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Colorectal cancer awareness month diagnosis, clinical course, and surgical management of metastatic colorectal cancer 2023

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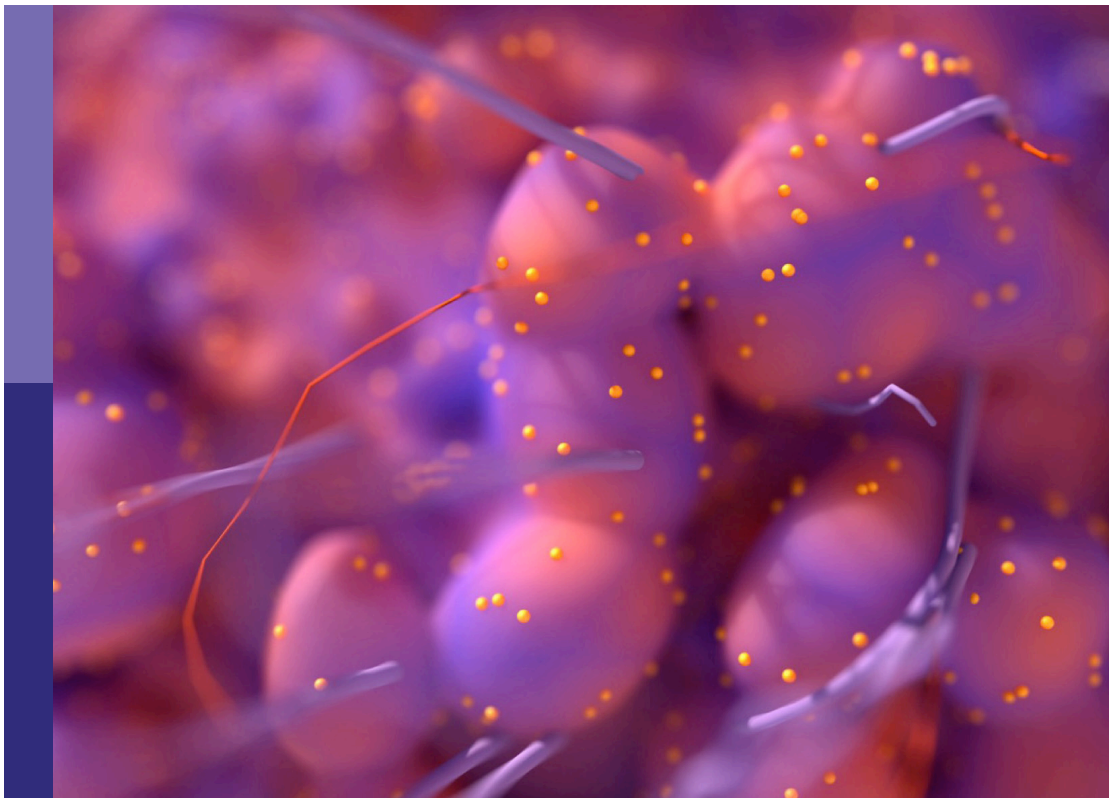

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Colorectal cancer awareness month 2023: diagnosis, clinical course, and surgical management of metastatic colorectal cancer

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Editorial: Colorectal cancer awareness month 2023: diagnosis, clinical course, and surgical management of metastatic colorectal cancer

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Editorial on the Research Topic
Colorectal cancer awareness month 2023: diagnosis, clinical course, and surgical management of metastatic colorectal cancer

Despite advances in medical care, Colorectal Cancer (CRC) is still a challenging health problem, representing the third most common cancer in terms of incidence and one of the leading causes of cancer-related mortality in the Western world (1).

Researchers are addressing various aspects of CRC, encompassing prevention, diagnosis, and treatment at different stages, from precancerous lesions to locally advanced and metastatic tumors (2–6). After pandemic era (7), advances in technology and cancer research are rapidly providing valuable and innovative insights for clinicians, researchers, and policymakers. Physicians must make clinical decisions among several options, pursuing a personalized approach for each patient in a continuously evolving scenario. Multidisciplinarity is the key, combining the expertise of medical oncologists, surgical oncologists, radiation oncologists, gastroenterologists, endoscopists, interventional radiologists, nuclear medicine physicians, pathologists, palliatives, and nurses in a patient-centered process (8–12). It is the only way to provide cutting-edge treatments, balancing benefits, risks, and costs in light of the latest evidence.

Following the considerations above, this editorial introduces a collection of articles entitled: "Colorectal Cancer Awareness Month 2023: Diagnosis, Clinical Course, and Surgical Management of Metastatic Colorectal Cancer," which deeply explores the actual complexity of research and clinical practice for CRC patients.

In such a heterogeneous scenario, we have merged preclinical and clinical research on CRC, aiming to outline a single fil-rouge. Progress is driven by hyper-specialized research activity, but interconnection among different specialists is crucial for translating discoveries into clinical practice. Considering the latest innovations in each field, a multidisciplinary

approach is essential to integrate them into the best clinical solution. For instance, medical and surgical oncologists strongly demand new biomarkers to guide their daily clinical decisions reliably (1, 13–15). The answer will likely be found by combining the results of genetic, radiomic, pathologic, and preclinical studies ongoing worldwide (16, 17). This is the spirit of the present Research Topic, in which the reader will navigate through the most recent advances and challenges in CRC research and treatment, always perceiving a unique aim: to build a multidisciplinary benchmark to answer clinical questions. Here are some of the most relevant insights from the published articles.

Schnitzer et al. analyzed the cost-effectiveness analysis of different imaging modalities for detecting colorectal liver metastases eligible for hepatic resection.

This study is critical for optimizing clinical outcomes and resource allocation, underscoring the importance of economic considerations in modern clinical reasoning (18–20).

At the same time, as reported by Zhang et al., the most recent laboratory researches, ranging from circulating biomarkers to single-cell RNA sequencing and bulk RNA transcriptome sequencing, pave the way to new approach to CRC, by unveiling heterogeneous immune landscape and identifying pivotal cell subpopulations associated with prognosis.

New biomarkers for CRC were also discussed. Lucarelli et al. proposed a potential role for the superior mesenteric vein ectasia in predicting liver metastases from rectal cancer, while Wang et al. suggested that serum mannose levels could predict the tumor N staging. A deeper knowledge of tumor biology is the basis for new therapeutic targets, which are crucial for developing personalized medicine approaches, and better prognostic models (21).

The term "Personalized medicine", beside its therapeutic implication, also underscores the need for a patient-centered care. The patients and their relatives should be actively involved in the decision-making process and their feelings and behavior (o life-style) should be considered. According to the study by Gu et al., this remains an unmet need, with several patients not having a dominant role in clinical decision-making.

This issue is even more relevant in elderly patients: as reported by Huemer et al., patients aged 70 years or older with metastatic CRC can be effectively treated, but their comorbidities and specific physiological responses to treatment must be considered to find the right balance between efficacy and tolerability of interventions (22, 23). Ding et al. reported in a propensity score matching study the benefit of regional block techniques on postoperative high-grade complications in elderly patients with thoracic and abdominal cancers.

On the same line, the meta-analysis by Zeng et al. outlined the risk factors for lateral pelvic lymph node metastases in patients with low rectal cancer. The non-invasive stratification of risk for nodal metastases is essential to plan treatment and modulate aggressiveness of surgery. Finally, the increasing minimal invasiveness of therapeutic options enhances the access to treatment.

Shi et al., using a large database of over 25,000 patients, elucidated the indications for endoscopic treatment of T1N0 tumors, which offers a chance of cure even for frail patients.

In conclusion, this Research Topic aims to provide a deeper understanding of CRC, offering readers new perspectives on diagnosis, treatment, and patient management. The proposed papers strongly highlight the commitment of the medical and scientific community to improving the lives of patients affected by CRC through rigorous research and innovative solutions. While new complexities are continuously uncovered, the collected manuscripts provide invaluable contributions to shaping the future of CRC treatment.

In conclusion, this Research Topic aims to provide a deeper understanding of CRC, giving readers new perspectives concerning diagnosis, treatment, and patient management. From the proposed papers, it emerges with strength the commitment of the medical and scientific community to improve the lives of patients affected by CRC through rigorous research and innovative solutions. While new complexities are continuously uncovered, the collected manuscript give an invaluable contribution in shaping the near future of CRC treatment. As we continue to uncover the complexities of this disease, such contributions are invaluable in shaping the future of colorectal cancer care.

Author contributions

AR: Writing – original draft, Writing – review & editing. LV: Writing – original draft, Writing – review & editing. AR: Writing – review & editing.

Conflict of interest

The 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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Cost-effectiveness analysis of MRI, CE-CT and 18F-FDG PET/CT for detecting colorectal liver metastases eligible for hepatic resection

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Objectives: Colorectal cancer (CRC) is a serious challenge for the health system. In 2022 CRC represented 8% of cancer diagnoses in the United States. 30% of patients already show metastases at the initial tumor staging. The majority of these metastases are sited in the liver. According to their extension and the status of the tumor colorectal liver metastases can be treated in several ways, with hepatic resection being the gold-standard. Contrast-enhanced computed tomography (CE-CT), positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) can be used for evaluation of resectability of these liver metastases. The aim of this study is to assess the most economic imaging modality for detecting liver metastases eligible for hepatic resection by analyzing their cost-effectiveness.

Materials and methods: In our study, a Markov state transition model was built to calculate the quality-adjusted life years (QALYs) and overall costs for each diagnostic strategy in accord with the stated input values obtained from scientific research. Further, probabilistic sensitivity analyses by means of Monte Carlo simulations were performed to consider possible model uncertainties. For evaluation of the cost-effectiveness on an economic threshold, the Willingness-to-pay (WTP) was set at $ 100,000. The applied values and the calculated results are based on the U.S. healthcare system.

Results: CE-CT led to overall costs of $ 42,874.02 and 8.47 QALYs, whereas MRI led to $ 40,863.65 and 8.50 QALYs. PET/CT resulted in overall costs of $ 43,216.74 and 8.48 QALYs. Therefore, MRI was determined to be the dominant strategy in the model. According to the performed sensitivity analyses, MRI remained cost-effective over a wide range of WTPs.

Conclusion: In conclusion, according to our analysis, MRI is the dominant strategy for detecting hepatic metastases eligible for hepatic resection in colorectal cancer.

KEYWORDS

cost-effectiveness, CRLM, PET/CT, MRI, hepatic resection

1 Introduction

Colorectal cancer (CRC) poses a significant challenge to global health, as it is one of the most prevalent cancer types in the world. In the United States, CRC accounts for approximately 8% of newly diagnosed tumors and 9% of all cancer-related deaths (1). Risk factors for CRC include family history, metabolic diseases such as diabetes and obesity, chronic inflammatory intestinal diseases, and the use of nicotine and alcohol (2–4). Notably, the incidence of CRC in individuals under the age of 50 has increased significantly over the past few decades (5). Approximately 50% of CRC patients develop metastases during the course of their disease, with 26.5% of these metastases occurring in the liver (6, 7).

Fortunately, curative therapy for Colorectal liver metastases (CRLM) is achievable, and a complete remission can be achieved. Patients with untreated metastases have a median three-year overall survival of 27.5% (8). The gold standard for the treatment of liver metastases is surgical resection, which is recommended as the standard procedure for R0-resectable metastases in the new 2022 ESMO guidelines (9). However, due to a poor health status of the mainly elderly patients or inconvenient metastatic location near important liver structures, approximately 80% of patients are still not suitable for surgical resection (10). Therefore, it is essential to select liver metastases that are suitable for surgical resection during the diagnostic process. For liver lesions that are not eligible for resection, the most common treatment options are thermal ablation methods such as microwave ablation (MWA), radiofrequency ablation (RFA), or cryotherapy. The gold standard in CRLM treatment is currently under contention as the COLLISION Trial, which compares thermal ablation to surgical resection in the presence of a resectable and ablatable liver lesion (10).

An accurate and timely diagnosis is critical for identifying metastases accurately and selecting the most appropriate treatment for the patient, which can improve survival rate and overall health (11). In addition, proper imaging is vitally important for Follow-Up of the patients, as the local recurrence rates of liver metastases may reach to 55-60% (12).

Contrast-enhanced computed tomography (CE-CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT) with 18F-fluorodeoxyglucose (18F-FDG) as a tracer are the preoperative imaging modalities for detecting CRLM (13). MRI is in fact superior to 18F-FDG PET/CT and CE-CT for detecting liver metastases due to its better soft-tissue contrast with contrast-agencies (14). Despite the diagnostic value of each imaging method, the monetary value of the investigated strategies still needs to be examined. The goal of this article is to estimate the long-term cost-effectiveness of MRI, CE-CT, and 18F-FDG PET/CT for detecting CRLM eligible for hepatic resection in relation to each other.

2 Materials and methods

2.1 Markov model design

To evaluate the financial value of imaging techniques for identifying CRLM suitable for ablation, a decision analysis was conducted using TreeAge Pro 2021 (Williamstown, MA) software. A Markov model was employed to forecast the long-term outcomes of patients based on the chosen imaging approach. A Markov model is a statistical tool that estimates the probabilities of all predefined model states and transitions between states in a complex system (Figures 1A, B). The model includes the model states “tumor-free”, “diagnosed tumor/no treatment”, “diagnosed tumor/hepatic resection”, and “death”. At the start of each measured cycle - in our model every cycle is one year for an overall duration of 5 years - the patient’s model state transits to a different state according to preset probabilities. At every moment in the model, the patient can be sorted into one of the preset model states. Each model state can also be associated with specific preset expenses and quality of life.

2.2 Input values

According to guidelines for executing cost-effectiveness analyses, costs and utilities are discounted by 3.00%. Additionally, Willingness-to-pay (WTP) is set to $ 100,000 per quality-adjusted

Abbreviations: CE-CT, Contrast enhanced computed tomography; MRI, Magnetic resonance tomography; PET/CT, Positron emission tomography/computed tomography; 18F-FDG, Fluordesoxyglucose; WTP, Willingness-to-pay; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; CRC, Colorectal cancer; CRLM, Colorectal liver metastases; omCRC, oligometastatic colorectal cancer; RFA, Radiofrequency Ablation; MWA, Microwave Ablation; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CE-MRI, Contrast enhanced magnetic resonance tomography; PET/MRI, Positron emission tomography/Magnetic resonance tomography.

