. However, there were no significant differences in cAMP nor PKA expression between both types of tissues and in expression in any of the analyzed variables by recurrence status. The MOR and OGFR expression data from TCGA database were similar to our sample size data with lower expression of MOR and higher expression of OGFR in tumoural samples with a skewed distribution for MOR expression in tumor tissue both in patients with and without recurrence.

Conclusion: In patients with stage II and III colorectal cancer, overall expression of MOR and OGFR was significantly increased but was not different between previously matched patients with or without recurrence. No differences were found in the analyzed metabolic pathway of cAMP–PKA: These results were confirmed by an *in silico* analysis of samples from the TCGA–GTEx database.

Keywords: neoplasm, tumor, cancer, immunohistochemistry, opioid receptors, perioperative opioid, cancer, surgery

INTRODUCTION

Opioids are potent analgesics indicated for moderate-to-severe pain management in patients undergoing cancer surgery. Opioids have several cellular targets such as μ, κ and δ (MOR, KOR, and DOR, respectively) and opioid growth factor (OGFR) receptors (1–3). Preclinical studies suggest that opioids could promote direct tumor growth, angiogenesis, metastasis, and cellular and humoral immunosuppression (4–6). Among the proposed mechanisms for these pro–tumoral effects is the activation of MOR, which has been shown to be overexpressed by tumor cells in colorectal cancer (7–9).

While guidelines exist for evaluating the expression of receptors in cancer cells (10), there is no validated consensus for immunohistochemistry (IHC) staining for opioid receptors. Typically, MOR expression is determined by using IHC and measuring staining intensity on a grading scale. Some variability depending on the type of sample and reagents is documented in studies assessing MOR expression in various types of cancers (8, 9, 11–18). Furthermore, IHC can have a considerable intraobserver and interobserver (19, 20) and can be only moderately correlated with quantitative methods such as the real-time quantitative reverse transcription-polymerase chain reaction (RT–qPCR) that do not require visual assessment and can be automated (19, 21–23).

As for the other opioid receptor targets, the OGFR has shown inhibitory effects in tumor growth (3), while the role of DOR and KOR are even more controversial with data showing both activating (24) and suppressing effects (25) which can be explained by a different profile of receptor expression (16). In addition, activated opioid receptors trigger several intracellular responses that are responsible for their divergent pharmacological outcomes. For instance, many morphine analogs target MOR *via* two distinct signaling pathways independently associated with analgesic properties and unwanted side effects (26). Analgesia is achieved through a classical G-protein pathway that suppresses neuronal excitability and promotes neuronal hyperpolarization by regulating intracellular cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) activity (27).

This study aimed to assess by IHC the difference in opioid receptors expression between healthy and tumor tissues in patients with stage II and III colorectal cancer undergoing elective surgery. Our primary objective was to determine the difference in MOR expression measured by IHC between tumor and healthy tissue in patients who experience tumor recurrence versus patients who do not suffer it. Secondary objectives were to evaluate the differences in OGFR receptor, cAMP, and PKA expression and to evaluate the difference in expression of MOR and OGFR between tumor and healthy tissues from samples of colorectal cancer stored in the Cancer Genome Atlas (TCGA) and Genotype Tissue Expression Project (GTEx).

METHODS

This was a propensity score matched case-control study nested in a retrospective cohort of patients with stage II or III colorectal cancer undergoing elective surgery from an investigator-initiated single–center study carried out at the University and Polytechnic Hospital la Fe in Valencia, Spain, which was conducted after Institutional Review Board approval (#Morocco, March 2018) and registration at clinicaltrials.gov (NCT03601351) and is published elsewhere (9).

Study Population

The original study included 174 patients who underwent scheduled colorectal surgery for stage II and III primary colorectal cancer from January 2010 to December 2014 and excluded patients with stage I or IV colorectal cancer, those undergoing emergency or non–oncological surgery, and those with poor quality histological samples. This cohort of patients was followed for five years starting from the day of surgery, and the primary tumor recurrence was recorded. From this cohort, we randomly sampled 27 patients with recurrence and matched them in a 1:1 ratio with the optimal method and a caliper of < 0.1 without replacement with subjects without recurrence. The variables used for matching were: Dukes stage, number of affected lymph nodes, and tumoral tissue differentiation. Only subjects with stage II or III cancer and good or moderate tissue differentiation were included in the analysis.

Laboratory Methods

To grade the IHC we used the same scale as previously described. (9) Antibodies against OGFR (Proteintech), MOR1 (ORMU) (Abcam, Cambridge, United Kingdom), cAMP(Millipore, Merck, Burlington, Massachusetts, United States) and PKA (Cell Signaling, Danvers, Massachusetts, United States) were used to measure the expression of each biomarker, in paraffin sections of colorectal adenocarcinoma and adjacent normal tissues (control tissue). All antibodies were used following the company instructions. We used different dilutions for OGFR (1:1000), ORMU (1:300), cAMP (1:200), and PKA (1:200), according to

our previous tests on different tissue controls. The slides were stained for 10 minutes with 3,3′-diaminobenzidine chromogen and counterstained for ten minutes with hematoxylin.

The quantification of MOR, OGFR, cAMP, and PKA expression in study samples was done by microscopic evaluation of immunoreactivity carried out by one experienced pathologist. Immunostaining control was previously tested successfully in central nervous system tissue sample without MOR expression. After the first immunostaining reading, the same pathologist conducted a second assessment to minimize interindividual variability. If good concordance was observed, the final reading was used for analysis; otherwise, a median score was calculated. To grade the IHC we used the same scale as previously described (9). Immunostaining was read in a semi-quantitative manner. Positive staining was defined as a sample showing brown signals in the cell cytoplasm, nucleus, or membrane. The staining intensity was scored as 0 (no staining), 1 (weakly stained), 2 (moderately stained), or 3 (strongly stained). The percentage of cell positivity was scored as 0 (< 5%, negative), 1 (5%-25%, sporadic), 2 (25%-50%, focal), or 3 (>50%, diffuse). MOR expression was scored by adding the intensity staining scores and the percentage area positively stained, producing a total range from 0 to 6.

Gene Expression Analysis

To assess the expression of the opioid receptor at genomic levels, we used RNA–sequencing (RNA–seq) data from the TCGA and GTEx repositories. These are big repositories containing genetic data from cancer tissues and healthy individuals, respectively. However, these large databases are not directly comparable as differences in samples processing, and analysis pipeline across the different studies whose data are stored in the databases make an integrative analysis difficult. Thus, we used normalized data from a publicly available database (https://figshare.com/articles/dataset/Data_record_1/5330539). In addition, this study removed batch effects through an *ad hoc* developed pipeline (28). The details of the used code are available at: https://github.com/mskcc/RNAseqDB and https://github.com/mskcc/RNAseqDB/blob/master/README.md. RNA–seq expression data were log–transformed for the analysis. We selected stage II and III samples from the retrieved cases.

Statistical Analysis

Since the purpose of the analysis was exploring physiological hypotheses, we did not specify any *a priori* effect size and performed analysis without formal sample size calculations.

Quantitative variables are expressed according to the distribution recorded as mean and standard deviation (SD) or median and interquartile range [25^{th} – 75^{th} percentile], and categorical variables as proportions and counts. We checked the normality of each variable's distribution by applying the Shapiro-Wilk test and examining quantile–quantile plots.

The overall and by recurrence difference in MOR, OGFR, cAMP and PKA expression between tumor and healthy tissues was evaluated using the Wilcoxon signed rank test for paired samples. In addition, the difference between MOR and OGFR between subjects with or without recurrence in the TCGA database was performed by the Wilcoxon rank sum test.

Statistical significance was set at two-tailed $P < 0.05$. Bonferroni multiple comparison correction was carried out. No imputation routine of missing values was performed. The statistical analysis was performed using the statistical software R (version 4.0.1, The R Foundation for Statistical Computing, www.r-project.org).

RESULTS

We analyzed 27 subjects, 13 with and 14 without recurrence, satisfactorily matched for the preselected variables (i.e. Dukes stage, number of affected lymph nodes, and tumor tissue differentiation) (**Figure 1**). Some examples of IHC staining are shown in **Figure 2** to provide a graphical depiction of staining intensities. The concordance between readings was good.

The distribution density plots by tissue type, i.e., control versus tumor, for MOR, OGFR, cAMP, and PKA are reported in **Figure 3**. There was a significant difference between control and tumor tissue in MOR and OGFR receptors, with higher expression levels in the tumor tissue. However, there were no significant differences in cAMP nor PKA expression between both types of tissues.

Baseline characteristics and expression levels by tumor recurrence and tissue types are reported in **Table 1** and **Figure 4**. There were no significant differences in expression in any of the analyzed variables by recurrence status (**Figure 4**). The MOR and OGFR expression data from TCGA database were similar to our sample size data with low expression of MOR and higher for OGFR with a skewed distribution for MOR expression having values hovering towards 0 with few extreme outliers in tumor tissue both in patients with and without recurrence (**Table 1**).

DISCUSSION

In this work, we investigated the association between MOR and OGFR receptor and the cAMP–PKA axis in colorectal cancer recurrence. Findings can be summarized as follows; first, the overall expression of MOR and OGFR receptor was significantly increased in colorectal cancer samples compared to paired control samples as assessed by IHC. Second, we did not find significant cAMP–PKA in colorectal cancer samples compared to paired control samples as assessed by IHC. Third, when we analyzed a sample of cases matched for relevant oncological features there were no differences between tumor and control tissue for receptor expression and secondary messengers. Lastly, these results were confirmed by an *in silico* analysis of samples from the TCGA–GTEx database.

To our knowledge, this is the first study evaluating how opioid receptor expression translates at the cellular level. Second, to minimize significant biases, we controlled the confounders by matching cases of recurrence with a similar

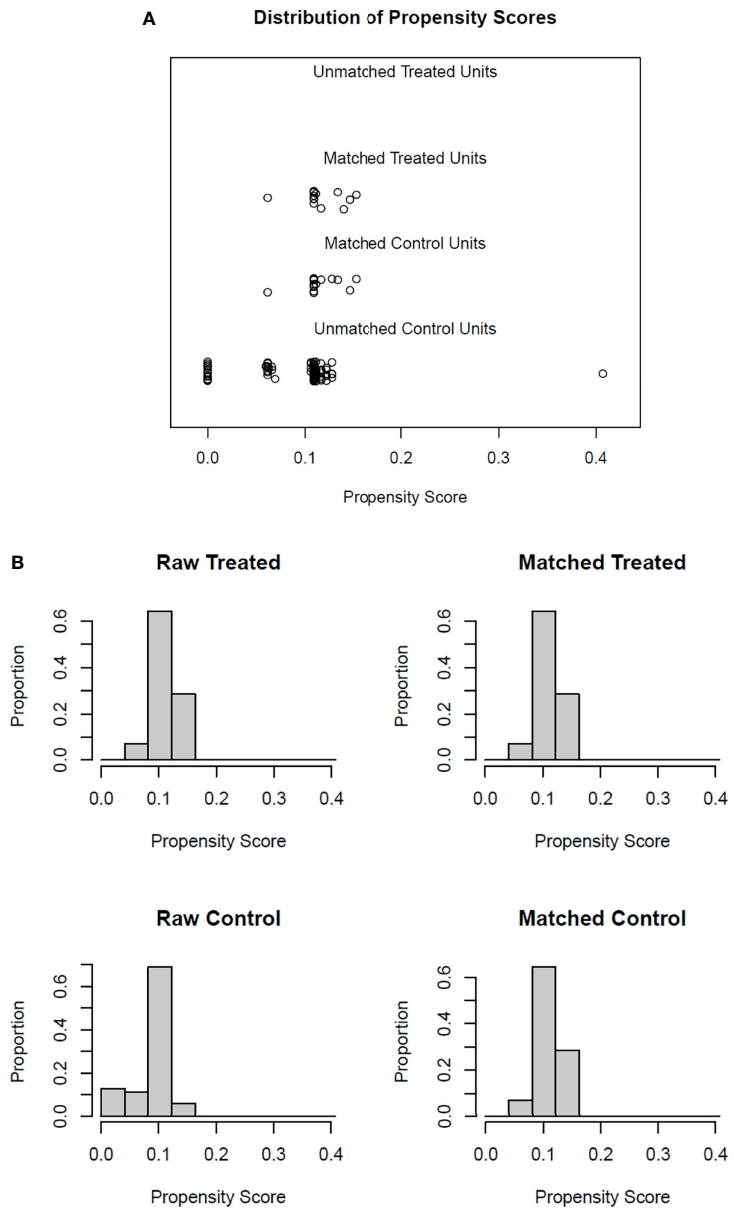

FIGURE 1 | Propensity score matching diagnostic plots. Panel **(A)** jitter plot of propensity scores. The middle lines show the close match between the randomly selected treatment units and the matched control units. The bottom line shows the unmatched control units not included in the analysis. Panel **(B)** Histogram distribution before and after the matching process.

sample of patients without recurrences. And third, we analyzed normalized data from large publicly available datasets to further corroborate our hypothesis and results from our retrospective single-center cohort of patients.