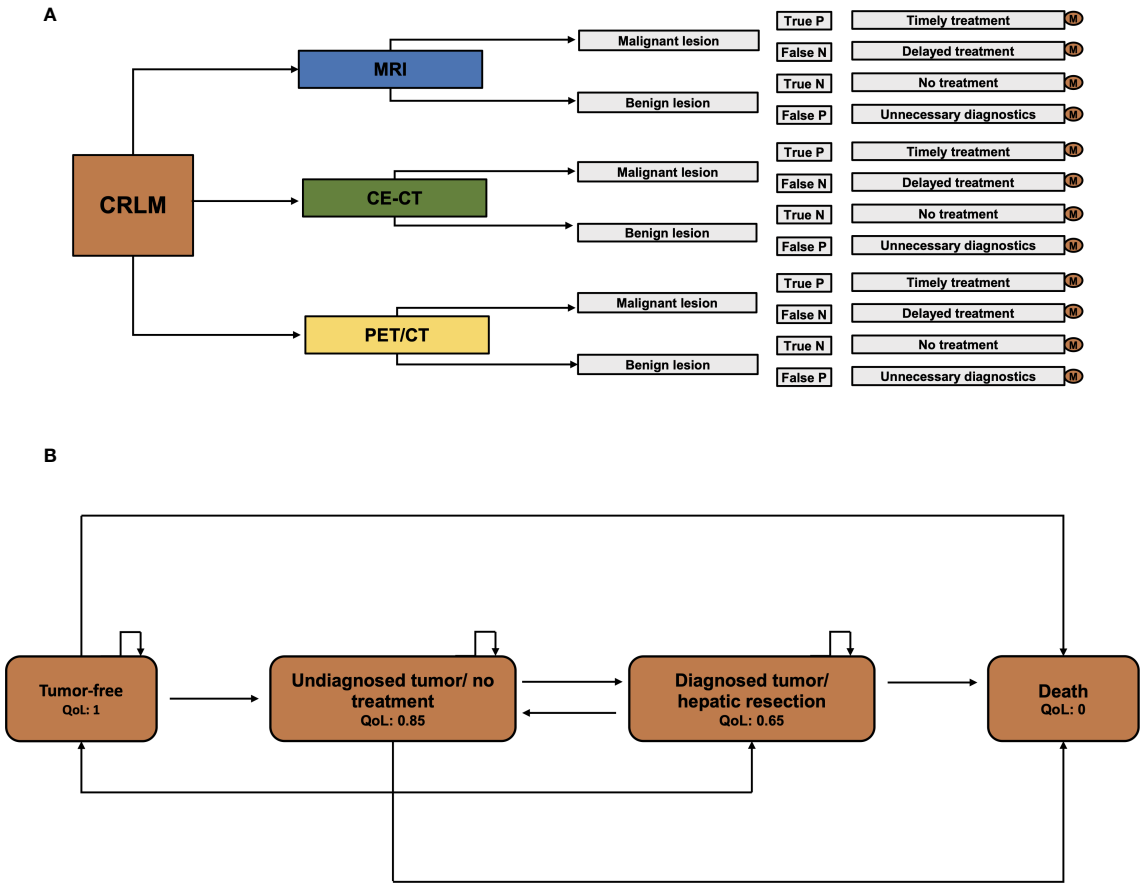

FIGURE 1
Model scheme. **(A)** Decision model for CE-CT, PET/CT, and MRI. For every single pathway, separate Markov calculations were executed. **(B)** The Markov model with the specified health stages "tumor-free", "Undiagnosed tumor/no treatment", "Diagnosed tumor/hepatic resection", and "Death".

life-year (QALY). The WTP can be seen as a limit of costs that the healthcare system of a society is willing to pay for a certain health profit. The mean age of the patient undergoing diagnostics for CRLM was 68 years in accordance with CRLM collectives. The applied values and the calculated results are based on the U.S. healthcare system. An overview of the applied input values is given in Table 1.

2.2.1 Diagnostic accuracy

The sensitivity and specificity values of the imaging methods in question are based on a European Radiology published article from Sivesgaard et al., 2018 comparing the diagnostic accuracy of CE-CT, MRI and 18F-FDG PET/CT (14). The sensitivities of CE-CT, 18F-FDG PET/CT, and MRI are therefore 65.70%, 72.05%, and 84.85%, whereas the specificities are 93.65%, 92.85%, and 92.05%. These values are averages of the diagnostic accuracy of the two reader results in the study.

2.2.2 Utilities, costs and probabilities

Utilities are assessed as quality-adjusted life years (QALYs) as a value of the patients' health status in every model state.

The costs of the imaging methods in question were obtained from Medicare in 2023. The costs for each modality may increase in future, as they undergo a yearly increase of around 10% (21). These increases of costs were not considered in the analysis. In addition, the costs for hepatic resection and the hospital stay after hepatic resection for every day were added to the analysis. Moreover, false negative imaging results that lead to a delayed treatment were estimated to be 1.3 times as high as a treatment in time.

The probability for a patient without tumor, for a diagnosed tumor without a treatment started, for a diagnosed hepatic tumor with surgical treatment and for death were incorporated in the model. To estimate the probability of the patient's demise for any other reason than a tumor-related, US Life Tables were utilized as a reference. Additionally, the values for the probabilities for changing between the model states were assessed from scientific literature.

2.3 Economic analysis

QALYs and overall costs were calculated in the base-case scenario and customized in accordance with the applied discount rates and the Willingness-to-Pay. Further, incremental cost-effectiveness ratios (ICER) were calculated. The ICER is a parameter that measures the economic value of a diagnostic strategy and is calculated by the following formula:

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TABLE 1 Input values.

Name	Estimate	Distribution	Source
Expected value at diagnostic procedure	68	β	Engstrand et al., 2018 (6)
WTP	$ 100,000.00		Sanders et al., 2016 (15)
Discount for costs and utilities	3.00%		Sanders et al., 2016 (15)
Markov Model time frame	5 years		Sanders et al., 2016 (15)
Diagnostic test performances			
CE-CT sensitivity	65.70%	β	Sivesgaard et al., 2018 (14)
CE-CT specificity	93.65%	β	Sivesgaard et al., 2018 (14)
MRI sensitivity	84.85%	β	Sivesgaard et al., 2018 (14)
MRI specificity	92.05%	β	Sivesgaard et al., 2018 (14)
PET/CT sensitivity	72.05%	β	Sivesgaard et al., 2018 (14)
PET/CT specificity	92.85%	β	Sivesgaard et al., 2018 (14)
Costs (Acute)			
CE-CT	$ 464.00	Γ	Medicare (74177)
MRI (contrast-enhanced)	$ 964.00	Γ	Medicare (74183, 72197)
PET/CT	$ 1,615.00	Γ	Medicare
Cost of hospital stay (per day)	$ 2,606.00	Γ	Henry J Kaiser Foundation, KFF.org
Hepatic resection costs	$ 4.450.00	Γ	Medicare
Days in hospital	7		NG KKC et al., 2017 (16)
Overall resection costs	$ 21,592.00	Γ	Medicare
Delayed resection, further tests	$ 28,069.60	Γ	Expert opinion (1.3x as expensive)
Costs (Long Term)			
Annual expenses without tumor	$ 0	Γ	Assumption
Annual expenses with active CRLM	$ 63,063.00	Γ	Chen et al., 2018 (17)
Utilities			
QOL of patients without tumor	1	β	Assumption
QoL after resection	0.78	β	Wiering et al., 2011 (18)
QoL with recurrence	0.65	β	Kim et al., 2016 (19)
QoL with undetected recurrence	0.85	β	Assumption
Death	0		Assumption
Transition probabilities			
Risk of death without tumor	(age dependent)	β	US Life Tables 2015
Probability of successful treatment	70%	β	Expert opinion
Probability of recurrence after resection	62%	β	Hirokawa et al., 2019 (20)
Probability of hepatic metastases	27.50%	β	Engstrand et al., 2018 (6)
Probability of death without treatment	24.17%	β	Siebenhüner et al., 2020 (8)

$$\mathbf{ICER} = (\mathbf{e1} - \mathbf{e0})/(\mathbf{q1} - \mathbf{q0})$$

In the ICER-formula, e1 and e0 are describing the cumulative short- and long-term costs of each diagnostic strategy, whereas q1 and q0 are describing the utilities and therefore effectiveness of each diagnostic strategy. The value of the ICER stands for the additional cost per QALY for each diagnostic strategy.

2.4 Sensitivity analysis

To simulate the influence of input parameter changes on imaging strategies' cost-effectiveness, a deterministic sensitivity analysis was performed. The analysis altered overall costs and diagnostic accuracy within a reasonable range to highlight their impact. A tornado diagram was used to display the ICERs after various changes.

Meanwhile, a probabilistic sensitivity analysis was conducted to investigate the general uncertainty of input parameters and their effect on cost-effectiveness. Using probability distributions, a Monte Carlo data simulation was carried out with 50,000 iterations to assess the model results' overall stability.

2.5 CHEERS statement

The fundamental basics of the methodology are based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. The major criteria of the checklist on how to perform cost-effectiveness analyses are met in this study (22, 23).

3 Results

3.1 Cost-effectiveness analysis

The strategies MRI, CE-CT, and PET/CT generated overall costs of $ 40,863.65, $ 42,874.02, and $ 43,216.74 with the effectiveness of 8.50, 8.47, and 8.48 QALYs in the baseline calculations with a WTP of $ 100,000. As a result, MRI dominated CE-CT and PET/CT in overall costs as well as in its effectiveness. The cost-effectiveness ranking is shown in Figure 2.

3.2 Sensitivity analysis

The study investigated how changes in input parameters affected the cost-effectiveness of different imaging strategies using deterministic sensitivity analysis. The results are presented in a Tornado Diagram (Figure 3), which shows that the specificities of MRI and PET/CT have the most significant impact on cost-effectiveness. However, since MRI is cheaper and more effective than PET/CT, even changes in the input parameters within the range tested did not significantly affect the cost-effectiveness of MRI.

To assess the general uncertainty of the input parameters and their influence on cost-effectiveness, the study used a Monte Carlo Simulation with 50,000 iterations. Across a broad range of costs, MRI was found to be the most cost-effective modality compared to CE-CT and PET/CT in the majority of iterations (Figure 4A). Furthermore, when considering a willingness-to-pay threshold of $100,000, MRI was the cost-effective modality in 82.99% of the

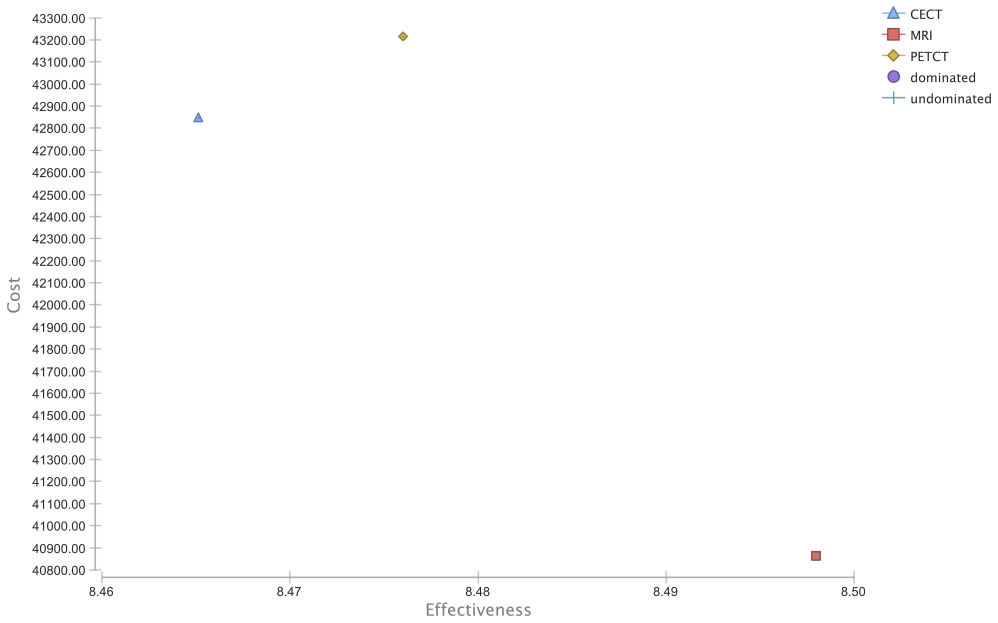

FIGURE 2
Cost-effectiveness analysis.

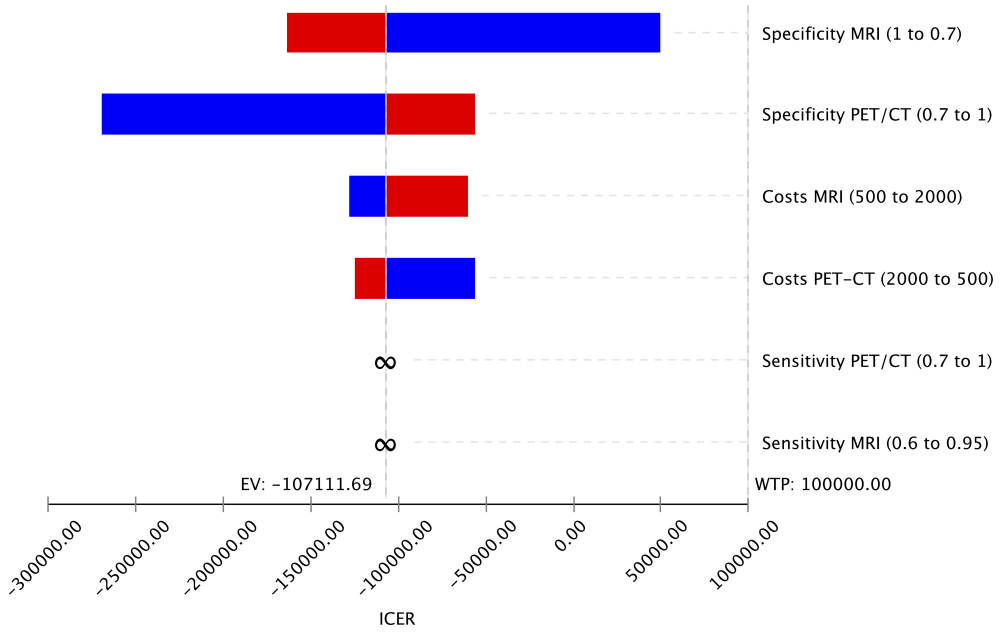

FIGURE 3
Tornado Diagram displaying variable changes of input parameters on the cost-effectiveness of the imaging strategies MRI and PET/CT showing that the specificities of both imaging methods have the highest impact on the cost-effectiveness.

simulations, whereas CE-CT and PET/CT were cost-effective in only 6.16% and 10.85%, respectively (Figure 4B). These results, based on 50,000 patient cases, demonstrate the economic superiority of MRI over CE-CT and PET/CT and suggest that MRI may be the preferred strategy for detecting CRLM eligible for hepatic resection.