While we found a significantly higher MOR and OGFR expression in tumor tissue samples, we did not detect differences in expression of the receptors between subjects with and without recurrence in the matched analysis. The higher expression of MOR in tumor tissue is in line with previous findings from other authors that assessed such expression in different tumor types such as gastric (13), liver (15), esophagus (12), prostate (17), pancreas (11), lung (12), laryngeal (18), and colorectal cancer (9) as well as in cancer cell lines (8). Although most studies focused on the MOR receptor, more recent findings broadened the spectrum to other opioid receptors such as OGFR, suggesting that specific expression profiles may be behind an oncogenic propensity (16). For instance, OGFR has been linked to decreased cell proliferation in lung carcinoma (3) and breast cancer (29), and indeed, we did find that OGFR was overexpressed in our cancer samples. The rationale behind

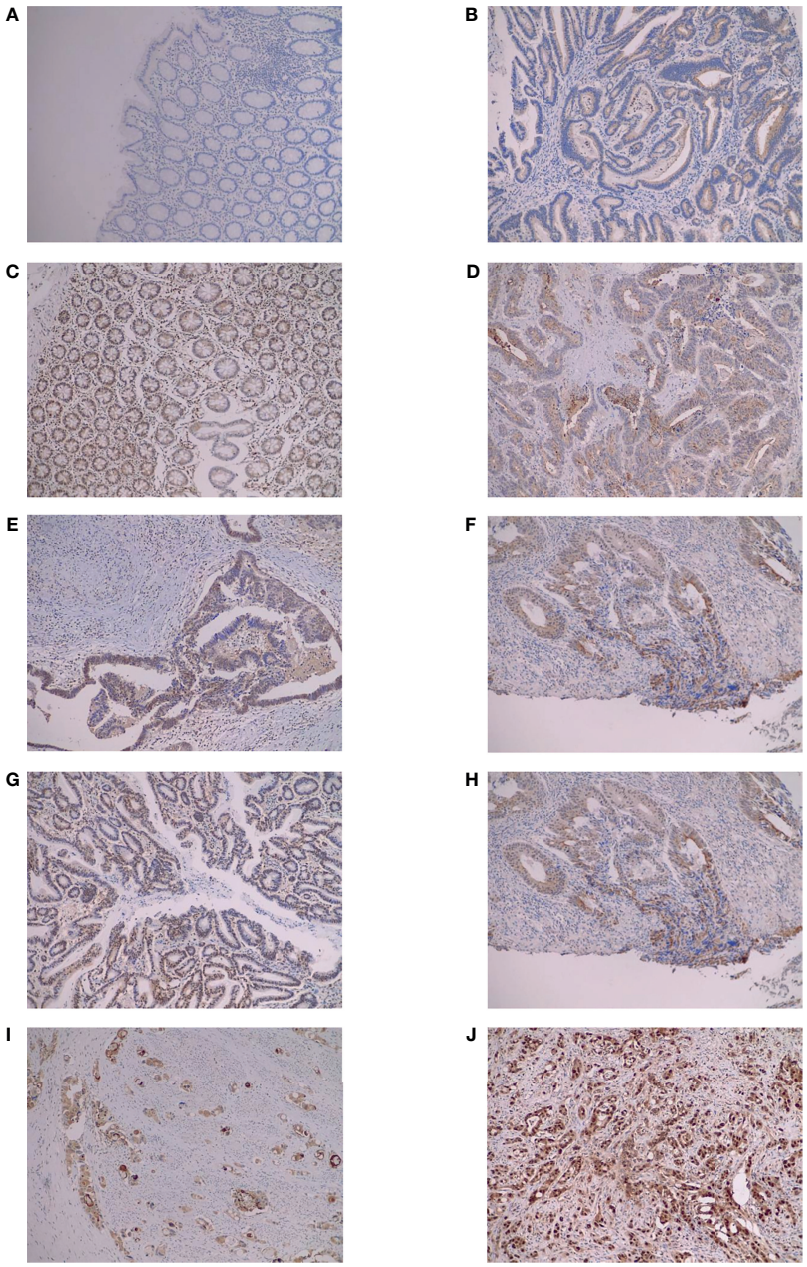

FIGURE 2 | Immunohistochemical staining examples to describe scoring. All pictures are at 10X magnification. **(A)** Score 0 control cAMP; **(B)** score 1 tumor cAMP; **(C)** score 2 tumor OGFR; **(D)** score 3 tumor MOR; **(E)** score 4 tumor OGFR; **(F)** score 4 tumor MOR; **(G)** score 5 tumor OGFR; **(H)** score 5 tumor OGFR; **(I)** score 6 tumor MOR; **(J)** score 6 tumor OGFR. MOR, μ opioid receptor; OGFR, opioid growth factor receptor; cAMP, cyclic adenosine monophosphate.

studying different molecular targets of opioid drugs is that a different balance between those exerting a protumor and antitumor effect can ultimately lead to a different modulating effect. In addition, other receptors such as the σ receptor (SR) have been shown to have an induction effect on MOR and DOR, although not technically an opioid receptor (30). Following and expanding on this concept it would be interesting to assess the entire roster of opioid receptors since there are seven known (i.e. MOR, DOR, KOR, SR, and ϵ, ζ, and λ opioid receptors), or to investigate the role of the different receptor subtypes. For instance, MOR type 1, which is the most studied subtype, is a well-known member of this receptor family with up to ten different variants already identified, although it is unclear if a different action can be attributed solely to a specific subtype (31).

The clinical significance of opioid receptors on long-term oncologic outcomes has been a subject of intense research in the

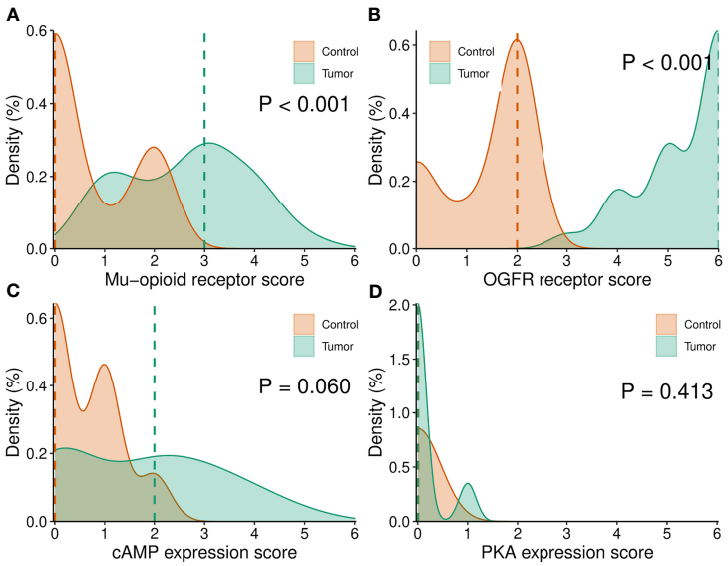

FIGURE 3 | **(A–D)** Density plots of MOR, OGFR, cAMP and PKA expression determined by IHC by type of tumor. MOR, μ opioid receptor; OGFR, opioid growth factor receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A.

TABLE 1 | Sample baseline characteristics, receptors, and metabolic pathway expression.

Nested case-control sample			
	Recurrence		**P value**
	No (N = 14)	**Yes (N =13)**	
Stage = III % (N)	42.9 (6/14)	38.5 (5/13)	0.999
Tumor differentiation = (moderate) % (N)	92.9 (13/14)	92.3 (12/13)	0.999
Lymph node affected (N)	0 [0 – 3]	0 [0 – 2]	0.870
MOR expression			0.999*
Control	0 [0 – 1]	0 [0 – 2]	
Tumor	2 [1 – 3]	3 [2 – 4]	
OGFR expression			0.999*
Control	2 [1 – 2]	2 [0 – 2]	
Tumor	6 [5 – 6]	5 [5 – 6]	
MOR expression			0.999*
Control	0 [0 – 1]	0 [0 – 2]	
Tumor	2 [1 – 3]	3 [2 – 4]	
cAMP expression			0.999*
Control	1 [0 – 1]	0 [0 – 1]	
Tumor	2 [0 – 3]	2 [0 – 3]	
PKA expression			0.999*
Control	0 [0 – 0]	0 [0 – 0]	
Tumor	0 [0 – 0]	0 [0 – 0]	
TCGA sample			
	Recurrence		P value
	No (N = 89)	**Yes** (N= 20)	
MOR gene expression (Log scale)			0.999**
Control (N = 16)	0.5 [0 – 1.3]	0 [0 – 0.2]	
Tumor (N = 93)	0 [0 – 0]	0 [0 – 0]	
OGFR expression (Log scale)			0.705**
Control (N = 16)	6.7 [6.7 – 6.9]	6.6 [6.6 – 6.8]	
Tumor (N = 93)	7.1 [6.8 – 7.3]	7.2 [7.1 – 7.5]	

**The Wilcoxon singed rank test is performed on the difference in expression between control and tumor tissue in subject with or without recurrence. *The wilconos rank sum test is performed on the difference in overall expression in subject with or without recurrence. ** The Mann-Whitney test is performed on the difference in overall expression in subject with or without recurrence. MOR, μ opioid receptor; OGFR, opioid growth factor receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A.*

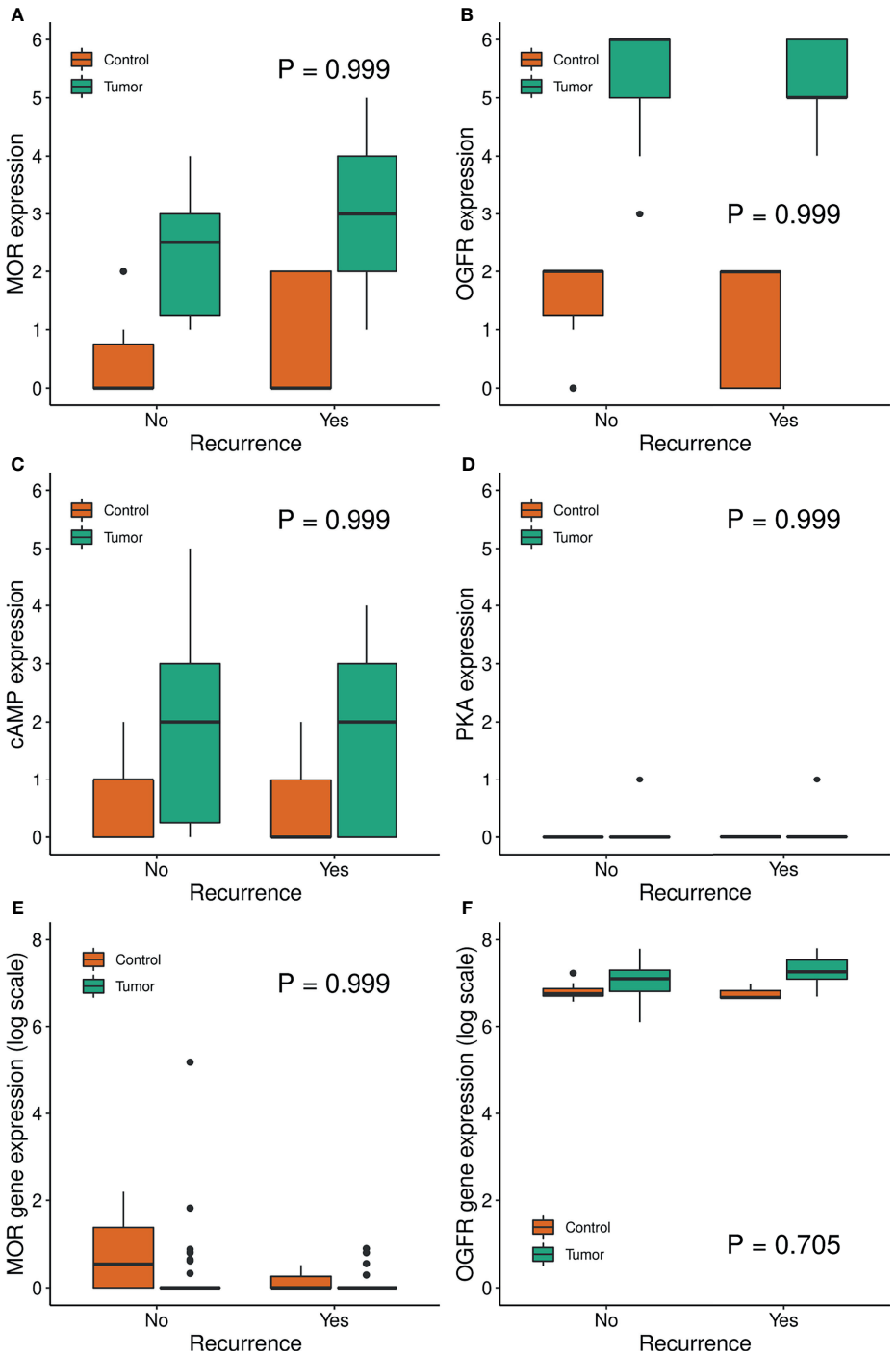

FIGURE 4 | Boxplot of MOR, OGFR, cAMP, PKA expression by recurrence group. Panels **(A–D)** show results from IHC staining from the nested matched case-control sample. Panels **(E, F)** show gene expression from the TCGA and GTEx repositories.