4 Discussion

Our model reveals the cost-effectiveness of MRI for detecting CRLM eligible for hepatic resection compared to CE-CT and 18F-FDG PET/CT. MRI offers - alongside its economic superiority - the advantage of having the most reliable diagnostic accuracy compared to CE-CT and PET/CT. In addition to its economic advantages, MRI offers superior diagnostic accuracy compared to CE-CT and PET/CT, with the Diffusion-Weighted Imaging and T2-weighted fat suppression sequences being crucial for ensuring the highest accuracy. MRI also has an advantage for detecting recurrence of local metastases (24, 25). For instance, Sakai et al. (2022) discovered that the fat signal fraction in MRI after hepatic resection is associated with local recurrence. Therefore, due to the technological features of MRI, local recurrence can be detected earlier than in CE-CT (26). Furthermore, the importance of MRI especially for the clinical management of CRLM was proved in a meta-analysis of Vreugdenburg et al., 2016. This meta-analysis including 13 studies with 1025 patients on the one hand shows the diagnostic superiority of MRI over CE-CT with sensitivity values ranging from 86.9 to 100% for MRI and from 51.8 to 84.6% for CE-CT, and on the other hand it demonstrates that MRI had a significant influence on the clinical management of CRLM in 16.8% of patients with prior CE-CT. The fact that 1 of 6 patients is able to get a better treatment only through an additional MRI is huge and endorses the importance of MRI for treatment planning (27). In addition, it must be emphasized that most important driver for cost-effectiveness is not the cost of imaging, but more the costs for the treatment and the potential retreatment of a heavier tumor burden caused by an insufficient diagnostic workup in the first place, meaning that even if the costs for certain imaging methods vary in the real world, it does not have a strong influence on the cost-effectiveness outcome as the costs for imaging are just a small fraction compared to the overall costs of surgery and ongoing treatment. In order to minimize the risk of such a scenario, a diagnostic workup with MRI as the best imaging method for this indication is recommended that the patient can have the best possible treatment available and even has the chance for being cured.

In the baseline scenario, the cost-effectiveness of MRI is quite stable. In order to determine where a possible breaking point for CE-CT may be, we ran a supplementary 2-way deterministic sensitivity analysis (Supplementary Figure 1). On the vertical axis the sensitivity of CE-CT is shown, whereas the horizontal axis represents the sensitivity of MRI over a wide range. The colored areas represent the cost-effectiveness of each modality. As one can see, there may be a breaking point to CE-CT if sensitivity values of CE-CT increases unproportionally whit simultaneously decreasing sensitivities for MRI. With a stable sensitivity value for MRI over 85%, a breaking point for CE-CT is only a hypothetical one, as an increase of CE-CT sensitivity beyond 85% may be unrealistic. Nonetheless, the technological improvement in CT technology with Photon-counting CTs may change the outcome in the future. Therefore, it may become interesting to reevaluate the

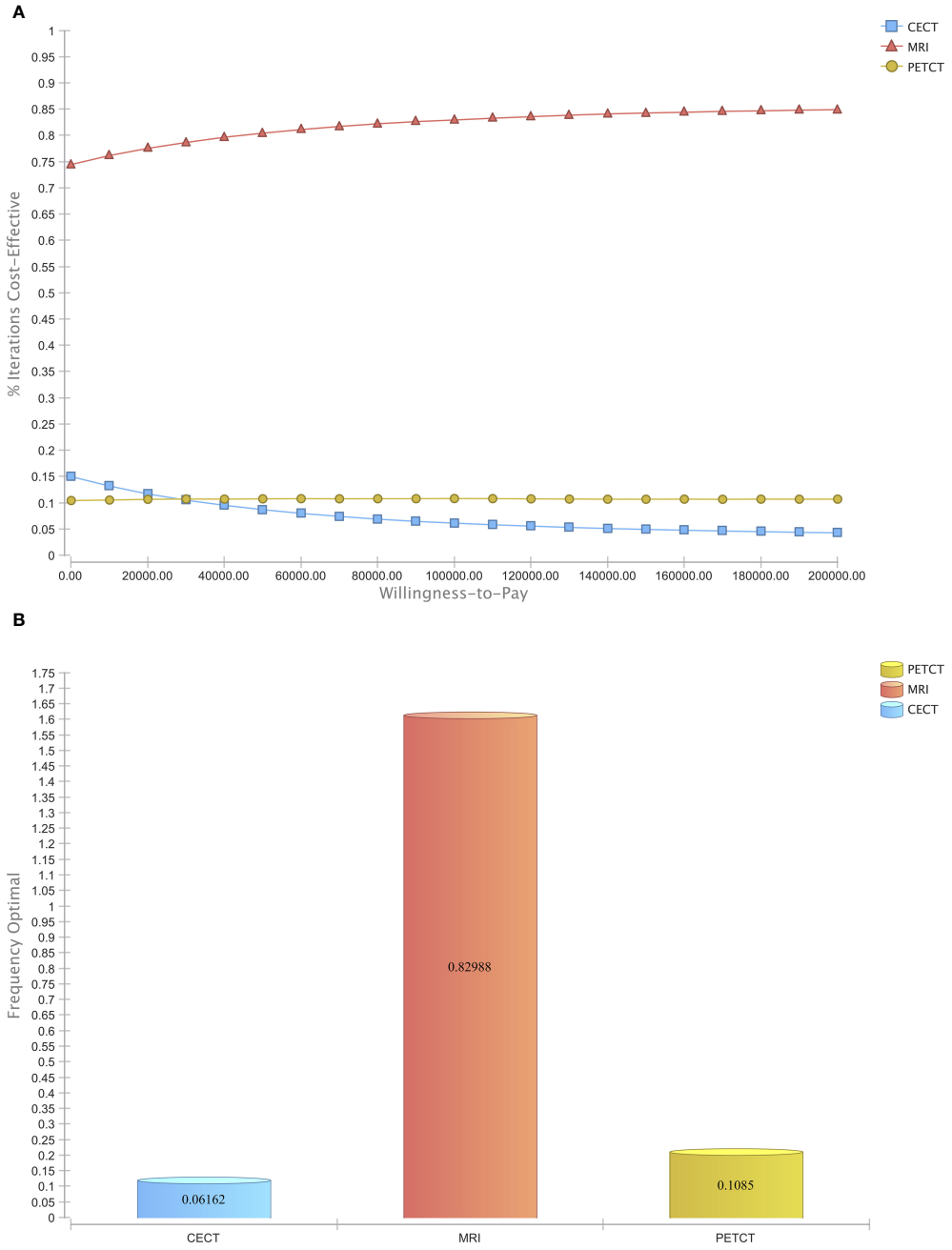

FIGURE 4
Probabilistic sensitivity analysis. **(A)** Acceptability Curve visualizing the economic dominance of MRI in the majority of reiterations over a wide span of WTPs **(B)** Acceptability at Willingness-to-Pay of $ 100,000.

results when the diagnostic performance of photon-counting CT has been investigated over a larger patient number.

Another issue that needs to be acknowledged are disappearing liver metastases (DLM) due to preoperative chemotherapy. In 7 to 48% of cases of patients with neoadjuvant chemotherapy before resection of the liver metastases, these metastases become undetectable by CE-CT and CE-MRI after their chemotherapy cycles. However, an invisibility in imaging does not necessarily correlate with pathological remission. This can lead to overseen metastases during the primary resection and result in rising recurrence rates after resection, as not every single metastasis is targeted in therapy. Surgical studies recommend that even if the metastases disappeared in imaging, they should still be resected. Disappearing liver metastases on the one hand are still macroscopically visible during surgery at 25-45%, but on the other hand, the successfully treated metastases do have a

recurrence rate of 50-80%. This may be another field where PET-MRI may have a significant impact on future clinical practices, which is to be discussed later in this article (28, 29).

Although MRI was cost-effective in 82.99% of repeats in the baseline calculations and was very stable even after alterations in the sensitivity analyses, it is vitally important to recognize some limitations. Like any model, the results are heavily reliant on the input parameters used. While we sourced most of our data from reputable scientific sources, these sources may not accurately reflect daily clinical reality, which could affect the results. Additionally, we consulted experienced physicians for their expert opinion on some input parameters without any previously published data to ensure accuracy. Further, the results of our model are based on the U.S. healthcare system. The results may deviate depending on the healthcare system of each country and cannot be blindly applied to all countries in the world. Nonetheless, with minor adjustments tailored to each respective healthcare system, this model is adaptable to most western industrialized nations.

It is worth noting that Saing et al. (2018) published an article on cost-effective imaging methods for resectable liver metastases, in which they compared the economic value of contrast-enhanced MRI (CE-MRI) and CE-CT and found CE-MRI to be cost-effective. However, their study did not consider PET/CT as a diagnostic modality, which offers significantly better diagnostic accuracy than CE-CT. Therefore, the cost-effectiveness of diagnostic modalities for CRLM for resectable liver metastases needs to be reconsidered. Nonetheless, our investigation showed that MRI is still the most cost-effective modality even compared to 18F-FDG PET/CT, strengthening MRI's position as the most economic modality for detecting CRLM eligible for hepatic resection (30).

Despite MRI's cost-effectiveness, there may be situations where a physician encounters patients with MRI examination contraindications, such as some cardiac pacemakers or metallic foreign bodies. Under these circumstances, the most economic examination method would have to be disregarded. In such cases, alternative imaging methods should be considered. On the one hand, PET/CT offers superior outcomes than CE-CT, but it comes with a significantly higher radiation dose. Therefore, we recommend individual decisions for every patient as the improved diagnostic and long-term treatment outcomes may outweigh any potential long-term effects of higher radiation exposure for a severe illness such as CRLM (31).

Over the last years, PET/MRI as an upcoming diagnostic modality has caused quite a stir in imaging of many tumor entities. Despite its higher costs and its limited availability, PET/MRI offers many advantages over PET/CT. It combines the supreme soft tissue contrast of MRI and the versatility of functional imaging in PET and offers a significant reduction of radiation dose. Nonetheless, the future role of PET/MRI in broad clinical reality is still unsettled (32, 33). Yet, studies proved the value of PET/MRI in imaging of CRLM, as PET/MRI offers a significantly higher diagnostic accuracy with 96.1% compared to 18F-FDG PET/CT with 82.4% for detecting liver metastases (34–36). According to Zhou et al., 2021, a one-stop protocol with 18F-FDG PET/CT combined with an abdominal PET/MRI has an significant impact on the choice of therapeutic management of liver metastases (37). Further, a one-stop 18F-FDG PET/MRI protocol is reported to be a valid diagnostic workup for rectal cancer staging (38). In another study, FDG-PET/CT was compared to pelvic MRI and abdominal and thoracic CT for detecting synchronous distant metastases in rectal cancer. The investigation proved PET/MRI to be clearly superior compared to a MRI and CT workup not only for lymph nodes and hepatic lesions, but as well for pulmonary lesions, which is a weak point of MRI for staging of CRC (39). Overall, PET/MRI offers a broad range of possibilities and advantages. Yet, the lack of availability and the costs speak against a widespread use of PET/MRI. Nevertheless, Gassert et al., 2021 proved the cost-effectiveness of 18F-FDG PET/MRI with hepatocyte-specific contrast agent for M-staging of rectal cancer compared to conventional staging workup (40). The most relevant and unstable factor for cost-effectiveness in this study was in fact the costs for PET/MRI. This indicates that if PET/MRI gets used more often in clinical practice and the costs for every singular procedure decrease, it may become a serious competitor to the currently established imaging modalities. However, to really prove the rentability of PET/MRI on a larger scale, there needs to be deeper investigation in further studies.

5 Conclusion

In conclusion, MRI can be considered the cost-effective strategy for detecting liver metastases eligible for hepatic resection and should therefore be seen as the modality of choice in the diagnostic workup routine.

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

MS, JRü, MF, and CK contributed to conception and design of the study. MS, NM, and MF performed the economic modelling. MF, MS, GB, FG, JRun, TG, FH, and JRü contributed to input data collection. MS, NM, and GB wrote the first draft of the manuscript. MF, MS, GB, FG, JRun, TG, FH, CK, and JRü edited the first draft and made final adjustments. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1161738/full#supplementary-material

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Management of metastatic colorectal cancer in patients ≥70 years - a single center experience

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Background: Age-standardized mortality rates for metastatic colorectal cancer (mCRC) are highest among elderly patients. In current clinical guidelines, treatment recommendations for this patient population are based on a limited number of clinical trials.

Patients and methods: In this monocentric, retrospective analysis we characterized patients aged ≥70 years undergoing systemic therapy for mCRC and overall survival (OS) was investigated.

Results: We included 117 unselected, consecutive mCRC patients aged ≥70 years undergoing systemic therapy for mCRC between February 2009 and July 2022. Median OS was 25.6 months (95% CI: 21.8-29.4). The median age was 78 years (range: 70-90) and 21%, 48%, 26% and 5% had an ECOG performance score of 0, 1, 2, and 3, respectively. The median number of systemic therapy lines was 2 (range: 1-5). The choice of first-line chemotherapy backbone (doublet/triplet versus mono) did not impact OS (HR: 0.83, p=0.50) or the probability of receiving subsequent therapy (p=0.697). Metastasectomy and/or local ablative treatment in the liver, lung, peritoneum and/or other organs were applied in 26 patients (22%) with curative intent. First-line anti-EGFR-based therapy showed a trend towards longer OS compared to anti-VEGF-based therapy or chemotherapy alone in left-sided mCRC (anti-EGFR: 39.3 months versus anti-VEGF: 27.3 months versus chemotherapy alone: 13.8 months, p=0.105). In multivariable analysis, metastasectomy and/or local ablative treatment with curative intent (yes versus no, HR: 0.22, p<0.001), the ECOG performance score (2 versus 0, HR: 3.07, p=0.007; 3 versus 0, HR: 3.66, p=0.053) and the presence of liver metastases (yes versus no, HR: 1.79, p=0.049) were independently associated with OS.

Conclusions: Our findings corroborate front-line monochemotherapy in combination with targeted therapy as the treatment of choice for elderly mCRC patients with palliative treatment intent. Metastasectomy and/or local ablative treatment with curative intent are feasible and may improve OS in selected elderly mCRC patients.