last few years. A vast number of studies found an association between increased receptor expression and decreased disease-free survival (12, 15, 17, 18), while others did not find it (9, 14). Furthermore, more recent trials assessing several receptors found a diverging receptor expression layout with lower MOR and TLR4 but increased OGFR, KOR, and DOR expression and a protective effect of opioid administration on recurrence free survival (16). This protective effect confirmed a previous study

that evaluated opioid administration without receptor expression assessment (32). It can be argued that to advance our knowledge of the effect of opioids on long-term oncologic outcomes, we must explore the entire molecular target profile and its interaction with opioid drugs administration in the perioperative period, even considering genetic variants (33).

Interestingly, while we found no differences between tumor and control tissue expression of MOR and OGFR in the TCGA–GTEx sample analysis, we observed a skewed distribution, which is even more remarkable given that the distribution is Log–transformed. Typically, whole tumor biopsies are used for qRT-PCR or RNA-seq analysis, limiting the ability to differentiate specific cell gene expression in various cell types. Whole tumor analysis may not provide sufficient resolution to identify changes in tissue sub-compartments. The assigning expressed genes could be confounded when gross extracts are used as mRNA source. Therefore, isolating individual cells or specific cell types from tissue sections will allow accurate detection of gene expression in that population. Altogether, this highlights the importance of tissue composition in data generation and the need to correctly define the extraction source to compare different experiments. The method of laser-capture microdissection (LCM) is an option to procure subpopulations of tissue cells under direct microscopic visualization to use in the following procedures (34, 35). These methodological issues are well documented in the literature, but there is no established standard yet (36).

Opioid receptors are G–coupled proteins and agonist-induced conformational changes favoring G-protein binding results in dissociation of its α-subunit from the β- and γ-subunit complex. The α-subunit inhibits adenylyl cyclase activity, reducing intracellular cAMP (26, 37, 38). Thus, cAMP and PKA levels measured by IHC may reflect the degree of MOR activation. However, this molecular pathway is not specific to opioid receptors (39). Also, opioid drugs also mediate their action *via* activation of the β-arrestin pathway, which regulates opioid receptor desensitization and internalization and is responsible for the opioid–mediated undesirable effects (37, 40). Even if exploring the activation of MOR pathways can be a promising path to gain insights on the effect of opioids on cancer, the scope has to be probably expanded to other known pathways and probably even to oncological pathways as recent trials are starting to explore (33).

Several limitations must be highlighted. First, the study's retrospective design and the small sample size the findings should be seen as hypothesis-generating. Also, the small sample size limited the number of confounders we could introduce in the matching process to not exceed the recommended variable to case ratio. In addition, we focused on a specific MOR expression; thus, the influence of polymorphisms, other cellular pathways such β-arrestins or cannabinoid receptors, and opioid antagonists administration cannot be evaluated (41–43). Second, our analysis is limited to a specific subset of patients, i.e., stage II and III colorectal cancer patients; thus, extrapolation to other populations should be done with caution. Also, the matched cohort is based on Dukes' stage, and TCGA–GTEx analysis is based on TNM classification. Thus, although significant overlap is present, this can limit the comparability between samples. Fourth, we observed a higher albeit non–significant MOR expression in control samples in the TCGA–GTEx samples analysis, which can be due to unpaired samples reading. In addition, although IHC readings were performed in a blinded fashion and showed good agreement, a certain degree of subjectivity inherent to semiquantitative IHC assays cannot be ruled out.

To conclude, in patients with stage II and III colorectal cancer, overall expression of MOR and OGFR was significantly increased but was not different between previously matched patients with or without recurrence. These findings were confirmed in a similar cohort extracted from the TCGA and GTEx databases. No differences were found in the analyzed metabolic pathway of cAMP–PKA. Further studies are warranted to comprehensively assess both the molecular footprint and metabolic pathways to elucidate whether opioids and specific expression profiles can impact long-term oncologic outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Instituto de Investigación Sanitaria la Fe. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB: This author conceived the idea, helped with data acquisition, critical review of the content, and manuscript preparation. GM: This author conceived the idea, helped with data acquisition, critical review of the content, and manuscript preparation. IG-C: This author provided a critical review of the content, and helped with manuscript preparation. FG: This author carried out the immunohistochemistry readings, critical review of the content, and manuscript preparation. AM: This author provided a critical review of the content, and helped with manuscript preparation. PE: This author provided a critical review of the content, and helped with manuscript preparation. MA-N: This author provided a critical review of the content, and helped with manuscript preparation. JC: This author provided a critical review of the content, and helped with manuscript preparation. OD-C: This author provided a critical review of the content, and helped with manuscript preparation. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Waldhoer M, Bartlett SE, Whistler JL. Opioid Receptors. *Annu Rev Biochem* (2004) 73:953–90. doi: 10.1146/annurev.biochem.73.011303.073940
2. Xie N, Matigian N, Vithanage T, Gregory K, Nassar ZD, Cabot PJ, et al. Effect of Perioperative Opioids on Cancer-Relevant Circulating Parameters: Mu Opioid Receptor and Toll-Like Receptor 4 Activation Potential, and Proteolytic Profile. *Clin Cancer Res* (2018) 24:2319–27. doi: 10.1158/1078-0432.CCR-18-0172
3. Kim JY, Ahn HJ, Kim JK, Kim J, Lee SH, Chae HB. Morphine Suppresses Lung Cancer Cell Proliferation Through the Interaction With Opioid Growth Factor Receptor: An *In Vitro* and Human Lung Tissue Study. *Anesth Analg* (2016) 123:1429–36. doi: 10.1213/ANE.0000000000001293
4. Brack A, Rittner HL, Stein C. Immunosuppressive Effects of Opioids - Clinical Relevance. *J Neuroimmune Pharmacol* (2011) 6:490–502. doi: 10.1007/s11481-011-9290-7
5. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the Critical Perioperative Period to Improve Long-Term Cancer Outcomes. *Nat Rev Clin Oncol* (2015) 12:213–26. doi: 10.1038/nrclinonc.2014.224
6. Alexander M, Daniel TJ, Chaudry IH, Schwacha MG. Opiate Analgesics Contribute to the Development of Post-Injury Immunosuppression. *J Surg Res* (2005) 129:161–8. doi: 10.1016/j.jss.2005.04.028
7. Karaayvaz M, Cristea S, Gillespie SM, Patel AP, Mylvaganam R, Luo CC, et al. Unravelling Subclonal Heterogeneity and Aggressive Disease States in TNBC Through Single-Cell RNA-Seq. *Nat Commun* (2018) 9:3588. doi: 10.1038/s41467-018-06052-0
8. Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional Expression of μ-Opioid Receptors in the Human Colon Cancer Cell Line, HT-29, and Their Localization in Human Colon. *Dig Dis Sci* (2008) 53(2):461–6. doi: 10.1007/s10620-007-9897-y
9. Díaz-Cambronero O, Mazzinari G, Giner F, Belltall A, Ruiz-Boluda L, Marqués-Marí A, et al. Mu Opioid Receptor 1 (MOR-1) Expression in Colorectal Cancer and Oncological Long-Term Outcomes: A Five-Year Retrospective Longitudinal Cohort Study. *Cancers (Basel)* (2020) 12:134. doi: 10.3390/cancers12010134
10. kJorand R, Biswas S, Wakefield DL, Tobin SJ, Golfetto O, Hilton K, et al. Molecular Signatures of Mu Opioid Receptor and Somatostatin Receptor 2 in Pancreatic Cancer. *Mol Biol Cell* (2016) 27:3659–72. doi: 10.1091/mbc.E16-06-0427
11. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-Opioid Receptor Expression in Metastatic Lung Cancer. *Br J Anaesth* (2014) 113:103–8. doi: 10.1093/bja/aeu165
12. Yao Y-S, Yao R-Y, Zhuang L-K, Qi W-W, Lv J, Zhou F, et al. MOR1 Expression in Gastric Cancer: A Biomarker Associated With Poor Outcome. *Clin Transl Sci* (2015) 8(2):137–42. doi: 10.1111/cts.12246
13. Zhang YF, Xu QX, Liao LD, Xu XE, Wu JY, Wu ZY, et al. Association of Mu-Opioid Receptor Expression With Lymph Node Metastasis in Esophageal Squamous Cell Carcinoma. *Dis Esophagus* (2015) 28:196–203. doi: 10.1111/dote.12165
14. Chen DT, Pan JH, Chen YH, Xing W, Yan Y, Yuan YF, et al. The Mu-Opioid Receptor is a Molecular Marker for Poor Prognosis in Hepatocellular Carcinoma and Represents a Potential Therapeutic Target. *Br J Anaesth* (2019) 122:e157–67. doi: 10.1016/j.bja.2018.09.030
15. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative Opioids are Associated With Improved Recurrence-Free Survival in Triple-Negative Breast Cancer. *Br J Anaesth* (2021) 126:367–76. doi: 10.1016/j.bja.2020.10.021
16. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid Requirement, Opioid Receptor Expression, and Clinical Outcomes in Patients With Advanced Prostate Cancer. *Cancer* (2013) 119:4103–10. doi: 10.1002/cncr.28345
17. Zhang H, Sun M, Zhou D, Gorur A, Sun Z, Zeng W, et al. Increased Mu-Opioid Receptor Expression is Associated With Reduced Disease-Free and Overall Survival in Laryngeal Squamous Cell Carcinoma. *Br J Anaesth* (2020) 125:722–9. doi: 10.1016/j.bja.2020.07.051
18. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol* (2020) 38:1346–66. doi: 10.1200/JCO.19.02309
19. Sinn HP, Schneeweiss A, Keller M, Schlombs K, Laible M, Seitz J, et al. Comparison of Immunohistochemistry With PCR for Assessment of ER, PR, and Ki-67 and Prediction of Pathological Complete Response in Breast Cancer. *BMC Cancer* (2017) 17:1–10. doi: 10.1186/s12885-017-3111-1
20. De Gramont A, Watson S, Ellis LM, Rodón J, Tabernero J, De Gramont A, et al. Pragmatic Issues in Biomarker Evaluation for Targeted Therapies in Cancer. *Nat Rev Clin Oncol* (2015) 12:197–212. doi: 10.1038/nrclinonc.2014.202
21. Amsellem-Ouazana D, Bièche I, Molinié V, Elie C, Vieillefond A, Tozlu S, et al. Is Quantitative Real-Time RT-PCR an Adjunct to Immunohistochemistry for the Evaluation of ErbB2 Status in Transitional Carcinoma of the Bladder? *Eur Urol* (2006) 49:1035–43. doi: 10.1016/j.eururo.2006.01.021
22. Varga Z, Diebold J, Dommann-Scherrer C, Frick H, Kaup D, Noske A, et al. How Reliable is Ki-67 Immunohistochemistry in Grade 2 Breast Carcinomas? A QA Study of the Swiss Working Group of Breast- and Gynecopathologists. *PloS One* (2012) 7:1–12. doi: 10.1371/journal.pone.0037379
23. Bohmann K, Hennig G, Rogel U, Poremba C, Mueller BM, Fritz P, et al. RNA Extraction From Archival Formalin-Fixed Paraffin-Embedded Tissue: A Comparison of Manual, Semiautomated, and Fully Automated Purification Methods. *Clin Chem* (2009) 55:1719–27. doi: 10.1373/clinchem.2008.122572
24. Tripolt S, Knab V, Neubauer H, Elmer D, Aberger F, Moriggl R, et al. Opioids Trigger Breast Cancer Metastasis Through E-Cadherin Downregulation and STAT3 Activation Promoting Epithelial-Mesenchymal Transition. *bioRxiv* (2018) 443663. doi: 10.1101/443663
25. Chen D, Chen Y, Yan Y, Pan J, Xing W, Li Q, et al. Down-Regulation of the Tumour Suppressor K-Opioid Receptor Predicts Poor Prognosis in Hepatocellular Carcinoma Patients. *BMC Cancer* (2017) 17:1–11. doi: 10.1186/s12885-017-3541-9
26. Huang W, Manglik A, Venkatakrishnan AJ, Laeremans T, Feinberg EN, Sanborn AL, et al. Structural Insights Into μ-Opioid Receptor Activation. *Nature* (2015) 524:315–21. doi: 10.1016/j.eururo.2006.01.021
27. Siuda ER, Carr R, Rominger DH, Violin JD. Biased Mu-Opioid Receptor Ligands: A Promising New Generation of Pain Therapeutics. *Curr Opin Pharmacol* (2017) 32:77–84. doi: 10.1016/j.coph.2016.11.007
28. Wang Q, Armenia J, Zhang C, Penson AV, Reznik E, Zhang L, et al. Data Descriptor: Unifying Cancer and Normal RNA Sequencing Data From Different Sources. *Sci Data* (2018) 5:1–8. doi: 10.1038/sdata.2018.61
29. Zagon IS, Porterfield NK, McLaughlin PJ. Opioid Growth Factor - Opioid Growth Factor Receptor Axis Inhibits Proliferation of Triple Negative Breast Cancer. *Exp Biol Med* (2013) 238:589–99. doi: 10.1177/1535370213489492
30. Kim FJ, Kovalyshyn I, Burgman M, Neilan C, Chien CC, Pasternak GW. ς1 Receptor Modulation of G-Protein-Coupled Receptor Signaling: Potentiation of Opioid Transduction Independent From Receptor Binding. *Mol Pharmacol* (2010) 77:695–703. doi: 10.1124/mol.109.057083
31. Dietis N, Rowbotham DJ, Lambert DG. Opioid Receptor Subtypes: Fact or Artifact? *Br J Anaesth* (2011) 107:8–18. doi: 10.1093/bja/aer115
32. Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, et al. Effects of Intraoperative Opioid Use on Recurrence-Free and Overall Survival in Patients With Esophageal Adenocarcinoma and Squamous Cell Carcinoma. *Anesth Analg* (2018) 127:210–6. doi: 10.1213/ANE.0000000000003428
33. Connolly JG, Tan KS, Mastrogiacomo B, Dycoco J, Caso R, Jones GD, et al. Intraoperative Opioid Exposure, Tumour Genomic Alterations, and Survival Differences in People With Lung Adenocarcinoma. *Br J Anaesth* (2021) 127:75–84. doi: 10.1016/j.bja.2021.03.030
34. Datta S, Malhotra L, Dickerson R, Chaffee S, Sen CK, Roy S. Laser Capture Microdissection: Big Data From Small Samples. *Histol Histopathol* (2015) 30:1255–69. doi: 10.14670/HH-11-622
35. Ong CAJ, Tan QX, Lim HJ, Shannon NB, Lim WK, Hendrikson J, et al. An Optimised Protocol Harnessing Laser Capture Microdissection for Transcriptomic Analysis on Matched Primary and Metastatic Colorectal Tumours. *Sci Rep* (2020) 10:1–12. doi: 10.1038/s41598-019-55146-2
36. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker Testing for Patients With Advanced Non–Small Cell Lung Cancer: Real-World Issues and Tough Choices. *Am Soc Clin Oncol Educ B* (2019) 39:531–42. doi: 10.1200/EDBK_237863
37. Chan HCS, McCarthy D, Li J, Palczewski K, Yuan S. Designing Safer Analgesics *via* μ-Opioid Receptor Pathways. *Trends Pharmacol Sci* (2017) 38:1016–37. doi: 10.1016/j.tips.2017.08.004

38. Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E, et al. Structure of the Human κ-Opioid Receptor in Complex With JDTic. *Nature* (2012) 485:327–32. doi: 10.1038/nature10939
39. Rasmussen SGF, Devree BT, Zou Y, Kruse AC, Chung KY, Kobilka TS, et al. Crystal Structure of the β 2 Adrenergic Receptor-Gs Protein Complex. *Nature* (2011) 477:549–57. doi: 10.1038/nature10361
40. Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, et al. Structure-Based Discovery of Opioid Analgesics With Reduced Side Effects. *Nature* (2016) 537:185–90. doi: 10.1038/nature19112
41. Shukla AK, Dwivedi-Agnihotri H. Structure and Function of β-Arrestins, Their Emerging Role in Breast Cancer, and Potential Opportunities for Therapeutic Manipulation. DJ, Lambert DG. Opioid Receptor Subtypes: Fact or Artifact? *Br J Anaesth* (2011) 107:8–18. doi: 10.1093/bja/aer115
42. Iozzo M, Sgrignani G, Comito G, Chiarugi P, Giannoni G. Endocannabinoid System and Tumour Microenvironment: New Intertwined Connections for Anticancer Approaches. *Cells* (2021) 10(12):3396. doi: 10.3390/cells10123396
43. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment With Methylnaltrexone is Associated With Increased Survival in Patients With Advanced Cancer. *Ann Oncol* (2016) 27:2032–8. doi: 10.1093/annonc/mdw317

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Impact of local anesthetics on epigenetics in cancer

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Defective silencing of tumor suppressor genes through epigenetic alterations contributes to oncogenesis by perturbing cell cycle regulation, DNA repair or cell death mechanisms. Reversal of such epigenetic changes including DNA hypermethylation provides a promising anticancer strategy. Until now, the nucleoside derivatives 5-azacytidine and decitabine are the sole DNA methyltransferase (DNMT) inhibitors approved by the FDA for the treatment of specific hematological cancers. Nevertheless, due to their nucleoside structure, these inhibitors directly incorporate into DNA, which leads to severe side effects and compromises genomic stability. Much emphasis has been placed on the development of less toxic epigenetic modifiers. Recently, several preclinical studies demonstrated the potent epigenetic effects of local anesthetics, which are routinely used during primary tumor resection to relief surgical pain. These non-nucleoside molecules inhibit DNMT activity, affect the expression of micro-RNAs and repress histone acetylation, thus exerting cytotoxic effects on malignant cells. The in-depth mechanistic comprehension of these epigenetic effects might promote the use of local anesthetics as anticancer drugs.

KEYWORDS

local anesthetics, epigenetic, cancer, demethylation, miRNA

Abbreviations: Ca^{2+}, calcium ion; DAC, dacogen (decitabine); DNMT, DNA methyltransferase; EGFR, Epithelial Growth Factor Receptor; EMA, European Medicines Agency; ERK, Extracellular signal-Regulated Kinases; FDA, Food and Drug Administration; 5-FU, 5 fluorouracil; IL, interleukin; LA, local anesthetics; mTOR, mammalian target of rapamycin; NK, natural killer cells; RARβ, retinoic acid receptor β; RASSF1A, Ras association domain family 1A.

Introduction

Epigenetic alterations and cancer

Epigenetic alterations are common molecular hallmarks of most cancers (1). In normal cells, epigenetic changes are fundamental for the control of gene expression, for the maintenance of cellular identities and for acquisition of an ever more differentiated and specialized phenotype (2). Epigenetic changes are highly regulated to maintain the stability of the epigenome and cellular homeostasis. However, aberrant patterns of DNA methylation, histone modifications (acetylation, methylation, phosphorylation, etc.) and dysregulation of non-coding RNAs correlate with the development of various kinds of cancers by inactivating tumor suppressor genes, by perturbing DNA repair and chromatin remodeling, or by promoting oncogenic pathways (2, 3). These modifications are under the control of interconnected regulators. For instance, many micro-RNAs (miRNAs) can stimulate cellular proliferation by directly interacting with cell-cycle components, as this has been reported for miR-17-92, miR-221/222, miR-663, miR-302 or miR-24, which target the transcription factor E2F1 or the cyclin dependent kinase (CDK) inhibitors p27Kip1, p21CIP1 and p16INK4a, respectively (4–8). The hypermethylation of DNA, which is associated with multiple pathologies, is characterized by the transfer of methyl groups to the position 5 of cytosine residues at CpG islands, which may be located in the promoter regions of tumor suppressive genes, thus inducing their inactivation (9). This reaction is catalyzed by a family of DNA methyltransferases encoded by four specific genes (DNMT1, DNMT2, DNMT3a and DNMT3b) that synergistically promote oncogenesis (9–11). Of note, hypermethylation of DNA is perfectly reversible, and silent genes can be reactivated by administration of hypomethylating agents. Two demethylating drugs were approved by the FDA for this purpose: 5-azacytidine and the cytidine analog 5-aza-2'-deoxycytidine also known as decitabine (sold under the brand name dacogen, DAC). After their incorporation into genomic DNA, both agents directly inhibit DNMTs. In the clinic, they are exclusively prescribed for the treatment of myelodysplasia and acute myeloid leukemia (12). However, despite promising preliminary preclinical data (such as the promotion of cancer cell apoptosis *in vitro* and the reduction of tumor growth in mouse models), 5-azacytidine and decitabine provoke considerable side-effects in patients (e.g. mutagenicity, thrombocytopenia and prolonged neutropenia), limiting their employment and motivating their continuous investigation in clinical trials (13). For this reason, the search for ever less toxic hypomethylating agents is ongoing.

Recently, local anesthetics (LA) such as bupivacaine, levobupivacaine, lidocaine, ropivacaine and procaine were described to act as non-nucleoside DNA demethylating agents responsible for upregulating transcriptionally silent genes (14–21), to interfere with the expression of several miRNAs and to impact on the level of histone acetylation (22). These LA are currently employed for their analgesic and anti-inflammatory properties, but also turned out to be endowed with potent anti-tumor effects (23–33).

Local anesthetics induce anticancer effects

LA are commonly used during oncological surgery to relief the acute pain generated by the surgical procedure. Several retrospective clinical trials reported a notable improvement of overall survival and a reduction in recurrence after primary tumor resection under local anesthesia compared to general anesthesia alone (23, 26, 34–36). This epidemiological evidence suggests that LA might have anticancer effects. Several pathways that may explain such antineoplastic effects have been described in the literature. Indeed, preclinical data indicate that LA influence the migration and the survival of cancer cells. At clinically relevant concentrations, LA inhibit the proliferation of cancer cells by provoking cell cycle arrest, by triggering mitochondrial dysfunction or by causing apoptotic cell death (28, 29, 37). Moreover, LA abrogate the migration of cancer cells after inducing intracellular Ca2+ changes that affect the cytoskeleton (24). LA also inhibit the secretion of matrix metalloproteinases necessary for the invasion of cancer cells into the extracellular matrix (38). The anti-inflammatory property of LA reduces the levels of procarcinogenic cytokine interleukin-6 (IL-6) detectable in the serum of patients during oncological surgery (25, 39). *In vivo*, LA elicit an anticancer immune response, thus causing tumor growth reduction in mice and extending the lifespan of animals with solid tumors (20, 40). When combined with chemotherapeutic agents such as 5-fluorouracil, paclitaxel or platinum salts, LA induce a synergistic antitumor effect, meaning that they sensitize cancer cells to the cytotoxicity of chemotherapy (14, 41). Taken together, the current state of the literature supports the contention that LA may directly kill cancer cells and also promote immune responses against neoplastic cells.

Hitherto, only few prospective trials investigated the role of local anesthetics on oncological prognosis (42). Most studies failed to support a direct impact on clinical outcome. However, the continued accumulation of irrefutable preclinical data demonstrating antitumor effects of local anesthetics encourages clinicians to further pursue investigations as illustrated by several randomized controlled trials recorded at www.clinicaltrials.gov and summarized in (43). Among the published scientific readouts, it can be suspected that at least some of these effects are secondary to LA effects on the tumor epigenome. Here, we summarize preclinical data highlighting

the epigenetic mode of action through which LA could exert their antineoplastic activity.

Local anesthetics promote DNA demethylation and restore expression of tumor suppressor genes

Several studies observed that aminoamide-type local anesthetics such as bupivacaine, lidocaine, ropivacaine and ester-type local anesthetic like procaine mediate antitumor effects as well as global DNA demethylation in many types of solid cancers in a time-and dose-dependent manner (Table 1). For instance, bupivacaine, lidocaine and ropivacaine turned out to be potent DNA-demethylating agents of RASSF1A, hampering the proliferation of human hepatocarcinoma HepG2 and BEL-7402 cells (45). Lidocaine triggered apoptosis of human breast cancer BT-20 and MCF-7 cells by inducing the expression of the tumor suppressive RARβ2 and RASSF1A genes (14). Procaine reduced global DNA methylation by 40% in breast cancer MCF-7 cells by inhibiting DNMT1 (21) and showed an outstanding ability to minimize the growth, the proliferation and the invasion of various human cancers both *in vitro* and *in vivo* (15, 17, 20, 21). Interestingly, LA can sterically inhibit DNMT binding to CpG islands or to DNA (15, 21, 47) (Figure 1). As a consequence, the epigenetic regulation by LA could represent a therapeutic option. Indeed, the cytotoxic effects of conventional chemotherapeutic agents such as cisplatin or carboplatin are significantly potentiated when they are combined with LA (14, 17, 45). The association of both lidocaine and cisplatin triggers a higher level of cancer cell apoptosis than lidocaine or cisplatin alone because of the re-expression of the RASSF1A and RARβ2 genes (14). Combined with 5-aza-2'-deoxycytidine, an interesting additive demethylating effect was observed for lidocaine (44).

The effects induced by LA-mediated epigenetic modulation are not limited to the restoration of tumor suppressor gene expression but also modulate the sensitivity to pain (48) and influence the response to corticoid stress during surgery (49, 50), altogether profoundly impinging on the activity of anti-tumor effectors (49, 51). Until now, opioids have been the most commonly used analgesics for controlling acute pain. However, preclinical data indicate that opioids mediate pro-tumorigenic effects via the activation of matrix metalloproteinases and oncogenes like c-Myc as well as *via* an increase in DNA methylation (52–54). Of note, DNA methylation leads to the expression of the mu opioid receptor and predicts the response to endogenous endorphins and opioid analgesics (55). Paradoxically,

TABLE 1 Local anesthetics and DNA demethylation.

Agents	Cancer	Human cell lines	Epigenetic changes	Anticancer effects	Ref
Lidocaine Ropivacaine	Breast	BT-20 (estrogen receptor negative) MCF-7 (estrogen receptor positive)	Global DNA demethylation Lidocaine + 5-aza-2′-deoxycytidine induce additive demethylating effect		(44)
Lidocaine	Breast	BT-20 (estrogen receptor negative) MCF-7 (estrogen receptor positive)	Global DNA demethylation Unchanged mRNA expression of tumor suppressor genes *RASSF1A, MYOD1* and *GSTP1*		(16)
Lidocaine	Breast	MCF-7 (estrogen receptor positive) MDA-MB-231	Global DNA demethylation Demethylation of tumor suppressor genes *RARβ2* and *RASSF1A* (restoration of expression) Increased cisplatin cytotoxicity	Apoptosis	(14)
Lidocaine Ropivacaine Bupivacaine	Liver	HepG2 BEL-7402	Demethylation of tumor suppressor genes *RASSF1A* (restoration of expression) Local anesthetics + cisplatin potentiate *RASSF1A* expression	Proliferation inhibition	(45)
Procaine	Breast	MCF-7 (estrogen receptor positive)	Global DNA demethylation by inhibiting DNMT1 Demethylation of the CpG islands of the tumor suppressor gene *RARβ2* (restoration of expression)	Growth inhibition	(21)
Procaine	Liver	HLE HuH6 HuH7	Global DNA demethylation Demethylation of *p16INK4a, HAI-2/PB, 14-3-3-sigma* and *NQO1* genes (restoration of expression)	Proliferation inhibition (HLE cells) Growth inhibition (xenograft tumor)	(20)
Procaine	Colon	HCT116	Procaine alone (3μM) or combined with carboplatin (3μM) induce demethylation	Reduced viability	(17)
Procaine	Gastric	SGC-7901	Global DNA demethylation by repressing DNMT1 and DNMT3a activity Demethylation of the tumor suppressor genes *CDKN2A* and *RARβ2*	Proliferation inhibition Apoptosis	(15)
Procaine	Lung	H460 A549	Demethylation of *WIF-1* (restoration of expression)		(46)

DNMT, DNA methyltransferase; RARβ, retinoic acid receptor β; RASSF1A, Ras Association Domain Family 1A.

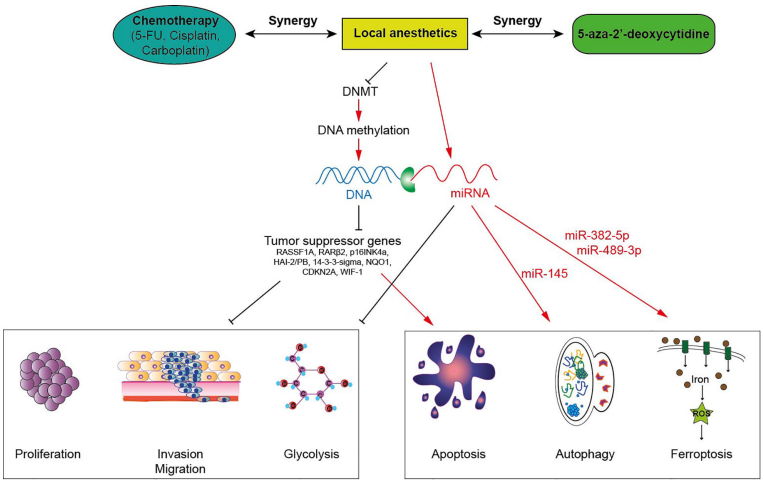

FIGURE 1
Local anesthetics induce anti-tumor effects *via* epigenetic modulation in cancer cells. Local anesthetics inhibit DNA methyltransferases (DNMT) decreasing the level of DNA methylation. This hypomethylation (or demethylation) restores the expression of various tumor suppressor genes impeding the proliferation, the invasion and the mitochondrial metabolism of tumor cells. This epigenetic effect of local anesthetics potentiates the cytotoxic activity of antineoplastic therapies.

excessive administration of opioids increases the risk of hyperalgesia during the postoperative period. It is tempting to speculate that the epigenetic demethylating activity of LA could prevent the hyperalgesia induced by both hypermethylation and opioids and hence counteract the opioid-mediated protumoral effects as well. Thus, opioid-free anesthesia, in which opioids are replaced by a mix of local anesthetics and other analgesic agents, offers a possibility to relieve pain, and to alleviate surgical stress-induced epigenetic changes, thereby restoring the expression of tumor suppressor genes.

Local anesthetics regulate non-coding RNAs

MiRNAs belong to the family of non-coding RNAs. Their main role is to control gene expression at different levels, and their dysregulation may trigger malignant transformation (56). LA are endowed with the capacity to enhance or suppress the expression of a variety of miRNAs, which differ according to the employed molecules and cancer cell lines (Table 2). The regulation of miRNAs by LA impacts several signaling pathways that mediate oncosuppression. Most of these pathways repress the downstream signaling pathway mediated by protein kinase B (PKB, best known as AKT) and mammalian target of rapamycin (mTOR), thus deeply affecting the proliferation, migration and invasion of cancer cells and inducing apoptosis (Figures 1, 2) (81). Interestingly, mTOR was described as a major regulator of energy metabolism by controlling oxidative phosphorylation (84). LA are known to induce mitochondrial dysfunction leading to the production of reactive oxygen species. Indeed, the antitumor activity of ropivacaine involves both the disruption of mitochondrial function and the inhibition of Akt and mTOR phosphorylation, highlighting a putative link between AKT/mTOR and mitochondrial activity in cancer (85). Moreover, the inhibition of the AKT-mTOR pathway by LA demonstrated a relevant impact in preclinical experiments. Indeed, lidocaine-promoted miRNA regulation reversed cisplatin-resistance in MGC-803/DDP gastric cells, minimized the cisplatin resistance in lung cancer cells A549/DDP and increased the cytotoxicity of 5-fluorouracil against SK-MEL-2 melanoma cells *via* upregulation of miR-493 (67, 72, 74). LA also exert antineoplastic properties by acting on the epithelial growth factor receptor (EGFR) axis. For instance, lidocaine inhibits the proliferation of lung cancer cells *via* upregulation of miR-539, which directly targets EGFR (71). Lidocaine also minimizes the progression of retinoblastoma both *in vitro* and *in vivo* by downregulating EGFR expression through the upregulation of miR-520a-3p (77).

The extracellular signal-regulated kinases (ERK) signaling pathway is also impacted by the modulation of miRNA expression induced by LA. In a model of osteosarcoma, procaine significantly blocked the proliferation and migration of tumor cells and promoted apoptosis by upregulating miR-133b. In parallel, the level of p/t-ERK was profoundly decreased. The employment of miR-133b inhibitors reversed all the observed effects including the phosphorylation of ERK, revealing the interaction between this pathway and non-coding RNAs (31). Interestingly, the regulation of miRNAs by LA can target several pathways, thus inducing synergistic effect. Thus, lidocaine can upregulate the expression of miR-145b,

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TABLE 2 Local anesthetics and non-coding RNAs regulation.

Agents	Cancer	Human cell lines	Epigenetic changes	Target	Anticancer effects	Ref
Bupivacaine	Neuroblastoma	SH-SY5Y	miR-132 upregulation	IGFR1 Decrease in p-Akt	Proliferation inhibition Apoptosis	(57)
Bupivacaine	Neuroblastoma	SH-SY5Y	lncRNA ZFAS1 upregulation	miR-421 downregulation ZNF564 upregulation	Apoptosis	(58)
Bupivacaine	Neuroblastoma	SH-SY5Y	lncRNA MALAT1 upregulation	miR-101-3-3p downregulation PDCD4 upregulation	Apoptosis	(59)
Bupivacaine	Neuroblastoma	SH-SY5Y	LINC00665 downregulation	hsa-miR-34a-5p	Apoptosis	(60)
Bupivacaine	Gastric	AGS HGC27	miR-145-5p upregulation	Decrease in Circ_0000376	Migration and invasion inhibition Glycolysis inhibition Apoptosis	(61)
Bupivacaine	Breast	MCF-7	miR-187-5p upregulation	lncRNA DANCR and MYB downregulation	Inhibition of migration Apoptosis	(62)
Levobupivacaine	Gastric	HGC27 SGC7901	miR-489-3p upregulation	SLC7A11	Growth inhibition Ferroptosis	(63)
Lidocaine	Breast	MCF-7	miR-187-5p upregulation	lncRNA DANCR and MYB downregulation	Migration inhibition Apoptosis	(62)
Lidocaine	Cervix	HeLa	lncRNA-MEG3 upregulation	miR-421 downregulation BTG1 upregulation	Proliferation inhibition Tumor growth inhibition Apoptosis	(64)
Lidocaine	Colon Rectum	SW480 HCT116 NCM460	miR-520a-3p upregulation	EGFR inhibition	Proliferation inhibition Apoptosis	(65)
Lidocaine	Colon Rectum	SW620 LoVo	CirclTFG2 upregulation	miR-1204 downregulation SOCS2 upregulation	Proliferation invasion and promotion inhibition Apoptosis	(66)
Lidocaine	Gastric	MGC-803 MGC-803/DDP	miR10b downregulation	AKT/mTOR inhibition	Migration and invasion inhibition Cisplatin-resistance reduction	(67)
Lidocaine	Gastric	GES-1 AGS HGC-27	Circ_ANO5 upregulation	miR-21-5p downregulation LIFR upregulation	Proliferation, migration and invasion inhibition Tumor growth inhibition Apoptosis	(68)
Lidocaine	Gastric	MKN45	miR-145 upregulation	MEK/ERK and NF-κB Inactivation	Growth, migration and invasion inhibition Apoptosis	(18)
Lidocaine	Glioma	U-251MG T98G	CircEZH2 downregulation	miR-181b-5p upregulation	Proliferation, migration and invasion inhibition Tumor growth inhibition	(69)
Lidocaine	Liver	Huh7 Hep3B	Circ_ITCH upregulation	miR-421 downregulation CPEB3 upregulation	Proliferation, migration and invasion inhibition Apoptosis	(70)
Lidocaine	Lung	A549 NCI-H1299	miR-539 upregulation	EGFR inhibition	Migration and invasion inhibition Apoptosis	(71)
Lidocaine	Lung	A549 A549/DDP	miR-21 downregulation	PTEN/PI3K/AKT PDCD4/JNK	Migration and invasion inhibition Apoptosis	(72)
Lidocaine	Lung	A549 PC9	Circ_PDZD8 downregulation	miR-516b-5p upregulation GOLT1A downregulation	Apoptosis	(73)
Lidocaine	Melanoma	SK-MEL-2	miR-493 upregulation	Sox4 downregulation Decrease in p-PI3K, p-AKT, p-Smad2	Apoptosis 5-FU cytotoxicity increase	(74)
Lidocaine	Neuroblastoma	SH-SY5Y	miR-145 upregulation	PI3K/AKT/mTOR inhibition	Growth inhibition Autophagy	(75)
Lidocaine	Neuroblastoma	SH-SY5Y	LINC01347 downregulation	hsa-miR-145-5p upregulation	Apoptosis	(76)