KEYWORDS

elderly, age, ECOG performance score, colorectal cancer, sidedness, local ablative treatment, metastasectomy

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death worldwide (1). The incidence rate of CRC considerably increases with age and age-standardized CRC mortality rates are highest among elderly patients (2, 3). Elderly metastatic CRC (mCRC) patients (≥70 years) are underrepresented in clinical trials and one out of four elderly mCRC patients does not receive chemotherapy-based palliative systemic therapy due to comorbidities, chronological age or poor performance status (4).

Therapeutic decision making and treatment recommendations by the European Society of Medical Oncology (ESMO) (5) and National Comprehensive Cancer Network (NCCN) (6) for elderly mCRC patients are mainly based on a limited number of clinical trials focusing on the elderly mCRC population (7–9). Fluorouracil-based monochemotherapy in combination with anti-VEGF-based therapy irrespective of sidedness (7, 9) or in combination with anti-EGFR-based therapy (8) as well as anti-EGFR monotherapy (10) in patients with RAS wild-type left-sided tumors represent recommended first-line protocols (5). A median overall survival of 14 and 21 months is achieved with the abovementioned first-line protocols among patients ≥75 years (10) and ≥70 years (7), respectively; however, data on the clinical outcome in the elderly mCRC population in the real-world setting are sparse.

While metastasectomy and/or local ablative treatment (+/- perioperative chemotherapy or previous conversion therapy) represent established approaches in eligible patients with oligometastatic CRC (5, 6), there is a paucity of evidence supporting this treatment concept with putative curative intent in the elderly oligometastatic CRC population.

The primary aim of this unicentric retrospective analysis was to evaluate the therapeutic management of mCRC patients ≥70 years of age and clinical outcome in a real-world setting. Furthermore, this analysis aimed at investigating the frequency, feasibility and efficacy of metastasectomy and/or local ablative treatment with putative curative intent in this elderly population.

Patients and methods

Patients

This retrospective analysis was approved by the Ethics Committee of the provincial government of Salzburg, Austria (415-E/2343/5-2018). Patients with an age ≥70 years at the time point of histologically confirmed mCRC diagnosis and who received systemic therapy for mCRC at our tertiary cancer center (Department of Internal Medicine III, Paracelsus Medical University Salzburg, Austria) between February 2009 and July 2022 were included in this analysis. All included patients alive at the date of analysis signed an informed consent form. Early access within a named patient program was available for patients who had received regorafenib and/or TAS-102 before the respective approval by the European Medicines Agency (EMA). Data were extracted from medical records, including:

1. patient characteristics: mCRC diagnosis date, age, sex, Eastern Cooperative Oncology Group (ECOG) performance score
2. tumor characteristics: time point of metastases detection (synchronous versus metachronous), sidedness (right versus left), histological grade, metastatic distribution pattern at mCRC diagnosis, predictive tumor-tissue-based biomarkers (KRAS-, NRAS-, BRAF-, microsatellite-/mismatch-repair-status)
3. systemic therapy characteristics: number of systemic therapy lines, first-line chemotherapy backbone (mono- versus doublet or triplet chemotherapy), application of targeted therapy during first-line (no antibody versus anti-VEGF versus anti-EGFR), regorafenib and/or TAS-102 exposure and
4. local ablative treatment with curative intent: metastasectomy, microwave ablation (MWA), radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), transarterial chemoembolization (TACE) and involved organ(s): liver, lung, peritoneum, other.

In order to draw a comparison in regard to age distribution and treatment intent between our unicentric elderly mCRC cohort and mCRC patients ≥70 years in the province of Salzburg (Austria), data from the Tumor Registry of the Province of Salzburg from 2013 to 2020 were used.

Statistical analyses

Baseline characteristics were compared using crosstabulation together with the chi-squared test, in case of categorical data.

Continuous data were summarized using medians and ranges and compared between groups with the Mann-Whitney test. Uni- and multivariable analyses were based on Cox proportional hazard models. For multivariable analysis covariable selection, a backward stepwise procedure was performed using the Akaike information criterion (AIC) as selection criterion (11). OS was calculated from the date of mCRC diagnosis until death from any cause. Metastasectomy and/or local ablative treatment (yes versus no) as well as regorafenib and/or TAS-102 exposure were taken into account as time-dependent covariates, respectively. Patients alive at the last contact were censored. IBM SPSS Statistics version 27 (Armonk, NY, US) and the statistical software environment R (version 4.1.2, survival and MASS package) were used for statistical analyses. The complete data set is available from the corresponding author on reasonable request.

Results

Baseline characteristics

In this retrospective monocentric analysis, 117 mCRC patients aged ≥70 years, diagnosed between February 2009 and July 2022, and undergoing systemic therapy for mCRC were included. The baseline characteristics are depicted in Table 1.

Patient characteristics

The median age at mCRC diagnosis was 78 (range: 70-90). 21%, 48%, 26% and 5% had an ECOG PS of 0, 1, 2, and 3 with a median age of 75, 78, 78.5, and 82 years at mCRC diagnosis, respectively (p=0.087).

Tumor characteristics

Eighty-seven patients (74%) were diagnosed with synchronous mCRC. The primary tumor location was left-sided in 76 patients (65%). Liver, lung and peritoneal metastases were detected in 80 (68%), 40 (34%) and 22 (19%) patients at the time point of mCRC diagnosis, respectively.

Among patients with available tumor-tissue-based biomarkers, KRAS-mutations, NRAS-mutations, BRAF V600E-mutations and MSI/MMRd were detected in 53%, 3%, 8% and 8%, respectively.

Systemic therapy characteristics

In first line, a monochemotherapy backbone was applied in 32 patients (28%), whereas 83 patients (72%) received a doublet or triplet chemotherapy backbone. The likelihood of applying a doublet or triplet chemotherapy backbone declined with increasing age (p<0.001, Table A.1) and with a worse ECOG PS (p=0.007, Table A.1). Two patients with MSI/MMRd received immune-checkpoint blockade as palliative first-line therapy.

Sixty-one patients (52%) were treated with anti-VEGF-based therapy in first line, whereas anti-EGFR based therapy was applied in 21 patients (18%). The remaining 35 patients (30%) did not receive targeted therapy in first-line. Anti-VEGF-based therapy, anti-EGFR-based therapy or no targeted therapy were documented in 38 (50%), 14 (18%), and 24 (32%) patients with left-sided and in 23 (56%), 7 (17%) and 11 (27%) patients with right-sided primary tumor localization (p=0.812).

The EMA approved third-line therapy options, regorafenib and TAS-102, were applied in 26 patients (22%) during the course of disease (only regorafenib: n=4 (3%), only TAS-102: n=13 (11%), regorafenib followed by TAS-102 or vice versa: n=9 (8%)).

The median number of systemic therapy lines in the study population was 2 (range: 1-5) and 52%, 27% 12% and 3% received a second-line, third-line, fourth-line and fifth-line therapy (Figure 1). The chemotherapy backbone in first line (mono versus doublet/triplet) did not statistically significantly impact the probability of receiving subsequent therapy (p=0.697, Figure 1).

Metastasectomy and/or local ablative treatment with curative intent

Twenty-six patients (22%) underwent metastasectomy and/or local ablative treatment of metastases in the liver, lung, peritoneum or other organs with curative intent during their course of disease (Table A.2):

In twenty-three patients (20%) surgical metastasectomy was performed once, whereas nine (8%) and two patients (2%) underwent metastasectomy twice and three times during their course of disease, respectively. Stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA) or microwave ablation (MWA), and transarterial chemoembolization (TACE) were applied in six (5%), six (5%) and two (2%) cases, respectively.

Patients undergoing metastasectomy and/or local ablative treatment were more likely to receive a front-line doublet or triplet chemotherapy backbone (89% versus 67%, p=0.035) and showed a trend towards metachronous metastases (38% versus 22%, p=0.090) compared to patients without ablative measures (Table A.3).

Age and treatment intent of elderly mCRC patients in the province of Salzburg

According to the Tumor Registry of the Province of Salzburg (Austria), the following age distribution pattern was found between 2013 and 2020 in the province of Salzburg among mCRC patients ≥70 years: 70-74 years: 32%; 75-79 years: 35%; 80-84 years: 33%, ≥85 years: 0%.

Fifty-nine per cent of the abovementioned patients received palliative systemic therapy and the likelihood decreased with increasing age: 70-74 years: 74%, 75-79 years: 58%; 80-84 years: 44%.

Overall survival

After a median follow up of 38.4 months (95% CI: 29.3-47.5 months), the median OS in the entire monocentric cohort was 25.6 months (95% CI: 21.8-29.4 months).

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TABLE 1 Baseline characteristics of entire elderly mCRC cohort.

Parameter	N=117 (%)
Age (median)	78
Range	70-90
Age category	
70-74	36 (31)
75-79	42 (36)
80-84	32 (27)
≥85	7 (6)
Sex	
Female	48 (41)
Male	69 (59)
ECOG performance score	
0	24 (21)
1	55 (48)
2	30 (26)
3	5 (5)
NA	3
Time point of metastases detection	
Synchronous	87 (74)
Metachronous	30 (26)
Sidedness	
Left	76 (65)
Right	41 (35)
Exact primary tumor localization	
Rectum	32 (27)
Sigmoid colon	35 (30)
Descending colon	5 (4)
Left flexure	4 (3)
Transverse colon	6 (5)
Right flexure	3 (3)
Ascending colon	15 (13)
Cecum	17 (15)
Histological grade	
1	8 (8)
2	67 (66)
3	26 (26)
NA	16
Involved organs at mCRC diagnosis*	
Liver	80 (68)
Lung	40 (34)
Peritoneum	22 (19)
KRAS status	
Wild-type	49 (47)
KRAS G12C mutant	4 (4)
Non-KRAS G12C mutant	51 (49)
NA	13
NRAS status	
Wild-type	66 (97)
Mutant	2 (3)
NA	49
BRAF status	
Wild-type	61 (91)
V600E mutant	5 (8)
Non-V600E mutant	1 (1)
NA	50
Microsatellite/Mismatch-repair status	
MMRp/MSS	48 (92)
MMRd/MSI	4 (8)
NA	65
1L chemotherapy backbone	
Mono chemotherapy	32 (28)
Doublet or triplet chemotherapy	83 (72)
NA (anti-PD-1 therapy)	2
1L anti-VEGF or anti-EGFR therapy	
None	35 (30)
Anti-VEGF	61 (52)
Anti-EGFR	21 (18)
Regorafenib and/or TAS-102 exposure	
None	91 (78)
Regorafenib only	4 (3)
TAS-102 only	13 (11)
Regorafenib followed by TAS-102 (or vice versa)	9 (8)
Metastasectomy and/or local ablative treatment with curative intent	
No	91 (78)
Yes	26 (22)

*multiple designations possible.
ECOG, Eastern Cooperative Oncology Group; mCRC,metastatic colorectal cancer; MMRp, mismatch-repair proficient; MMRd, mismatch-repair deficient; MSI, microsatellite instability; MSS, microsatellite stability.

Univariable analyses

Patient-associated factors

A worse ECOG PS at diagnosis was associated with inferior OS (1 versus 0, HR: 1.45, p=0.24; 2 versus 0, HR: 1.58, p=0.22; 3 versus 0, HR: 4.97, p=0.01; Table 2). Chronological age at mCRC diagnosis did not impact survival (HR: 1.02, p=0.54; Table 2).

Tumor-associated factors

Neither sidedness (left-sided versus right-sided, HR: 1.10 p=0.71 log-rank, Figure 2A), nor KRAS mutational status (mutant versus wild-type, HR: 1.06 p=0.80; Table 2) proved as prognostic factors. The presence of liver metastases at the time point of mCRC diagnosis negatively influenced OS (present versus absent, HR: 1.82, p=0.03; Table 2).

Systemic therapy

The chemotherapy backbone of front-line therapy did neither affect OS in the entire cohort (doublet or triplet versus monochemotherapy, HR: 0.83, p=0.50; Table 2), nor among patients without metastasectomy and/or local ablative treatment (HR: 1.11, p=0.73). The addition of an anti-EGFR or anti-VEGF monoclonal antibody to chemotherapy in first line irrespective of the primary tumor localization resulted in a trend towards longer survival (anti-EGFR: 29.7 months versus anti-VEGF: 27.3 months versus no targeted therapy: 13.3 months, p=0.15 log-rank, Figure 2B). The choice of targeted therapy according to sidedness in first-line was associated with a trend towards superior survival with anti-EGFR-based therapy in left-sided disease (anti-EGFR: 39.3 months versus anti-VEGF: 27.3 months versus no targeted

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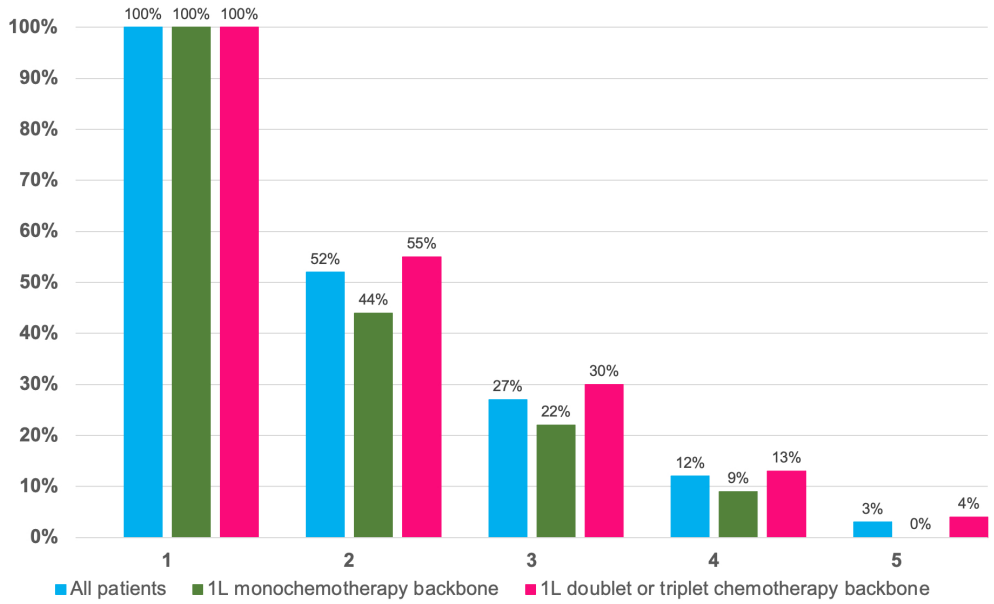

FIGURE 1
Impact of first-line chemotherapy backbone on number of subsequent therapy lines. Relative number of systemic therapy lines among elderly mCRC patients undergoing first-line therapy with any systemic therapy (blue), a monochemotherapy backbone (green) or a doublet or triplet chemotherapy backbone (red).

therapy: 13.8 months, p=0.105 log-rank; Figure 2D), while sidedness proved less predictive in right-sided disease (anti-VEGF: 27.1 months versus anti-EGFR: 11.2 months versus no targeted therapy: 10.6 months, p=0.325 log-rank; Figure 2C).

The application of more systemic therapy lines was associated with improved OS (≥2 versus 1, HR: 0.40, p<0.001; Table 2). Patients receiving regorafenib and/or TAS-102 during the course of disease did not show a survival benefit (yes versus no, HR: 1.14, p=0.67; Table 2) when considered as a time-dependent covariate. Seven patients were treated within clinical trials in first line and three patients in subsequent therapy lines.

Ablative therapies

Performing metastasectomy and/or applying local ablative treatment with curative intent statistically significantly improved OS (yes: 47.2 months versus no: 17.9 months, HR: 0.16, p<0.001, Table 2). The six-month survival rate was 100% after metastasectomy (liver, lung, peritoneum, other), SBRT (liver, lung), RFA/MWA (liver) and TACE (liver), respectively.

Multivariable analysis

Based on a backward stepwise regression the following covariates were selected for multivariable analysis: sidedness (left-sided versus right-sided), liver metastases (present versus absent), ECOG PS (0 versus 1, 0 versus 2, 0 versus 3), regorafenib and/or TAS-102 exposure (yes versus no) and metastasectomy and/or local ablative treatment (yes versus no).

In multivariable analysis, metastasectomy and/or local ablative treatment (yes versus no, HR: 0.22, p<0.001), the ECOG performance score (2 versus 0, HR: 3.07, p=0.007; 3 versus 0, HR: 3.66, p=0.053) and the presence of liver metastases (yes versus no, HR: 1.79, p=0.049) remained statistically significantly and independently associated with survival (Figure 3).

Discussion

As the aging population is highly represented among mCRC patients and due to the paucity of trial-based recommendations, therapeutic decision making in elderly mCRC patients remains challenging in clinical practice. In our unicentric, retrospective analysis we characterized patient and tumor characteristics and investigated clinical outcome in a representative elderly patient cohort undergoing systemic therapy for mCRC. The distribution of age categories within our elderly mCRC cohort was comparable to records of the Tumor Registry of the Province of Salzburg between 2013 and 2020: 70-74 years: 31% versus 32%; 75-79 years: 36% versus 35%; 80-84 years: 27% versus 33%, ≥85 years: 6% versus 0%. It is noteworthy, that only 59% of mCRC patients ≥70 years of age received palliative systemic therapy in the Province of Salzburg.

Based on the findings of our unicentric analysis we provide further evidence that OS of elderly mCRC patients undergoing systemic therapy in the real-world setting (mOS of 25.6 months) is comparable to landmark clinical trials (7, 12) (mOS of 19 to 21 months, Table A.4). Metastasectomy and/or local ablative treatment with curative intent proved feasible in selected elderly patients and resulted in a significant and clinically meaningful OS benefit (HR: 0.22, p<0.001, Figure 3). Furthermore, the observed trend towards superior OS with an anti-EGFR-based therapy in left-sided mCRC when compared to anti-VEGF-based therapy or chemotherapy alone (Figure 2D) sheds further light on the predictive value of sidedness and corroborates the preference of anti-EGFR-based

TABLE 2 Univariable analysis for overall survival.

Univariable analysis				
Parameter	N	HR	95% CI	p-value
Age (continuous)	117	1.02	0.96-1.08	0.54
Sex				
Female	48			
Male	69	1.11	0.69-1.80	0.66
ECOG PS				
0	24			
1	55	1.45	0.78-2.69	0.24
2	30	1.58	0.76-3.31	0.22
3	5	4.97	1.37-18.04	0.01
Histological grade				
1	8			
2	67	0.89	0.32-2.53	0.83
3	26	1.35	0.45-4.06	0.59
Sidedness				
Right-sided	41			
Left-sided	76	1.10	0.67-1.81	0.71
Liver metastases				
No	37			
Yes	80	1.82	1.07-3.09	0.03
Lung metastases				
No	77			
Yes	40	0.94	0.57-1.53	0.79
Peritoneal metastases				
No	95			
Yes	22	0.52	0.26-1.05	0.07
Time point of metastases detection				
Metachronous	30			
Synchronous	87	1.40	0.80-2.46	0.24
KRAS status				
Wild-type	49			
Mutant	55	1.06	0.65-1.74	0.80
1L chemotherapy backbone				
Mono	32			
Doublet/triplet	83	0.83	0.48-1.43	0.50
Regorafenib and/or TAS-102 exposure[#]				
No	50			
Yes	24	1.14	0.63-2.08	0.67
Number of therapy lines				
1	56			
≥2	61	0.40	0.25-0.65	<0.001
Metastasectomy and/or local ablative treatment with curative intent[#]				
No	57			
Yes	25	0.16	0.08-0.33	<0.001

ECOG, Eastern Cooperative Oncology Group.
[#]time-dependent covariate.

therapy also in elderly patients with RAS/BRAF wild-type left-sided disease.

In a cross-trial comparison between our retrospective analysis and a pooled analysis (13) of the TRIBE (14) and TRIBE2 (15) study, fewer patients received subsequent therapy lines in our elderly mCRC cohort (2L: 77% versus 52%, 3L: 53% versus 27%, 4L: 27% versus 12%, 5L: 11% versus 3%, Figure 1). It is noteworthy that the median age at mCRC diagnosis in the aforementioned studies (TRIBE: 60.0 and 60.5 years; TRIBE2: 60.0 and 61.0 years) was considerably lower when compared to our cohort (78 years, range: 70-90 years). However, the probability to receive subsequent systemic therapy was higher in our cohort compared to mCRC patients in the AVEX trial (7) (52% versus 37%).

The chemotherapy backbone in first line (doublet or triplet versus mono) did neither impact the number of subsequent therapy lines (p=0.697, Figure 1), nor had an impact on clinical outcome in

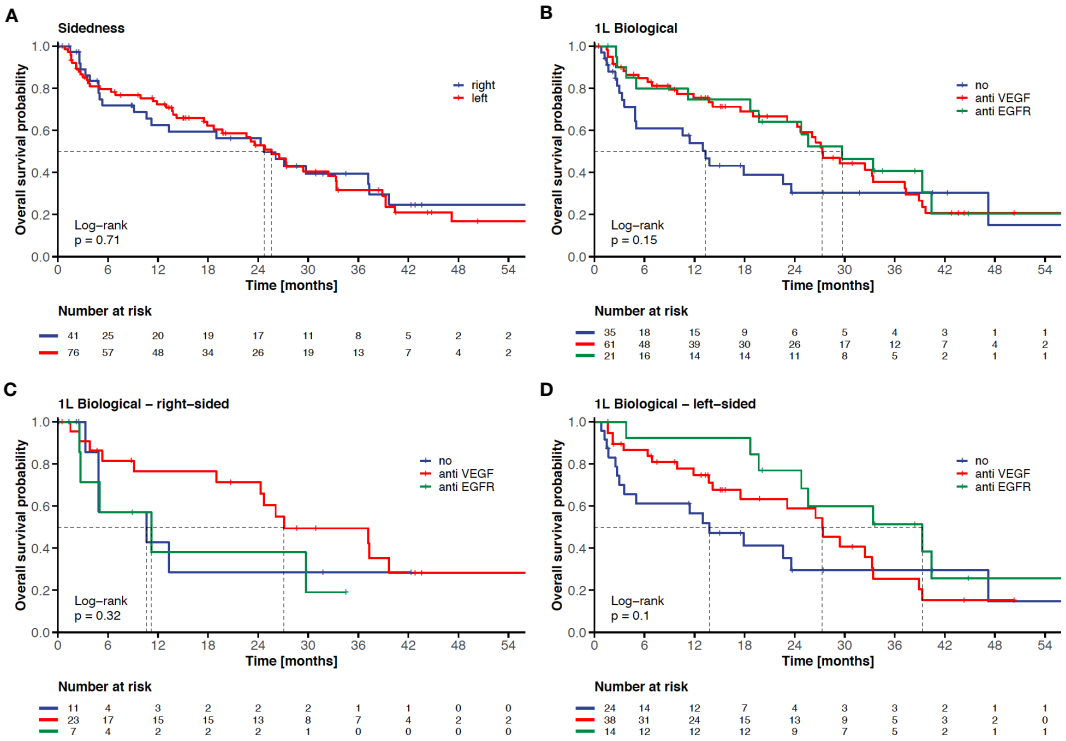

FIGURE 2
Impact of sidedness and 1L-targeted therapy on clinical outcome in elderly mCRC patients. KM-curves for overall survival according to sidedness (left-sided versus right-sided) **(A)**, according to 1L-targeted therapy (no targeted therapy versus anti-VEGF-based therapy versus anti-EGFR-based therapy **(B)**, according to 1L-targeted therapy in right-sided mCRC **(C)**, and according to 1L-targeted therapy in left-sided mCRC **(D)**. The tick marks on the curves represent censored patients.

the entire cohort (HR: 0.83, p=0.50) or among patients not eligible for metastasectomy and/or local ablative treatment (HR: 1.11, p=0.73). The latter findings are in line with the MRC FOCUS2 (16) and FFCD 2001-02 (17) trials, where the addition of oxaliplatin (16) or irinotecan (17) to 5-FU or capecitabine did not improve OS in elderly and/or frail mCRC patients, but significantly increased the frequency of grade 3-4 toxicities (17). In this regard, it is noteworthy that the ECOG PS in our elderly cohort was comparable to the study population of the MRC FOCUS2 trial (16): ECOG 0: 21%/21%, ECOG 1: 48%/50%, ECOG 2: 26%/29%, ECOG 3: 5%/0%.

Higher treatment-related toxicity rates with a doublet chemotherapy backbone and a higher frequency of comorbidities have also been observed with increasing age in the CALGB 80405 study (18). Age demonstrated as a considerable prognostic factor in the FIRE-3 study (19) (≥65 years: 25.9 versus <65 years: 29.3 months, p=0.02) and CALGB 80405 study (18) (≥70 years versus <70 years: HR 1.32, p<0.001). Within our study population (range: 70-90 years), older patients showed a trend towards a worse ECOG PS (p=0.087), however, age as a continuous parameter did not show any additional prognostic value among mCRC patients ≥70 years (Table 2).

A worse ECOG PS at mCRC diagnosis showed a statistically significant and independent association with inferior OS (2 versus 0, HR: 3.07; 3 versus 0: HR; 3.66; Figure 3). While classification into the ECOG PS categories (from 0: fully active to 4: completely disabled) can be rapidly performed in daily clinical practice in younger patients, the latter performance score assessment can be challenging in elderly cancer patients due to physicians' varying conception of the usual performance spectrum of elderly people. Considerable disparities between patient-reported and physician-reported ECOG PS ratings exist (20) and there is also a poor agreement in ECOG PS ratings between clinicians (21). Other scores such as the Charlson Comorbidity Index (22), which includes age and multiple comorbidities and classifies into four risk categories, proved as predictors of survival in (m)CRC (23–25). However, our findings confirm the ECOG PS as a time-saving prognosticator and helpful tool for therapeutic decision-making (e.g. chemotherapy intensity) in daily clinical practice in elderly mCRC patients. The International Society of Geriatric Oncology recommends geriatric assessment in older cancer patients aiming at influencing treatment choice, predicting treatment-related complications and predicting clinical outcome. Geriatric assessment should include functional status, comorbidities, cognition, mental health status, fatigue, social status and support, nutrition, and the presence of geriatric syndromes (26). Based on the retrospective nature of our analysis, only the functional status was extracted from medical records and geriatric assessment was not feasible.

Contrary to the literature (27), sidedness was not prognostic among elderly mCRC patients in our cohort (left-sided versus right-sided, HR: 1.10 p=0.71, Figure 2A), which may be explained by the

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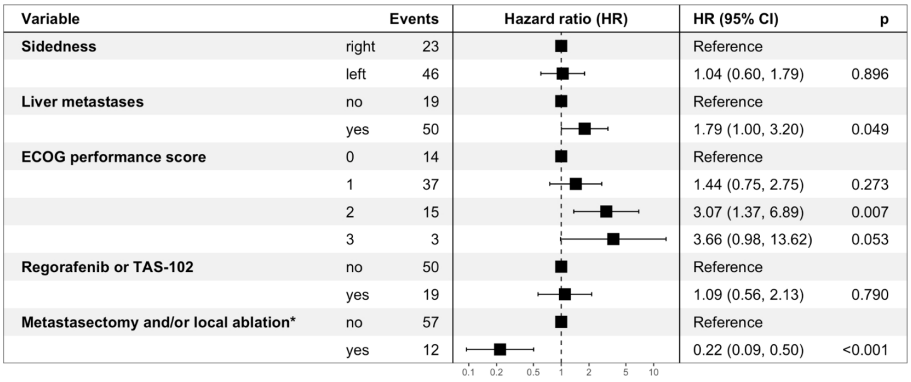

FIGURE 3
Multivariable analysis for overall survival – Forest Plot. ECOG performance score: Eastern Cooperative Oncology Group performance score. Regorafenib and/or TAS-102 exposure as well as metastasectomy and/or local ablative treatment were taken into consideration as time-dependent covariates. *involved organs: liver, lung, peritoneum, other.

application of front-line anti-VEGF-based therapy in the majority of cases with right-sided (58%) as well as left-sided (51%) primary tumor localization. Furthermore, a higher percentage of patients with right-sided primary tumors underwent metastasectomy and/or local ablative treatment (right-sided: 33% versus left-sided: 15%, Table A.3). This stands in contrast to the secondary metastasectomy rate among patients ≥65 years in the FIRE-3 study (19) (right-sided: 8%-13% versus left-sided: 15%-26%).

A *post-hoc* analysis of the FIRE-3 study in the subgroup of patients ≥ 65 years (n=199) could neither corroborate the survival benefit of cetuximab versus bevacizumab in left-sided mCRC (33.2 months versus 27.5 months, HR: 0.86, p=0.38), nor the disadvantage of first-line cetuximab-based therapy in right-sided disease (16.6 months versus 23.6 months, HR: 1.1, p=0.87) (19). Liver surgery for colorectal metastases with curative intent in elderly mCRC patients can yield a comparable OS benefit as in the young population (28, 29). For elderly mCRC patients undergoing CRC liver metastases resection an incidence of 60- to 90-day mortality ranging between 4% and 8% has been reported in population-based studies (29, 30).