(Continued)

TABLE 2 Continued

Agents	Cancer	Human cell lines	Epigenetic changes	Target	Anticancer effects	Ref
Lidocaine	Ovary Breast	SKOV-3 T47D	miR-382-5p upregulation	SLC7A11 downregulation	Proliferation, migration and invasion inhibition Tumor growth inhibition Reactive Oxygen Species production Ferroptosis	(19)
Lidocaine	Retinoblastoma	Y79 WERI-RB1 SO-RB50 SO-RB70	miR-520a-3p upregulation	EGFR inhibition	Proliferation inhibition Apoptosis	(77)
Lidocaine	Skin	A431	miR-30c upregulation	SIRT1 downregulation	Proliferation inhibition Inhibition of cisplatin resistance	(6)
Procaine	Osteosarcoma	MG63	miR-133b upregulation	Decrease in p/t-AKT, p/t-ERK, and p/t-S6	Proliferation and migration inhibition Apoptosis	(31)
Ropivacaine	Breast	MCF-7 MDA-MB-231	miR-27b-3p upregulation	YAP downregulation	Proliferation, migration and invasion inhibition Tumor growth inhibition Apoptosis	(78)
Ropivacaine	Cervix	Siha Caski	miR-96 downregulation	MEG2 upregulation	Growth inhibition Apoptosis	(79)
Ropivacaine	Choriocarcinoma	NA	LNCOGFRP1 downregulation	miR-4731-5p upregulation HIF3A downregulation	Viability, migration and invasion inhibition	(80)
Ropivacaine	Gastric	AGS BGC-823	miR-520a-3p upregulation	PI3K/AKT inhibition	Proliferation, migration and invasion inhibition Apoptosis	(81)
Ropivacaine	Glioma	T98G LN229	circSCAF11 downregulation	miR-145-5p upregulation	Proliferation, migration and invasion inhibition Tumor growth inhibition Reactive Oxygen Species Apoptosis	(30)
Ropivacaine	Glioma	T98G LN229	SNHG16 downregulation	miR-424-5 upregulation	Proliferation, migration and invasion inhibition Apoptosis	(82)
Ropivacaine	Glioma	U87 U373 U251	miR-21-5p upregulation	KANSL2 downregulation	Proliferation, migration and invasion inhibition Apoptosis	(83)

which simultaneously inactivates both ERK and NF-κB pathways, potentiating the inhibition of proliferation, migration and invasion of malignant gastric cells (18).

Interestingly, different modalities of cell death triggered by epigenetic modulation were observed after LA treatment. The upregulation of miR-145 by lidocaine promoted autophagic flux in neuroblastoma SH-SY5Y cells (75). Lidocaine and levobupivacaine both induced ferroptosis by upregulating miR-382-5p and miR-489-3p, respectively (19, 63). The impact of LA on cellular stress and death pathways *via* the control of non-coding RNA emphasizes the possibility to use LA as novel antineoplastic therapeutics.

Finally, several reports suggest an intertwined regulation of multiple non-coding RNAs by LA. Indeed, lncRNAs and circular RNAs (circRNAs), a group of non-coding RNAs described to be involved in oncogenesis, may act as miRNA sponges. In a model of glioma, the treatment with ropivacaine suppressed tumor progression by upregulating the circRNA circSCAF11, while downregulating miR-145-5p (30). Inversely, bupivacaine decreased the expression of circ_0000376 while enhancing miR-145-5p in gastric cancer cells (61). Lidocaine hampered the proliferation of colorectal cancer cells by upregulating circlTFG2 and then decreasing miR-1204 (66). In a model of gastric cancer, lidocaine hindered tumor progression by modulating the miR-21-5p/LIFR axis *via* the overexpression of circ-ANO5 (68). Bupivacaine impeded neuroblastoma progression by modifying the expression of various long non-coding RNAs (ZFAS1, MALAT1, LINC00665, which sponged

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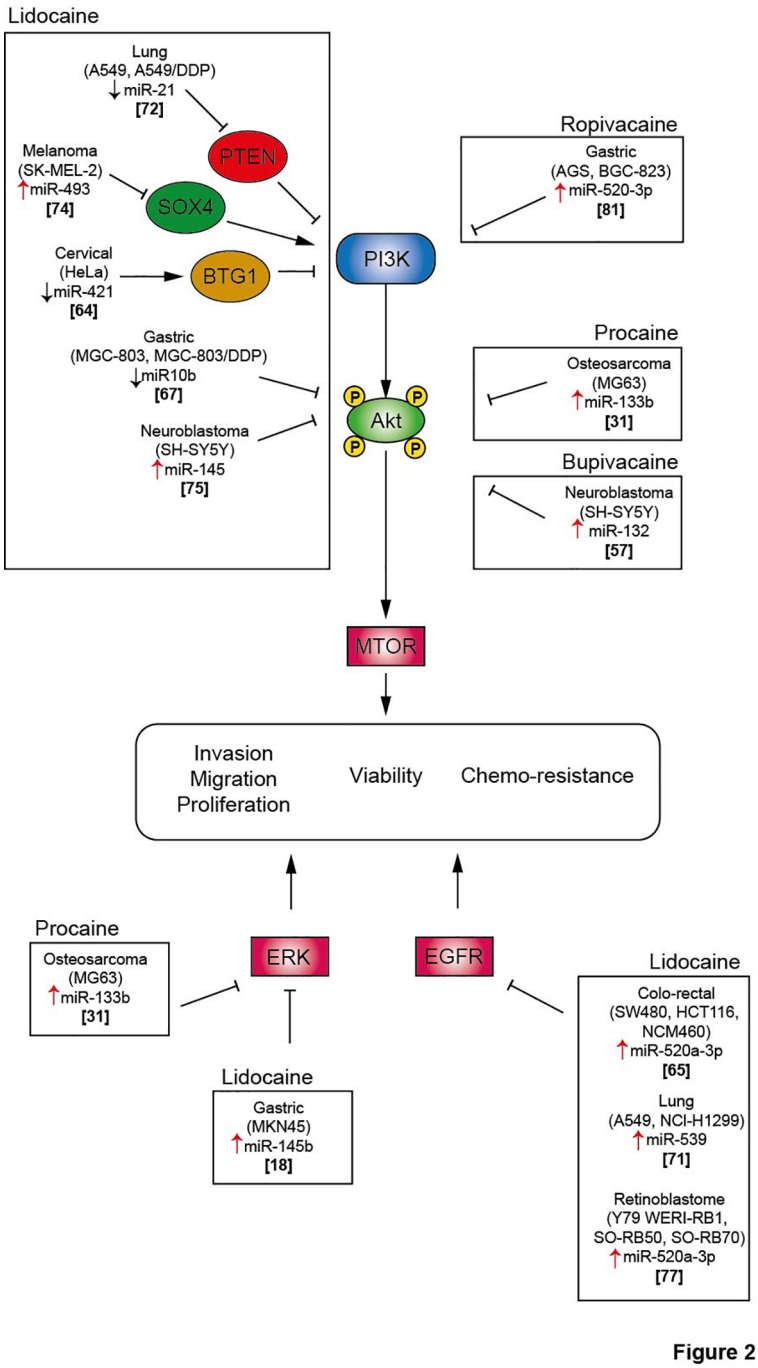

Figure 2

FIGURE 2
Local anesthetics inhibit cell proliferation, migration and invasion and promote cancer cell death *via* inhibition of several signaling pathway. Akt, protein kinase B; BTG1, B cell translocation gene 1; DDP, cisplatin; EGFR, Epithelial growth factor receptor; ERK, extracellular signal-regulated kinase; mTOR, mammalian Target of Rapamycin; PI3K, phosphoinositide-3 kinase; PTEN, Phosphatase and TENsin homolog; SOX4, SRY-Box Transcription Factor 4.

protumorigenic miR-421, miR-101-3-3p and miR-34a-5p, respectively) (58–60).

Local anesthetics repress histone acetylation in cancer cells

Previous publications reported that levobupivacaine, an amino amide LA widely used to control acute surgical pain, possesses the capacity to attenuate the oncological properties of several cancer types (86, 87). However, the mechanisms by which levobupivacaine exerts its anticancer activity remain poorly characterized. Lysine acetyltransferase 5 (KAT5) acetylates both non-histone and histone proteins and increases the invasiveness of cancer cells (88). Levobupivacaine inhibits the expression of KAT5 in osteosarcoma cells, thus inhibiting their proliferation and limiting their survival (22). This preclinical finding demonstrated the implication of LA in epigenetic changes on histones leading to anticancer properties. Interestingly, the inhibition of histone acetyltransferase activity decreases opioid-induced hyperalgesia in mice (89). Nevertheless, the impact of LA on histone modification as well as the oncological consequences remain unclear, calling for future exploration.

Discussion

The reversal of cancer-associated epigenetic dysregulations represents one possible antineoplastic strategy. Various demethylating molecules were characterized at the preclinical level (as exemplified by curcumin, (−)-epigallocatechin-3-gallate, N-phthalyl-tryptophan and zebularine) (90–94), and two agents (5-azacytidine and decitabine) have been approved by the FDA and EMA to treat patients with myelodysplastic syndrome or acute myeloid leukemia. These agents inhibit DNMT and hence reduce the global DNA methylation level in cancer cells. Despite their established anti-tumor activity, 5-azacytidine and decitabine induce severe myelosuppression, thus calling for the identification of novel epigenetic modulators.

Surprisingly, LA mediate significant antineoplastic activities by directly killing cancer cells and indirectly by eliciting anticancer immune responses (27, 32, 33, 37, 79, 95, 96). The detailed molecular comprehension of these effects may open a novel era in onco-anesthesia. Notably, the discovery of LA-promoted antitumor effects involving the induction of apoptosis secondary to the reduction of DNA methylation or the modulation of miRNAs has spurred much interest (18, 20, 30, 31, 67). Both amide and ester-type local anesthetics reduce global methylation levels in the promoter regions of tumor suppressor genes as a result of the inhibited interaction of DNMT with DNA. However, most preclinical studies have not yet investigated the effects of LA on the methylation of promoters of specific tumor suppressor genes as well as on the mRNA expression of such genes.

Beyond their effects on DNA methylation, LA also modulate (enhance or reduce) the expression of miRNAs in cancer cells, as summarized in a previous review (97). Compared to this published work, our review is the first one to critically evaluate all epigenetic changes induced by LA, including demethylating effects as well as miRNA regulation and histone acetylation, and to discuss their putative synergistic interaction with 5-azacytidine, decitabine and cytotoxicants. We surmise that the epigenetic effects of LA could be clinically relevant. Indeed, LA are well-known analgesics with a favorable toxicological profile that are commonly used during oncological intervention. A positive clinical impact of LA on cancer recurrence would provide a low-risk and low-cost benefit to oncological patients. However, before such a conclusion can be reached, further clinical and translational research must confirm the capacity of LA to improve the outcome of surgical procedures, especially if they are preceded or followed by (neo)adjuvant chemotherapy or immunotherapy. It will be particularly important to investigate the short-term (intra-operational) and long-term (post-operational) effects of LA on epigenetic signatures including DNA methylation patterns and the expression of non-coding RNAs in further translational studies.