According to the RAXO study, a nationwide Finnish prospective intervention study, up to 41% of mCRC patients can be classified as resectable with curative intent either upfront or after conversion therapy irrespective of chronological age (31). In our cohort, metastasectomy and/or local ablative treatment were performed in 22% of patients with technically resectable disease extent and adequate performance status and yielded a clinically meaningful and independent OS benefit (HR: 0.22, Figure 3). This is in line with the secondary metastasectomy rate (18%) and the OS advantage (HR: 0.44) of elderly patients in the FIRE-3 study (19). The latter findings should encourage us to identify eligible patients for metastasectomy and/or local ablative treatment with curative intent in the elderly mCRC population. The presence of liver metastases was a significant and independent negative prognostic factor (HR: 1.79, p=0.05) – presumably mainly driven by non-resectable and non-liver-limited disease.

However, we would like to emphasize that in the FIRE-3 and CALGB 80405 studies elderly patients were defined by ≥65 years and ≥70 years, respectively, and were all deemed fit for a doublet chemotherapy backbone (18, 19). Data from the Cardiovascular Health Study corroborate an increasing prevalence of frailty with higher chronological age (32). Therefore, the FIRE-3 and CALGB 80405 mCRC populations may not properly reflect the elderly and often frail mCRC population in the real-world setting.

Within the inclusion period of our retrospective analysis (2009-2022), regorafenib (33) as well as TAS-102 (34) have been established as EMA- and FDA-approved third-line therapy options based on a survival benefit versus placebo, respectively. In our cohort, one out of five patients received regorafenib and/or TAS-102 during the course of disease (Table 1). Since the availability of regorafenib and TAS-102 within named patient programs or based on the respective EMA approval, our treatment strategy has not favored one drug over the other in the time interval between 2014 and 2022 (Figure A.1). However, based on the toxicity profile of regorafenib (33), an increased skeletal muscle loss (35) and a higher frequency of hospitalizations with regorafenib compared to TAS-102 (36), regorafenib should be used with caution in elderly mCRC patients. Treatment with regorafenib and/or TAS-102 did not result in a survival advantage when taken into account as a time-dependent covariate (yes versus no, HR: 1.09, p=0.79, Figure 3). According to the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) (37), which is based on the extent of OS gain, QoL and toxicities, TAS-102 (MCBS: 3) proved superior to regorafenib (MCBS: 1) (5).

The SUNLIGHT study, a randomized phase 3 study comparing TAS-102 versus TAS-102 in combination with bevacizumab for third-line treatment of refractory mCRC, has met its primary endpoint, demonstrating an OS benefit with TAS-102 plus bevacizumab (10.8 months versus 7.5 months, HR: 0.61, p<0.001) (38). Due to the acceptable safety profile of TAS-102 combined with bevacizumab in previous studies (9, 38, 39) this combination may become a new third-line standard in the near future, particularly suitable for the elderly and frail mCRC population.

The availability of further new treatment options (40,) (41) within the inclusion period (2009-2022) may have also contributed to the encouraging clinical outcome (mOS of 25.6 months)

compared to the experimental arm of the AVEX trial (7) (mOS of 20.7 months, Table A.4).

Potential limitations of our study include the retrospective nature and the length of the inclusion period (2009-2022). Within the latter time span, biomarker refinement for established therapies (42), numerous new therapies for all-comers (33, 34) and biomarker-defined targeted-therapies (40, 41) changed daily clinical practice resulting in heterogenous treatments strategies in our elderly mCRC cohort. As a consequence, the predictive biomarker status is incomplete in a relevant number of patients. Furthermore, the implementation of sidedness into first-line decision making took place after the Annual ASCO Meeting 2016 (27, 43, 44), therefore, sidedness as a predictive biomarker could only be applied in less than half of our elderly mCRC patients. It is noteworthy, that elderly patients undergoing only a best supportive care strategy were excluded from our analysis. Although the number of included patients in our analysis (n=117) was limited, the sample size was comparable to the experimental arms of the AVEX (n=140) and PANDA (n=93) landmark trials (Table A.4).

Conclusions

Clinical outcome among real-world elderly (≥70 years) mCRC patients is comparable to the results of first-line elderly mCRC landmark trials. First-line monochemotherapy plus targeted therapy based on sidedness and molecular status should be the treatment of choice. Based on proper patient selection, one out of five elderly mCRC patients qualifies for metastasectomy and/or local ablative treatment with curative intent. A doublet chemotherapy backbone +/- targeted therapy may be expedient in elderly mCRC patients who are candidates for metastasectomy and/or local ablative treatment. The latter ablative measures are feasible and yield a clinically meaningful survival benefit in selected elderly mCRC patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the provincial government of Salzburg, Austria (415-E/2343/5-2018). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FH: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review and editing. CD: Investigation, Writing – review and editing. GR: Formal analysis, Investigation, Methodology, Writing – review and editing. KS: Investigation, Writing – review and editing. RH: Investigation, Writing – review and editing. KE: Investigation, Writing – review and editing. DN: Investigation, Writing – review and editing. EK: Investigation, Writing – review and editing. MD: Investigation, Writing – review and editing. FR: Investigation, Writing – review and editing. RG: Funding Acquisition, Resources, Supervision, Writing – review and editing. LW: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

Supplementary material

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SUPPLEMENTARY TABLE 1
Association between 1L chemotherapy backbone and ECOG PS as well as age at mCRC diagnosis.

SUPPLEMENTARY TABLE 2
Elderly mCRC patients undergoing metastasectomy and/or local ablative treatment with curative intent (N=26) MWA: microwave ablation, RFA: radiofrequency ablation, SBRT: stereotactic body radiation therapy, TACE: transarterial chemoembolization.

SUPPLEMENTARY TABLE 3
Comparison of baseline characteristics between elderly mCRC patients undergoing metastasectomy and/or local ablative treatment versus not #Mann-Whitney-U-Test.
ECOG, Eastern Cooperative Oncology Group, mCRC, metastatic colorectal cancer.

SUPPLEMENTARY TABLE 4
Comparison of baseline characteristics and clinical outcome between the Salzburg elderly mCRC real-world cohort and elderly mCRC landmark trials.

SUPPLEMENTARY FIGURE 1
Regorafenib and TAS-102 exposure among elderly mCRC patients between 2014 and 2022 Cumulative cases of regorafenib (blue), TAS-102 (green) and total regorafenib and TAS-102 applications (red) between 2014 and 2022 among elderly mCRC patients.

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Involvement in treatment decision-making and self-reported efficacy among patients with advanced colorectal cancer: a nationwide multi-center cross-sectional study

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Introduction: This cross-sectional study evaluated the involvement of patients with advanced colorectal cancer (CRC) in treatment decision-making, assessed the treatment efficacy according to their self-reports, and investigated the influencing factors.

Methods: Patients with advanced CRC were recruited from 19 hospitals from March 2020 to March 2021 by a multi-stage multi-level sampling method. A self-designed questionnaire was used to collect demographic and clinical characteristics, involvement of CRC patients in treatment decision-making, treatment methods, and self-reported efficacy. Univariate and unordered multinomial logistic regression analyses were used to evaluate the factors affecting the involvement in treatment decision-making and self-reported efficacy.

Results: We enrolled 4533 patients with advanced CRC. The average age at diagnosis was 58.7 ± 11.8 years. For the treatment method, 32.4% of patients received surgery combined with chemotherapy, 13.1% of patients underwent surgery combined with chemotherapy and targeted therapy, and 9.7% of patients were treated with surgery alone. For treatment decision-making, 7.0% of patients were solely responsible for decision-making, 47.0% of patients shared treatment decision-making with family members, 19.0% of patients had family members solely responsible for treatment decision-making, and 27.0% of patients had their physicians solely responsible for treatment decision-making. Gender, age, education level, family income, marital status, treatment cost, hospital type, and treatment method were significantly associated with the involvement of patients in treatment decision-making. A total of 3824 patients submitted self-reported efficacy evaluations during treatment. The percentage of patients with good self-reported efficacy was 76.5% (for patients treated for the first time), 61.7% (for patients treated for the second time), and 43.2% (for patients treated after recurrence and metastasis), respectively. Occupation, education level, average annual family income, place of residence, time since cancer diagnosis, hospital type, clinical stage, targeted therapy, and involvement in treatment decision-making were the main influencing factors of self-reported efficacy of treatment.

Discussion: Conclusively, CRC patients are not highly dominant in treatment decision-making and more likely to make treatment decisions with their family and doctors. Timely and effective communication between doctors and patients can bolster patient involvement in treatment decision-making.

KEYWORDS

colorectal cancer, treatment, decision making, self-reported efficacy, China

1 Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, with morbidity ranking third and mortality ranking second. More than half of new cases and CRC-related deaths are from China, Europe, and North America (1). It is estimated that approximately 1.9 million newly diagnosed CRC cases and 935,000 CRC-related deaths in 2020, accounting for approximately one-tenth of new cancer cases and deaths (2). In recent years, the morbidity and mortality of CRC have decreased in some countries in Europe and the United States. However, China is still suffering a remarkable CRC burden, which accounts for 28.11% of global deaths. In China, both men and women have higher crude mortality rates for CRC than the global average. Moreover, the prevalence of CRC is on the rise in China (3, 4).

In 2015, there were about 387,600 new CRC cases and 187,100 CRC-related deaths, accounting for 9.87% and 8.01% of all malignant tumors, respectively, in China (5, 6). In recent years, with the implementation of screening, early diagnosis, and treatment in China, the age-standardized mortality of CRC has decreased from 10.01/100,000 in 2005 to 9.68/100,000 in 2020, and the 5-year survival rate has increased from 47.2% in 2003-2005 to 56.9% in 2012-2015. However, it is worth noting that more than half of the patients have advanced CRC at initial diagnosis (7), with a 5-year survival rate of approximately 20% (8). It has been shown that there are significant differences in the prognosis of CRC between different treatment methods, countries, or regions (9, 10). Moreover, satisfaction and compliance with treatment may be improved by the involvement of patients in treatment

decision-making, thereby indirectly prompting outcomes (11). Therefore, the involvement of patients in treatment decisions making and further analysis of factors associated with the prognosis of advanced CRC is important for making individual diagnoses and treatment plans and for improving compliance and treatment efficacy, further reducing disease burden.

Previously, most of the studies on CRC were designed as single-centered (12) or focused on specific subjects in a certain clinical stage (13), the results of which could not be generalized. Generally, patients have high expectations of participating in treatment decision-making, but the actual involvement is low (14). Moreover, there are rare studies on the involvement of CRC patients in diagnosis and treatment decision-making. Additionally, several prognostic factors of CRC have been reported, such as distant metastasis of CRC, the location of the primary tumor, molecular markers, age, and radical surgery (15–17). However, there are few studies on the self-reported prognosis of patients.

Therefore, in this study, we conducted a nationwide multi-center cross-sectional study. The involvement of patients with advanced CRC in treatment decision-making and the influencing factors were evaluated. Moreover, the prognosis of advanced CRC patients was comprehensively assessed by using patient self-report efficacy. Additionally, the influencing factors of patient self-reported efficacy were also analyzed. Our findings may provide evidence for further improvement of treatment in patients with advanced CRC.

2 Materials and methods

2.1 Study design

This is a nationwide multicenter cross-sectional study and the details of the study design have been published (18). In brief, a multi-stage sampling method was used to identify the 19 tertiary hospitals (10 tertiary cancer hospitals and 9 tertiary general hospitals) in China from March 2020 to March 2021. Firstly, two cities were randomly selected from seven administrative regions in East China, North China, Central China, South China, Northeast China, Southwest China, and Northwest China; subsequently, one tertiary cancer hospital or tertiary general hospital in each city was selected as the research center. This study was approved by the Medical Ethics Committee of Henan Cancer Hospital (No. 2019273) and also by the Ethics Committee of all other participating hospitals subsequently. Informed consent was obtained from each participant.

2.2 Patients

As previously described (18), it was estimated that more than 4445 advanced CRC patients would be enrolled. The total sample size was proportionally allocated to each region according to its population size and based on the estimated sample size, patients should be recruited from each region. A total of 4,589 inpatients with advanced CRC who had stage III or IV CRC across seven geographic regions of China's mainland were included in this study from March 2020 to March 2021. Fifty-three cases were excluded due to a lack of essential information for the current analysis. Ultimately, 4,533 cases were included.

The Tumor Lymph Node Metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC) was used to identify the eligible subjects. The inclusion criteria were as follows: 1) CRC patients with TNM stage III or IV; 2) patients aged more than 18 years; 3) patients with normal cognitive ability; 4) patients willing to participate in the research and signed the informed consent. Exclusion criteria: patients with severe physical, cognitive, and/or verbal limitations were excluded.

2.3 Data collection

A self-designed questionnaire was used to collect the demographic and clinical characteristics, patient awareness of CRC risk factors, involvement in treatment decision-making, medical experience, treatment methods, treatment efficacy, etc. Before the formal survey, a preliminary survey was conducted among 50 CRC patients at the Henan Cancer Hospital and the First Affiliated Hospital of Baotou Medical College to evaluate the validity and reliability of the questionnaire. Then we revised the questionnaire based on the preliminary results. The final questionnaire consisted of four parts in 9 pages. To ensure the study quality, all investigators received standard training. Questionnaires were filled out face-to-face by the investigators, with a mean survey time of 20 min.

Involvement in treatment decision-making was classified into "full treatment decision-making by patients, joint treatment decision-making by patients and their family members, treatment decision-making by family members, and treatment decision-making by doctors". The evaluation of the efficacy was mainly based on the patient's self-report, and was designed as "poor, good, or stable (unchanged)". The awareness of CRC risk factors was evaluated by multiple-choice questions, namely, "What do you think are the risk factors for CRC before diagnosis?", "What do you think is the appropriate CRC screening method before diagnosis?", and "Which method do you use to acquire knowledge about CRC?", which contain 10, 6, and 10 options, respectively. Any selected option was scored as 1 point, while "don't know" or "seldom see" options were scored as 0 points. Therefore, the total score of each question was 9 points, 5 points, and 9 points, respectively.

The clinical characteristics and treatment methods in the questionnaire were provided by doctors according to patient medical records of diagnosis and treatment, mainly including clinical stage, metastasis, and the treatment and surgical methods during the treatment process.