Author contributions

LB, OK and GK wrote the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

OK is scientific co-founder of Samsara Therapeutics. GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, Osasuna, PharmaMar, Samsara, Sanofi, Sotio, Vascage and Vasculox/Tioma. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Deltour S, Chopin V, Leprince D. Epigenetics and cancer. *Medecine Sci M/S.* (2005) 21(4):405–11. doi: 10.1051/medsci/2005214405

2. Esteller M. Relevance of DNA methylation in the management of cancer. *Lancet Oncol* (2003) 4(6):351–8. doi: 10.1016/s1470-2045(03)01115-x

3. Bezu L, Chuang AW, Liu P, Kroemer G, Kepp O. Immunological effects of epigenetic modifiers. *Cancers* (2019) 11(12):1–20. doi: 10.3390/cancers11121911

4. Liu X, Zhao S, Sui H, Liu H, Yao M, Su Y, et al. MicroRNAs/LncRNAs modulate MDSCs in tumor microenvironment. *Front Oncol* (2022) 12:772351. doi: 10.3389/fonc.2022.772351

5. Liu QW, He Y, Xu WW. Molecular functions and therapeutic applications of exosomal noncoding RNAs in cancer. *Exp Mol Med* (2022) 54(3):216–25. doi: 10.1038/s12276-022-00744-w

6. Liu T, Jiang F, Yu LY, Wu YY. Lidocaine represses proliferation and cisplatin resistance in cutaneous squamous cell carcinoma *via* miR-30c/SIRT1 regulation. *Bioengineered.* (2022) 13(3):6359–70. doi: 10.1080/21655979.2022.2031419

7. Lal A, Kim HH, Abdelmohsen K, Kuwano Y, Pullmann R Jr., Srikantan S, et al. p16(INK4a) translation suppressed by miR-24. *PloS One* (2008) 3(3):e1864. doi: 10.1371/journal.pone.0001864

8. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. *Nature.* (2005) 435 (7043):828–33. doi: 10.1038/nature03552

9. Klose RJ, Bird AP. Genomic DNA methylation: the mark and its mediators. *Trends Biochem Sci* (2006) 31(2):89–97. doi: 10.1016/j.tibs.2005.12.008

10. Okano M, Bell DW, Haber DA, Li E. DNA Methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. *Cell.* (1999) 99(3):247–57. doi: 10.1016/s0092-8674(00)81656-6

11. Goll MG, Bestor TH. Eukaryotic cytosine methyltransferases. *Annu Rev Biochem* (2005) 74:481–514. doi: 10.1146/annurev.biochem.74.010904.153721

12. Ruter B, Wijermans PW, Lubbert M. DNA Methylation as a therapeutic target in hematologic disorders: recent results in older patients with myelodysplasia and acute myeloid leukemia. *Int J hematology.* (2004) 80(2):128–35. doi: 10.1532/ijh97.04094

13. Jabbour E, Issa JP, Garcia-Manero G, Kantarjian H. Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer.* (2008) 112(11):2341–51. doi: 10.1002/cncr.23463

14. Li K, Yang J, Han X. Lidocaine sensitizes the cytotoxicity of cisplatin in breast cancer cells *via* up-regulation of RARbeta2 and RASSF1A demethylation. *Int J Mol Sci* (2014) 15(12):23519–36. doi: 10.3390/ijms151223519

15. Li YC, Wang Y, Li DD, Zhang Y, Zhao TC, Li CF. Procaine is a specific DNA methylation inhibitor with anti-tumor effect for human gastric cancer. *J Cell Biochem* (2018) 119(2):2440–9. doi: 10.1002/jcb.26407

16. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines *in vitro*. *Br J anaesthesia.* (2012) 109(2):200–7. doi: 10.1093/bja/aes128

17. Sabit H, Samy MB, Said OA, El-Zawahri MM. Procaine induces epigenetic changes in HCT116 colon cancer cells. *Genet Res Int* (2016) 2016:8348450. doi: 10.1155/2016/8348450

18. Sui H, Lou A, Li Z, Yang J. Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145. *BMC cancer.* (2019) 19(1):233. doi: 10.1186/s12885-019-5431-9

19. Sun D, Li YC, Zhang XY. Lidocaine promoted ferroptosis by targeting miR-382-5p /SLC7A11 axis in ovarian and breast cancer. *Front Pharmacol* (2021) 12:681223. doi: 10.3389/fphar.2021.681223

20. Tada M, Imazeki F, Fukai K, Sakamoto A, Arai M, Mikata R, et al. Procaine inhibits the proliferation and DNA methylation in human hepatoma cells. *Hepatol Int* (2007) 1(3):355–64. doi: 10.1007/s12072-007-9014-5

21. Villar-Garea A, Fraga MF, Espada J, Esteller M. Procaine is a DNA-demethylating agent with growth-inhibitory effects in human cancer cells. *Cancer Res* (2003) 63(16):4984–9.

22. Wang Z, Song Y, Zhang H, Yang Y, Zhang S, Wang W. Local anesthetic levobupivacaine inhibits stemness of osteosarcoma cells by epigenetically repressing MAFB though reducing KAT5 expression. *Aging.* (2022) 14(6):2793–804. doi: 10.18632/aging.203975

23. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology*. (2008) 109(2):180–7. doi: 10.1097/ALN.0b013e31817f5b73

24. D'Agostino G, Saporito A, Cecchinato V, Silvestri Y, Borgeat A, Anselmi L, et al. Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. *Br J anaesthesia.* (2018) 121(4):962–8. doi: 10.1016/j.bja.2018.07.015

25. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Regional Anesth Pain Med* (2010) 35(6):490–5. doi: 10.1097/AAP.0b013e3181ef4d05

26. Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative epidural analgesia reduces cancer recurrence after gastro-oesophageal surgery. *Acta anaesthesiologica Scandinavica.* (2014) 58(3):281–90. doi: 10.1111/aas.12255

27. Jiang Y, Gou H, Zhu J, Tian S, Yu L. Lidocaine inhibits the invasion and migration of TRPV6-expressing cancer cells by TRPV6 downregulation. *Oncol letters.* (2016) 12(2):1164–70. doi: 10.3892/ol.2016.4709

28. Lu J, Xu SY, Zhang QG, Xu R, Lei HY. Bupivacaine induces apoptosis *via* mitochondria and p38 MAPK dependent pathways. *Eur J Pharmacol* (2011) 657(1-3):51–8. doi: 10.1016/j.ejphar.2011.01.055

29. Wang W, Zhu M, Xu Z, Li W, Dong X, Chen Y, et al. Ropivacaine promotes apoptosis of hepatocellular carcinoma cells through damaging mitochondria and activating caspase-3 activity. *Biol Res* (2019) 52(1):36. doi: 10.1186/s40659-019-0242-7

30. Yin D, Liu L, Shi Z, Zhang L, Yang Y. Ropivacaine inhibits cell proliferation, migration and invasion, whereas induces oxidative stress and cell apoptosis by circSCAF11/miR-145-5p axis in glioma. *Cancer Manage Res* (2020) 12:11145–55. doi: 10.2147/CMAR.S274975

31. Ying B, Huang H, Li H, Song M, Wu S, Ying H. Procaine inhibits proliferation and migration and promotes cell apoptosis in osteosarcoma cells by upregulation of MicroRNA-133b. *Oncol Res* (2017) 25(9):1463–70. doi: 10.3727/096504017X14878518291077

32. Zhang Y, Peng X, Zheng Q. Ropivacaine inhibits the migration of esophageal cancer cells *via* sodium-channel-independent but prenylation-dependent inhibition of Rac1/JNK/paxillin/FAK. *Biochem Biophys Res Commun* (2018) 501(4):1074–9. doi: 10.1016/j.bbrc.2018.05.110

33. Zheng Q, Peng X, Zhang Y. Cytotoxicity of amide-linked local anesthetics on melanoma cells *via* inhibition of ras and RhoA signaling independent of sodium channel blockade. *BMC anesthesiology.* (2020) 20(1):43. doi: 10.1186/s12871-020-00957-4

34. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology.* (2006) 105(4):660–4. doi: 10.1097/00000542-200610000-00008

35. Schlagenhauff B, Ellwanger U, Breuninger H, Stroebel W, Rassner G, Garbe C. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. *Melanoma Res* (2000) 10(2):165–9. doi: 10.1097/00008390-200004000-00009

36. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. *Oncotarget.* (2016) 7(12):15262–73. doi: 10.18632/oncotarget.7683

37. Chen J, Jiao Z, Wang A, Zhong W. Lidocaine inhibits melanoma cell proliferation by regulating ERK phosphorylation. *J Cell Biochem* (2019) 120 (4):6402–8. doi: 10.1002/jcb.27927

38. Piegeler T, Schlapfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, et al. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFalpha-induced invasion of lung adenocarcinoma cells *in vitro* by blocking the activation of akt and focal adhesion kinase. *Br J anaesthesia.* (2015) 115(5):784–91. doi: 10.1093/bja/aev341

39. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J anaesthesia.* (2006) 97(5):640–6. doi: 10.1093/bja/ael217

40. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine induces apoptosis and suppresses tumor growth in human hepatocellular carcinoma cells *in vitro* and in a xenograft model in vivo. *Anesthesiology.* (2017) 126(5):868–81. doi: 10.1097/ALN.0000000000001528

41. Zhang X, Pang W, Liu H, Wang J. Lidocine potentiates the cytotoxicity of 5-fluorouracil to choriocarcinoma cells by downregulating ABC transport proteins expression. *J Cell Biochem* (2019) 120(10):16533–42. doi: 10.1002/jcb.28913

42. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet.* (2019) 394(10211):1807–15. doi: 10.1016/S0140-6736(19)32313-X

43. Bezu L, Wu Chuang A, Sauvat A, Humeau J, Xie W, Cerrato G, et al. Local anesthetics elicit immune-dependent anticancer effects. *J immunotherapy Cancer* (2022) 10(4):1–17. doi: 10.1136/jitc-2021-004151

44. Lirk P, Hollmann MW, Fleischer M, Weber NC, Fiegl H. Lidocaine and ropivacaine, but not bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells in vitro. *Br J anaesthesia* (2014) 113 Suppl 1:i32–8. doi: 10.1093/bja/aeu201

45. Chen D, Yan Y, Xie J, Pan J, Chen Y, Li Q, et al. Amide-type local anesthetics may suppress tumor cell proliferation and sensitize human hepatocellular carcinoma cells to cisplatin via upregulation of RASSF1A expression and demethylation. *J Cancer.* (2020) 11(24):7312–9. doi: 10.7150/jca.46630

46. Gao Z, Xu Z, Hung MS, Lin YC, Wang T, Gong M, et al. Procaine and procainamide inhibit the wnt canonical pathway by promoter demethylation of WIF-1 in lung cancer cells. *Oncol Rep* (2009) 22(6):1479–84. doi: 10.3892/or_00000590

47. Stresemann C, Brueckner B, Musch T, Stopper H, Lyko F. Functional diversity of DNA methyltransferase inhibitors in human cancer cell lines. *Cancer Res* (2006) 66(5):2794–800. doi: 10.1158/0008-5472.CAN-05-2821

48. Lessans S, Dorsey SG. The role for epigenetic modifications in pain and analgesia response. *Nurs Res practice.* (2013) 2013:961493. doi: 10.1155/2013/961493

49. Lirk P, Fiegl H, Weber NC, Hollmann MW. Epigenetics in the perioperative period. *Br J Pharmacol* (2015) 172(11):2748–55. doi: 10.1111/bph.12865

50. Caputi FF, Carboni L, Rullo L, Alessandrini I, Balzani E, Melotti RM, et al. An exploratory pilot study of changes in global DNA methylation in patients undergoing major breast surgery under opioid-based general anesthesia. *Front Pharmacol* (2021) 12:733577. doi: 10.3389/fphar.2021.733577

51. Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, et al. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. *Nat Med* (2019) 25(9):1428–41. doi: 10.1038/s41591-019-0566-4

52. Khabbazi S, Hassanshahi M, Hassanshahi A, Peymanfar Y, Su YW, Xian CJ. Opioids and matrix metalloproteinases: the influence of morphine on MMP-9 production and cancer progression. *Naunyn-Schmiedeberg's Arch Pharmacol* (2019) 392(2):123–33. doi: 10.1007/s00210-019-01613-6

53. Liu Z, Cheng S, Fu G, Ji F, Wang C, Cao M. Postoperative administration of ketorolac averts morphine-induced angiogenesis and metastasis in triple-negative breast cancer. *Life Sci* (2020) 251:117604. doi: 10.1016/j.lfs.2020.117604

54. Sandoval-Sierra JV, Salgado Garcia FI, Brooks JH, Derefinko KJ, Mozhui K. Effect of short-term prescription opioids on DNA methylation of the OPRM1 promoter. *Clin epigenetics.* (2020) 12(1):76. doi: 10.1186/s13148-020-00868-8

55. Chidambaran V, Zhang X, Martin LJ, Ding L, Weirauch MT, Geisler K, et al. DNA Methylation at the mu-1 opioid receptor gene (OPRM1) promoter predicts preoperative, acute, and chronic postsurgical pain after spine fusion. *Pharmacogenomics personalized Med* (2017) 10:157–68. doi: 10.2147/PGPM.S132691

56. Peng Y, Croce CM. The role of MicroRNAs in human cancer. *Signal transduction targeted Ther* (2016) 1:15004. doi: 10.1038/sigtrans.2015.4

57. Zhang H, Lin J, Hu T, Ren Z, Wang W, He Q. Effect of miR-132 on bupivacaine-induced neurotoxicity in human neuroblastoma cell line. *J Pharmacol Sci* (2019) 139(3):186–92. doi: 10.1016/j.jphs.2019.01.014

58. Yuan L, Xu H, Guo R, Lu T, Li X. Long non-coding RNA ZFAS1 alle*via*tes bupivacaine-induced neurotoxicity by regulating the miR-421/zinc finger protein564 (ZNF564) axis. *Bioengineered.* (2021) 12(1):5231–40. doi: 10.1080/21655979.2021.1960776

59. Zhao Y, Ai Y. Knockdown of lncRNA MALAT1 alle*via*tes bupivacaine-induced neurotoxicity via the miR-101-3p/PDCD4 axis. *Life Sci* (2019) 232:116606. doi: 10.1016/j.lfs.2019.116606

60. Yang Z, Hu S, He Y, Ji L. LINC00665 rescues bupivacaine induced neurotoxicity in human neural cell of SH-SY5Y through has-miR-34a-5p. *Brain Res bulletin.* (2021) 177:210–6. doi: 10.1016/j.brainresbull.2021.10.004

61. Ju C, Zhou J, Miao H, Chen X, Zhang Q. Bupivacaine suppresses the progression of gastric cancer through regulating circ_0000376/miR-145-5p axis. *BMC anesthesiology.* (2020) 20(1):275. doi: 10.1186/s12871-020-01179-4

62. Lin CY, Tseng WT, Chang YY, Tsai MH, Chuang EY, Lu TP, et al. Lidocaine and bupivacaine downregulate MYB and DANCR lncRNA by upregulating miR-187-5p in MCF-7 cells. *Front Med* (2021) 8:732817. doi: 10.3389/fmed.2021.732817

63. Mao SH, Zhu CH, Nie Y, Yu J, Wang L. Levobupivacaine induces ferroptosis by miR-489-3p/SLC7A11 signaling in gastric cancer. *Front Pharmacol* (2021) 12:681338. doi: 10.3389/fphar.2021.681338

64. Zhu J, Han S. Lidocaine inhibits cervical cancer cell proliferation and induces cell apoptosis by modulating the lncRNA-MEG3/miR-421/BTG1 pathway. *Am J Trans Res* (2019) 11(9):5404–16.

65. Qu X, Yang L, Shi Q, Wang X, Wang D, Wu G. Lidocaine inhibits proliferation and induces apoptosis in colorectal cancer cells by upregulating mir-520a-3p and targeting EGFR. *Pathology Res Pract* (2018) 214(12):1974–9. doi: 10.1016/j.prp.2018.09.012

66. Wang H, Zhang X, Li Y, Li Y, Pang T. Lidocaine hampers colorectal cancer process *via* circITFG2/miR-1204/SOCS2 axis. *Anti-cancer Drugs* (2022) 33(3):235–44. doi: 10.1097/CAD.0000000000001091

67. Zhang X, Gu G, Li X, Zhang C. Lidocaine alle*via*tes cisplatin resistance and inhibits migration of MGC-803/DDP cells through decreasing miR-10b. *Cell Cycle* (2020) 19(19):2530–7. doi: 10.1080/15384101.2020.1809914

68. Guan E, Liu H, Xu N. Lidocaine suppresses gastric cancer development through Circ_ANO5/miR-21-5p/LIFR axis. *Digestive Dis Sci* (2022) 67(6):2244–56. doi: 10.1007/s10620-021-07055-6

69. Wen J, Li X, Ding Y, Zheng S, Xiao Y. Lidocaine inhibits glioma cell proliferation, migration and invasion by modulating the circEZH2/miR-181b-5p pathway. *Neuroreport.* (2021) 32(1):52–60. doi: 10.1097/WNR.0000000000001560

70. Zhao L, Ma N, Liu G, Mao N, Chen F, Li J. Lidocaine inhibits hepatocellular carcinoma development by modulating circ_ITCH/miR-421/CPEB3 axis. *Digestive Dis Sci* (2021) 66(12):4384–97. doi: 10.1007/s10620-020-06787-1

71. Sun H, Sun Y. Lidocaine inhibits proliferation and metastasis of lung cancer cell *via* regulation of miR-539/EGFR axis. *Artif cells nanomedicine Biotechnol* (2019) 47(1):2866–74. doi: 10.1080/21691401.2019.1636807

72. Yang Q, Zhang Z, Xu H, Ma C. Lidocaine alle*via*tes cytotoxicity-resistance in lung cancer A549/DDP cells *via* down-regulation of miR-21. *Mol Cell Biochem* (2019) 456(1-2):63–72. doi: 10.1007/s11010-018-3490-x

73. Zi H, Chen L, Ruan Q. Lidocaine represses the malignant behavior of lung carcinoma cells *via* the circ_PDZD8/miR-516b-5p/GOLT1A axis. *Histol histopathology.* (2022) 21:18423. doi: 10.14670/HH-18-423

74. Wang Y, Xie J, Liu W, Zhang R, Huang S, Xing Y. Lidocaine sensitizes the cytotoxicity of 5-fluorouacil in melanoma cells *via* upregulation of microRNA-493. *Die Pharmazie.* (2017) 72(11):663–9. doi: 10.1691/ph.2017.7616

75. Wang Z, Liu Q, Lu J, Cao J, Wang XY, Chen Y. Lidocaine promotes autophagy of SH-SY5Y cells through inhibiting PI3K/AKT/mTOR pathway by upregulating miR-145. *Toxicol Res* (2020) 9(4):467–73. doi: 10.1093/toxres/tfaa049

76. Zhang Y, Liu L, Xue P, Wang L. Long noncoding RNA LINC01347 modulated lidocaine-induced cytotoxicity in SH-SY5Y cells by interacting with hsa-miR-145-5p. *Neurotoxicity Res* (2021) 39(5):1440–8. doi: 10.1007/s12640-021-00363-9

77. Xia W, Wang L, Yu D, Mu X, Zhou X. Lidocaine inhibits the progression of retinoblastoma *in vitro* and in vivo by modulating the miR520a3p/EGFR axis. *Mol Med Rep* (2019) 20(2):1333–42. doi: 10.3892/mmr.2019.10363

78. Zhao L, Han S, Hou J, Shi W, Zhao Y, Chen Y. The local anesthetic ropivacaine suppresses progression of breast cancer by regulating miR-27b-3p/YAP axis. *Aging.* (2021) 13(12):16341–52. doi: 10.18632/aging.203160

79. Chen X, Liu W, Guo X, Huang S, Song X. Ropivacaine inhibits cervical cancer cell growth *via* suppression of the miR96/MEG2/pSTAT3 axis. *Oncol Rep* (2020) 43(5):1659–68. doi: 10.3892/or.2020.7521

80. Lu Y, Yang C, Zhang L, Ding J. Ropivacaine retards the *via*bility, migration, and invasion of choriocarcinoma cells by regulating the long noncoding RNA OGFRP1/MicroRNA-4731-5p/HIF3A axis. *Mol Biotechnol* (2022) 64(5):499–509. doi: 10.1007/s12033-021-00429-1

81. Zhang N, Xing X, Gu F, Zhou G, Liu X, Li B. Ropivacaine inhibits the growth, migration and invasion of gastric cancer through attenuation of WEE1 and PI3K/AKT signaling via miR-520a-3p. *OncoTargets Ther* (2020) 13:5309–21. doi: 10.2147/OTT.S244550

82. Liu R, Wu M, Xu G, Ju L, Xiao J, Zhong W, et al. Ropivacaine inhibits proliferation, migration, and invasion while inducing apoptosis of glioma cells by regulating the SNHG16/miR-424-5p axis. *Open Life Sci* (2020) 15(1):988–99. doi: 10.1515/biol-2020-0108

83. Deng Z, Jian Y, Cai H. Ropivacaine represses the proliferation, invasion, and migration of glioblastoma *via* modulating the microRNA-21-5p/KAT8 regulatory NSL complex subunit 2 axis. *Bioengineered.* (2022) 13(3):5975–86. doi: 10.1080/21655979.2022.2037955

84. Cunningham JT, Rodgers JT, Arlow DH, Vazquez F, Mootha VK, Puigserver P. mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex. *Nature.* (2007) 450(7170):736–40. doi: 10.1038/nature06322

85. Gong X, Dan J, Li F, Wang L. Suppression of mitochondrial respiration with local anesthetic ropivacaine targets breast cancer cells. *J Thorac disease.* (2018) 10 (5):2804–12. doi: 10.21037/jtd.2018.05.21

86. Kwakye AK, Kampo S, Lv J, Ramzan MN, Richard SA, Falagan AA, et al. Levobupivacaine inhibits proliferation and promotes apoptosis of breast cancer cells by suppressing the PI3K/Akt/mTOR signalling pathway. *BMC Res notes.* (2020) 13(1):386. doi: 10.1186/s13104-020-05191-2

87. Li T, Chen L, Zhao H, Wu L, Masters J, Han C, et al. Both bupivacaine and levobupivacaine inhibit colon cancer cell growth but not melanoma cells *in vitro*. *J anesthesia.* (2019) 33(1):17–25. doi: 10.1007/s00540-018-2577-6

88. Kwan SY, Sheel A, Song CQ, Zhang XO, Jiang T, Dang H, et al. Depletion of TRRAP induces p53-independent senescence in liver cancer by down-regulating mitotic genes. *Hepatology.* (2020) 71(1):275–90. doi: 10.1002/hep.30807

89. Liang DY, Li X, Clark JD. Epigenetic regulation of opioid-induced hyperalgesia, dependence, and tolerance in mice. *J pain.* (2013) 14(1):36–47. doi: 10.1016/j.jpain.2012.10.005

90. Cheng JC, Matsen CB, Gonzales FA, Ye W, Greer S, Marquez VE, et al. Inhibition of DNA methylation and reactivation of silenced genes by zebularine. *J Natl Cancer Institute.* (2003) 95(5):399–409. doi: 10.1093/jnci/95.5.399

91. Cheng JC, Weisenberger DJ, Gonzales FA, Liang G, Xu GL, Hu YG, et al. Continuous zebularine treatment effectively sustains demethylation in human bladder cancer cells. *Mol Cell Biol* (2004) 24(3):1270–8. doi: 10.1128/MCB.24.3.1270-1278.2004

92. Fang MZ, Wang Y, Ai N, Hou Z, Sun Y, Lu H, et al. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. *Cancer Res* (2003) 63(22):7563–70.

93. Liu Z, Xie Z, Jones W, Pavlovicz RE, Liu S, Yu J, et al. Curcumin is a potent DNA hypomethylation agent. *Bioorganic medicinal Chem letters.* (2009) 19(3):706–9. doi: 10.1016/j.bmcl.2008.12.041

94. Schneeberger Y, Stenzig J, Hubner F, Schaefer A, Reichenspurner H, Eschenhagen T. Pharmacokinetics of the experimental non-nucleosidic DNA methyl transferase inhibitor n-Phthalyl-L-Tryptophan (RG 108) in rats. *Basic Clin Pharmacol toxicology.* (2016) 118(5):327–32. doi: 10.1111/bcpt.12514

95. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. Local anesthetics inhibit kinesin motility and microtentacle protrusions in human epithelial and breast tumor cells. *Breast Cancer Res Treat* (2011) 129(3):691–701. doi: 10.1007/s10549-010-1239-7

96. Dan J, Gong X, Li D, Zhu G, Wang L, Li F. Inhibition of gastric cancer by local anesthetic bupivacaine through multiple mechanisms independent of sodium channel blockade. *Biomedicine pharmacotherapy = Biomedecine pharmacotherapie.* (2018) 103:823–8. doi: 10.1016/j.biopha.2018.04.106

97. Tabnak P, Masrouri S, Geraylow KR, Zarei M, Esmailpoor ZH. Targeting miRNAs with anesthetics in cancer: Current understanding and future perspectives. *Biomedicine pharmacotherapy = Biomedecine pharmacotherapie.* (2021) 144:112309. doi: 10.1016/j.biopha.2021.112309

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