2.4 Quality control and data processing

The questionnaire was designed in standard Chinese. To avoid possible biases, the survey was conducted face-to-face by trained

local investigators who were fluent in standard Chinese and the local language to ensure an adequate understanding of the questions by the study participants. To ensure the consistency and the quality of the questionnaire distribution process, in addition to standard training, each investigator had an implementation manual for timely review and to ensure that all processes were carried out following the standard steps and procedures specified in the manual. After the completion of the questionnaire by the investigators, members of the project team would review the questionnaire, and if any missing information or obvious logical errors were found, verification with the patients was required. After data collection, double data entry and validation were performed by two investigators using Epidata software V.3.1.

2.5 Statistical analysis

All statistical analyses were performed by using SASV.9.4 software. Continuous variables were expressed as mean and standard deviations and categorical variables were expressed as absolute frequencies and percentages. Univariate analysis was performed by using the t-test, analysis of variance, and chi-square test. The variables with P<0.1 in the univariate analysis were included in the multinomial logistic regression analysis. For treatment decision-making, full decision-making by patients served as the reference. For efficacy, the poor treatment effect was used as the reference. Unordered multinomial logistic regression was used to evaluate influencing factors. All statistical analyses were two-sided with a significance level of 0.05.

3 Results

3.1 Demographic characteristics

A total of 4533 patients with advanced CRC were enrolled. Their demographic characteristics are shown in Table 1. The average age at diagnosis of enrolled patients was 58.7 ± 11.81 years old, and there were 2694 males (59.4%) and 1839 females (40.6%). A total of 2063 (45.5%) patients had colon cancer, while 2470 (54.5%) cases were with rectal cancer. About 17.9% of patients were unemployed, 29% had an education level of primary school and below, 98.9% had medical insurance, 57.5% had an average annual family income of less than 50,000 Yuan, and, 56.2% had medical costs not covered by themselves or their spouses.

3.2 Clinical characteristics

The clinical characteristics of the 4533 enrolled patients are listed in Table 2. Among them, 45.9% were recruited from specialized tumor hospitals and 54.1% were from general hospitals. 18.3% of the patients visited more than 3 hospitals to further confirm their disease status, 87.6% found suspected symptoms themselves, while only 5.8% had hospital visits based on abnormal results during regular health examinations. For tumor stage, 76.8% of the patients were classified as stage III or IV CRC, and 37.9% had metastasis at their first diagnosis, of whom 14.0% had liver metastasis. In terms of treatment methods, 32.4% of the patients received surgery combined with chemotherapy, 13.1% underwent surgery combined with chemotherapy and targeted therapy, and 9.8% were treated with surgery alone.

3.3 Involvement in treatment decision-making

In terms of patient involvement in treatment decision-making, 7.0% of patients had full responsibility for treatment decision-making throughout treatment, 47.0% of patients shared treatment decision-making with family members, 19% of the patients relied exclusively on their family members for decision-making, while 27% of the patients left the responsibility of treatment decision-making entirely to their physicians (Figure 1).

3.4 Univariate and multinomial analysis of patient involvement in treatment decision-making

In univariate analysis, factors associated with involvement in treatment decision-making included gender, age at diagnosis, time since cancer diagnosis, occupation, marital status, education level, average annual family income, treatment cost burden, awareness of CRC-related factors, the type of visited hospital, the number of hospital visits, the clinical stage at diagnosis, and the treatment method (p<0.01 for all) (Table 3).

Multivariate logistic regression analysis was conducted by using full treatment decision-making by patients served as the reference. The results showed that gender, age, education level, annual family income, marital status, treatment cost burden, type of hospitals visited, and treatment methods were significantly related to involvement in treatment decision-making (Table 4). In detail, males were more likely to be solely responsible for treatment decision-making (OR 0.55 to 0.64). Patients under 50 years of age were more dominant in treatment decision-making compared to those over 65 years of age (OR 0.19 to 0.46). Compared with patients with an education level of university or above, patients with elementary school or less education level were less involved in making treatment decisions and were more likely to have family members or doctors make treatment decisions (OR 2.55 to 4.34). Patients with middle or high school education levels were more likely to make treatment decisions with family members (OR=1.96,95% CI=1.398-2.734). Patients with an average annual household income between 50,000 Yuan and 100,000 Yuan were more likely to make treatment decisions jointly with family members or by family members and physicians than patients with an average annual household income greater than 100,000 Yuan (OR 1.53-1.9). Married patients preferred shared treatment decision-making with family members or full treatment decision-making by family members than unmarried, divorced, or widowed patients (OR 1.7-1.88). Patients who paid treatment costs by themselves and their spouses were less likely to let family members make treatment decisions (OR=0.46, 95% CI=0.336-0.692). Patients from specialized cancer hospitals were more likely to share treatment decision-making with family members or

TABLE 1 Demographic characteristics of patients with advanced colorectal cancer.

Characteristics	Total number of cases, n (%)	Colon cancer, n (%)	Rectal cancer, n (%)	P-value
Gender				0.329
Male	2694 (59.4)	1210 (58.7)	1484 (60.1)	
Female	1839 (40.6)	853 (41.3)	986 (39.9)	
Age at diagnosis, years (mean ± SD)	58.7 ± 11.81	58.3 ± 12.02	59.0 ± 11.62	0.136
<50	922 (20.3)	443 (21.5)	479 (19.4)	
50~64	2134 (47.1)	972 (47.1)	1162 (47.0)	
≥65	1477 (32.6)	648 (31.4)	829 (33.6)	
Occupation				0.007
Government and public sector personnel	1918 (42.3)	925 (44.8)	993 (40.2)	
Service workers, migrant workers, and individuals	1805 (39.8)	789 (38.2)	1016 (41.1)	
Unemployment, layoffs, etc.	810 (17.9)	349 (16.9)	461 (18.7)	
Marital status				0.753
Married	4266 (94.1)	1939 (94.0)	2327 (94.2)	
Other	267 (5.9)	124 (6.0)	143 (5.8)	
Level of education†				<0.001
Elementary school and below	1314 (29.0)	539 (26.2)	775 (31.4)	
Middle or high school	2495 (55.1)	1157 (56.2)	1338 (54.2)	
University and above	721 (15.9)	364 (17.7)	357 (14.5)	
Medical insurance				0.823
No	51 (1.1)	24 (1.2)	27 (1.1)	
Yes	4482 (98.9)	2039 (98.8)	2443 (98.9)	
Average annual income (Yuan)				<0.001
<50000	2607 (57.5)	1091 (52.9)	1516 (61.4)	
5000-99999	1278 (28.2)	654 (31.7)	624 (25.3)	
≥100000	648 (14.3)	318 (15.4)	330 (13.4)	
Region				<0.001
East China	1312 (28.9)	570 (27.6)	742 (30.0)	
North China	556 (12.3)	254 (12.3)	302 (12.2)	
South China	650 (14.3)	340 (16.5)	310 (12.6)	
Central China	675 (14.9)	271 (13.1)	404 (16.4)	
Northeast China	363 (8.0)	196 (9.5)	167 (6.8)	
Southwest China	651 (14.4)	278 (13.5)	373 (15.1)	
Northwest China	326 (7.2)	154 (7.5)	172 (7.0)	
Bearer of the cost of treatment†				0.029
Payment by patients themselves and their spouses	1981 (43.8)	937 (45.6)	1044 (42.4)	
Not paid by patients themselves and their spouses	2539 (56.2)	1118 (54.4)	1421 (57.6)	
The score for awareness of risk factors (Mean ± SD)	0.91 ± 1.50	0.98 ± 1.58	0.85 ± 1.43	0.003

(Continued)

TABLE 1 Continued

Characteristics	Total number of cases, n (%)	Colon cancer, n (%)	Rectal cancer, n (%)	P-value
The score for awareness of the screening method (Mean ± SD)	0.26 ± 0.69	0.29 ± 0.74	0.23 ± 0.65	0.007
The score for awareness of the treatment method (Mean ± SD)	1.17 ± 1.58	1.23 ± 1.61	1.12 ± 1.56	0.022

†The total number varies due to missing values.

TABLE 2 Clinical characteristics of patients with advanced colorectal cancer.

Characteristics	Total number of cases, n (%)	Colon cancer, n (%)	Rectal cancer, n (%)	P-value
Type of visited hospital				0.094
Specialized cancer hospital	2083 (45.95)	920 (44.6)	1163 (47.1)	
General Hospital	2450 (54.05)	1143 (55.4)	1307 (52.9)	
Number of visited hospitals†				0.119
1	1328 (29.3)	609 (30.0)	719 (29.7)	
2	2290 (50.52)	1017 (50.1)	1273 (52.6)	
≥3	830 (18.31)	403 (19.9)	427 (17.7)	
Reason for the first hospital visit†				<0.001
Observation of suspected symptoms by patients themselves	3969 (87.56)	1722 (84.0)	2247 (91.4)	
Physical examination findings	264 (5.82)	155 (7.6)	109 (4.4)	
Detection of CRC during screening or treatment of other diseases	275 (6.07)	173 (8.4)	102 (4.1)	
Current treatment phase†				0.012
Treatment had not yet been started	155 (3.42)	65 (3.2)	90 (3.6)	
The first treatment was not replaced	2057 (45.38)	925 (44.9)	1132 (45.8)	
First treatment replacement regimen	524 (11.56)	241 (11.7)	283 (11.5)	
The stage of treatment after relapse	1124 (24.8)	554 (26.9)	570 (23.1)	
Periodic review phase	669 (14.76)	275 (13.3)	394 (16.0)	
Clinical staging at initial diagnosis†				<0.001
Stage I/II	871 (19.21)	405 (20.3)	466 (19.7)	
Stage III	1948 (42.97)	753 (37.8)	1195 (50.6)	
Stage IV	1535 (33.86)	834 (41.9)	701 (29.7)	
Metastasis at diagnosis†				<0.001
No metastasis	2817 (62.14)	1149 (56.0)	1668 (67.8)	
With liver metastasis only	635 (14.01)	362 (17.6)	273 (11.1)	
With lung metastasis only	178 (3.93)	70 (3.4)	108 (4.4)	
With both liver and lung metastases	191 (4.21)	98 (4.8)	93 (3.8)	
Metastases in other sites or multiple metastases throughout the body	689 (15.2)	372 (18.1)	317 (12.9)	
Time since cancer diagnosis (months)				0.347
<12	2543 (56.1)	1173 (56.9)	1370 (55.5)	
>=12	1990 (43.9)	890 (43.1)	1100 (44.5)	

(Continued)

TABLE 2 Continued

Characteristics	Total number of cases, n (%)	Colon cancer, n (%)	Rectal cancer, n (%)	P-value
Treatment modality				<0.001
Surgery + chemotherapy	1470 (32.43)	769 (37.3)	701 (28.4)	
Surgery + chemotherapy + targeted therapy	595 (13.13)	365 (17.7)	230 (9.3)	
Surgery + chemotherapy + radiotherapy	381 (8.41)	48 (2.3)	333 (13.5)	
Surgery	442 (9.75)	206 (10.0)	236 (9.6)	
Chemotherapy + targeted therapy	211 (4.65)	121 (5.9)	90 (3.6)	
Chemotherapy	164 (3.62)	82 (4.0)	82 (3.3)	
Surgery + radiotherapy + chemotherapy + targeted therapy	171 (3.77)	50 (2.4)	121 (4.9)	
Radiation therapy + chemotherapy	128 (2.82)	6 (0.3)	122 (4.9)	
Others	971 (21.42)	416 (20.2)	555 (22.5)	

†The total number varies due to missing values.

follow physicians' treatment decisions compared to those from general hospitals (OR=1.43-2.98). Patients with surgical treatment were more likely to make treatment decisions jointly with or solely by family members compared to those with palliative care (OR=8.49-9.23).

3.5 Self-reported efficacy

Self-reported efficacy evaluations were available for 3824 patients. For the first treatment, 76.5% of patients reported efficacy as good, 14.8% reported a stable condition, and 8.7% reported poor efficacy (Figure 2). Regarding the efficacy of the second treatment, the percentage of patients with self-reported good efficacy, stable condition, and poor efficacy was 61.7%, 26.2%, and 12.1%, respectively. Regarding the treatment efficacy for patients who had recurrence and metastasis, the percentage of patients with self-reported good efficacy, stable condition, and poor efficacy was 43.2%, 38.4%, and 18.4%, respectively (Figure 2).

3.6 Univariate and multinomial analysis of factors affecting self-reported efficacy

In univariate analysis, factors associated with self-reported efficacy included age at diagnosis, occupation, education level, average annual family income, region, time since cancer diagnosis, primary site, type of hospital, clinical stage at diagnosis, metastasis status, surgical treatment, chemotherapy, targeted therapy, and involvement in treatment decision-making (Table 5).

The multinomial analysis was conducted by using the poor self-reported efficacy as a reference. The results showed that occupation in

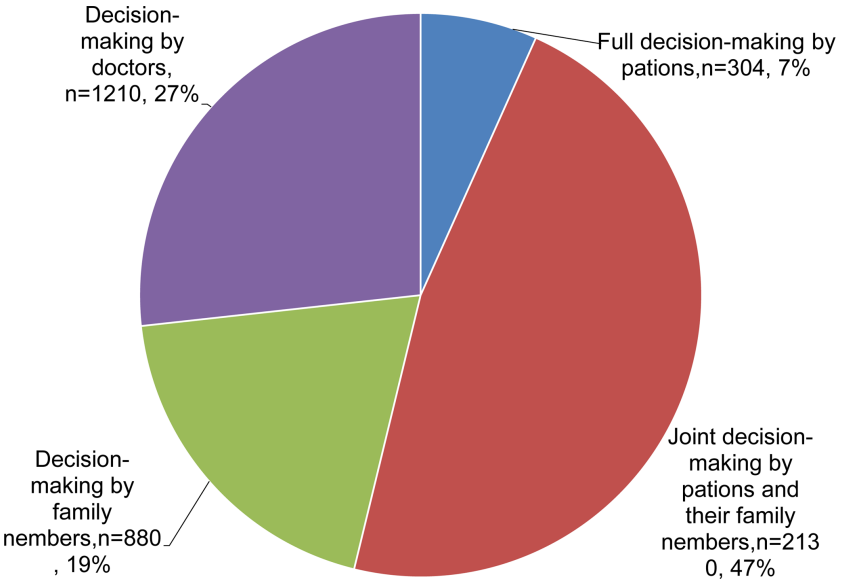

FIGURE 1
Pie chart showing the involvement in treatment decision-making in patients with advanced colorectal cancer.

TABLE 3 Univariate analysis of factors affecting patient involvement in treatment decision-making.

Factor	Total number of cases, n(%)	Full decision-making by patients, n(%)	Joint decision-making by patients and their family members, n (%)	Decision-making by family members, n (%)	Decision-making by doctors, n (%)	P
Gender						<0.001
Male	2694 (59.4)	218 (71.7)	1276 (59.9)	463 (52.6)	733 (60.6)	
Female	1839 (40.6)	86 (28.3)	854 (40.1)	417 (47.4)	477 (39.4)	
Age at diagnosis, years						<0.001
<50	922 (20.3)	103 (33.9)	452 (21.2)	87 (9.9)	279 (23.1)	
50~64	2134 (47.1)	141 (46.4)	1063 (49.9)	335 (38.1)	591 (48.8)	
≥65	1477 (32.6)	60 (19.7)	615 (28.9)	458 (52.0)	340 (28.1)	
Time since cancer diagnosis, months						0.001
<12	2543 (56.1)	162 (53.3)	1136 (53.3)	526 (59.8)	713 (58.9)	
≥12	1990 (43.9)	142 (46.7)	994 (46.7)	354 (40.2)	497 (41.1)	
Patient occupation						<0.001
Government and public sector personnel	1918 (42.3)	153 (50.3)	934 (43.8)	347 (39.4)	480 (39.7)	
Service workers, migrant workers, and individuals	1805 (39.8)	118 (38.8)	855 (40.1)	327 (37.2)	502 (41.5)	
Unemployment, layoffs, etc	810 (17.9)	33 (10.9)	341 (16.0)	206 (23.4)	228 (18.8)	
Marital status						0.012
Married	4266 (94.1)	277 (91.1)	2023 (95.0)	816 (92.7)	1142 (94.4)	
Other	267 (5.9)	27 (8.9)	107 (5.0)	64 (7.3)	68 (5.6)	
Level of education†						<0.001
Elementary school and below	1314 (29.0)	51 (16.8)	502 (23.6)	401 (45.6)	358 (29.6)	
Middle or high school	2495 (55.1)	149 (49.0)	1263 (59.3)	409 (46.5)	668 (55.3)	
University and above	721 (15.9)	104 (34.2)	364 (17.1)	70 (8.0)	182 (15.1)	
Average annual household income (Yuan)						<0.001
<50000	2607 (57.5)	140 (46.1)	1134 (53.2)	592 (67.3)	738 (61.0)	
50000~99999	1278 (28.2)	77 (25.3)	667 (31.3)	203 (23.1)	327 (27.0)	
≥100000	648 (14.3)	87 (28.6)	329 (15.4)	85 (9.7)	145 (12.0)	
Bearer of the cost of treatment†						<0.001
Payment by patients themselves and their spouses	1981 (43.8)	174 (57.4)	1005 (47.3)	231 (26.3)	567 (47.1)	
Not paid by patients themselves and their spouses	2539 (56.2)	129 (42.6)	1121 (52.7)	647 (73.7)	637 (52.9)	
The score for awareness of risk factors (Mean ± SD)	0.91 ± 1.50	1.13 ± 1.65	0.99 ± 1.57	0.82 ± 1.43	0.78 ± 1.38	<0.001

(Continued)

TABLE 3 Continued

Factor	Total number of cases, n(%)	Full decision-making by patients, n(%)	Joint decision-making by patients and their family members, n (%)	Decision-making by family members, n (%)	Decision-making by doctors, n (%)	P
The score for awareness of the screening method (Mean ± SD)	0.25 ± 0.70	0.34 ± 0.73	0.30 ± 0.75	0.19 ± 0.60	0.20 ± 0.64	<0.001
The score for awareness of the treatment method (Mean ± SD)	1.17 ± 1.58	1.43 ± 1.55	1.25 ± 1.59	1.13 ± 1.51	1.02 ± 1.62	<0.001
Type of hospital visited						<0.001
Specialized cancer hospital	2083 (46.0)	124 (40.8)	933 (43.8)	269 (30.6)	754 (62.3)	
General hospital	2450 (54.0)	180 (59.2)	1197 (56.2)	611 (69.4)	456 (37.7)	
Number of visited hospitals†						<0.001
1	1328 (29.9)	85 (28.1)	609 (29.3)	345 (40.1)	286 (23.9)	
2	2290 (51.5)	140 (46.4)	1070 (51.4)	391 (45.5)	686 (57.4)	
≥3	830 (18.7)	77 (25.5)	403 (19.4)	124 (14.4)	224 (18.7)	
Clinical staging at initial diagnosis†						0.028
Stage I/II	871 (20.0)	54 (18.6)	430 (21.0)	186 (22.3)	198 (16.9)	
Stage III	1948 (44.7)	126 (43.3)	895 (43.6)	380 (45.6)	543 (46.4)	
Stage IV	1535 (35.3)	111 (38.1)	726 (35.4)	268 (32.1)	428 (36.6)	
Treatment modality						<0.001
Surgical treatment	442 (9.8)	17 (5.6)	186 (8.7)	153 (17.4)	85 (7.0)	
Non-surgical treatment	4072 (89.8)	284 (93.4)	1939 (91.0)	719 (81.7)	1122 (92.7)	
Palliative care	19 (0.4)	3 (1.0)	5 (0.2)	8 (0.9)	3 (0.2)	

†The total number varies due to missing values.

government and public institutions (OR=1.44, 95%CI=1.044 -1.999), primary education and below (OR=1.57-2.18), annual family income of more than 100,000 Yuan (OR=0.59, 95%CI=0.341-1.005), living in less developed regions (OR=0.51-0.78), time since cancer diagnosis for less than 12 months (OR=1.94, 95%CI=1.547-2.43), admission in general hospitals (OR=0.7, 95%CI=0.558-0.881), clinical stage III (OR=1.41, 95% CI=0.961-2.078), surgery (OR=, 1.72, 95%CI=1.225-2.414), chemotherapy (OR=1.69, 95%CI= 1.101-2.598), targeted therapy (OR=2.03, 95%CI=1.585-2.593), and involvement in treatment decision-making (OR=1.33, 95%CI=1.061-1.665) were significantly associated with good self-reported treatment outcomes (all P<0.05, Table 6).

4 Discussion

For the first time, we conducted a nationwide multicenter hospital-based survey of patients with advanced CRC. Our results showed that the awareness of CRC-related knowledge such as risk factors, screening methods, and treatment methods was poor in patients with advanced CRC before diagnosis, which was similar to previous studies. For example, Amlani et al. showed that more than half of 2500 people from five European countries who had never received a colonoscopy were unaware that colonoscopy was a screening and prevention tool (14). Mueller et al. showed that only 36.0% of the respondents knew the starting age of CRC screening, and only 8.0% of the respondents answered all the screening knowledge correctly (19).

In this study, only 5.82% of the patients had hospital visits based on abnormal health examination results, while 87.6% found suspected symptoms themselves. Regarding tumor stage, 76.8% of the patients had stage III or IV CRC, and 37.5% had metastasis. These results were consistent with previous studies (20, 21). It has been shown that in countries with long-term and sustainable screening programs for CRC, CRC-related mortality is largely reduced and the diagnostic rate of early-stage CRC is increased (22, 23). Losurdo et al. showed that screening could significantly increase the rate of early diagnosis and surgery in CRC, reduce the incidence of complications, and improve survival outcomes (24). Kanth et al. showed that most of the CRC screening in the United States was based on opportunistic screening, and the goal of the screening rate reached 80.0% in 2018 (25). In China, Urban Cancer

TABLE 4 Multinomial analysis of factors affecting patient involvement in treatment decision-making.

Factor	Joint decision-making by patients and their family members		Decision-making by family members		Decision-making by doctors	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Gender						
Male	0.55 (0.409,0.73)	<.0001	0.47 (0.343,0.647)	<.0001	0.64 (0.47,0.863)	0.0036
Female	1	—	1	—	1	—
Age at diagnosis, years						
<50	0.45 (0.298,0.664)	<.0001	0.19 (0.121,0.305)	<.0001	0.46 (0.3,0.695)	0.0003
50~64	0.73 (0.512,1.029)	0.5305	0.41 (0.281,0.589)	0.6177	0.7 (0.488,1.012)	0.7741
≥65	1	—	1	—	1	—
Level of education						
Elementary school and below	1.87 (1.17,2.982)	0.143	4.34 (2.523,7.449)	<.0001	2.55 (1.563,4.174)	0.0042
Middle or high school	1.96 (1.398,2.734)	0.0083	2.65 (1.735,4.051)	0.1213	2.02 (1.406,2.9)	0.1012
University and above	1	—	1	—	1	—
Average annual household income						
<50000	1.13 (0.78,1.643)	0.3456	1.12 (0.717,1.749)	0.5746	1.47 (0.98,2.194)	0.7055
50000~99999	1.71 (1.187,2.475)	0.0017	1.53 (0.979,2.387)	0.0365	1.9 (1.273,2.833)	0.0054
≥100000	1	—	1	—	1	—
Marital status						
Married	1.88 (1.165,3.019)	0.0097	1.7 (1.004,2.884)	0.0483	1.59 (0.962,2.63)	0.0704
Other	1	—	1	—	1	—
Bearer of the cost of treatment						
Payment by patients themselves and their spouses	0.79 (0.603,1.047)	0.102	0.46 (0.336,0.629)	<.0001	0.81 (0.605,1.081)	0.1509
Not paid by patients themselves and their spouses	1	—	1	—	1	—
Type of visited hospital						
Specialized cancer hospital	1.43 (1.075,1.892)	0.0138	1.08 (0.782,1.482)	0.6507	2.98 (2.205,4.013)	<.0001
General Hospital	1	—	1	—	1	—
Treatment modality						
Surgical treatment	9.23 (1.835,46.391)	0.0047	8.49 (1.785,40.339)	0.001	4.91 (0.87,27.705)	0.0855
Non-surgical treatment	5.83 (1.253,27.114)	0.1207	3.38 (0.773,14.741)	0.7183	4.24 (0.814,22.054)	0.1496
Palliative care	1	—	1	—	1	—

Early Diagnosis and Early Treatment Project was carried out in 2012 to screen high-risk groups for CRC in urban areas (26).

In this study, the treatment methods for advanced CRC were mainly surgery, surgery combined with chemotherapy, and, surgery combined with chemotherapy, radiotherapy, and targeted therapy. According to the China guideline for diagnosis and comprehensive treatment of colorectal liver metastases (2020 edition) (27) and Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology (28), the conventional treatment for CRC is surgery combined with chemotherapy or radiotherapy. Approximately 66.0% and 61.0% of stage II and III colon and rectal patients, respectively, received further treatment with adjuvant chemotherapy and/or radiotherapy (29). For advanced unresectable metastatic CRC, the mainstay of treatment is systemic therapy, such as targeted therapy and immunotherapy (30). In 2021, the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) announced many research advances in immune and targeted therapy for advanced CRC (31–34), which greatly improved the survival rate of patients with advanced CRC.

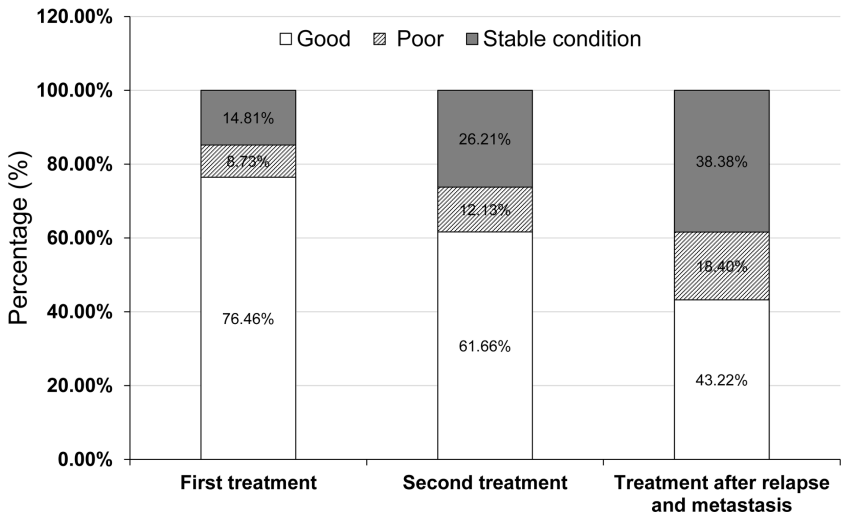

FIGURE 2
Self-reported efficacy of patients with advanced colorectal cancer.

TABLE 5 Univariate analysis of factors affecting self-reported treatment efficacy.

Factor	Total number of cases, n (%)	Good efficacy, n (%)	Poor efficacy, n (%)	Stable condition, n (%)	P-value
Gender					0.574
Male	2265 (59.2)	1842 (59.2)	270 (58.2)	153 (62.2)	
Female	1559 (40.8)	1272 (40.8)	194 (41.8)	93 (37.8)	
Age at diagnosis					0.001
<50	799 (20.9)	621 (19.9)	116 (25.0)	62 (25.2)	
50~64	1809 (47.3)	1460 (46.9)	223 (48.1)	126 (51.2)	
≥65	1216 (31.8)	1033 (33.2)	125 (26.9)	58 (23.6)	
Patient occupation					0.026
Government and public sector personnel	1617 (42.3)	1337 (42.9)	179 (38.6)	101 (41.1)	
Service workers, migrant workers, and individuals	1527 (39.9)	1214 (39.0)	198 (42.7)	115 (46.7)	
Unemployment, layoffs, etc	680 (17.8)	563 (18.1)	87 (18.8)	30 (12.2)	
Marital status					0.643
Married	3610 (94.4)	2935 (94.3)	440 (94.8)	235 (95.5)	.
Other	214 (5.6)	179 (5.7)	24 (5.2)	11 (4.5)	.
Level of education†					0.014
Elementary school and below	1120 (29.3)	943 (30.3)	113 (24.4)	64 (26.1)	
Middle or high school	2084 (54.5)	1691 (54.3)	259 (55.8)	134 (54.7)	.
University and above	617 (16.1)	478 (15.4)	92 (19.8)	47 (19.2)	.
Average annual household income (Yuan)					0.004
<50000	2204 (57.6)	1821 (58.5)	268 (57.8)	115 (46.7)	
50000~99999	1071 (28.0)	857 (27.5)	134 (28.9)	80 (32.5)	
≥100000	549 (14.4)	436 (14.0)	62 (13.4)	51 (20.7)	

(Continued)

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TABLE 5 Continued

Factor	Total number of cases, n (%)	Good efficacy, n (%)	Poor efficacy, n (%)	Stable condition, n (%)	P-value
Region					<0.001
Less developed region	1758 (46.0)	1423 (45.7)	248 (53.4)	87 (35.4)	
Developed region	2066 (54.0)	1691 (54.3)	216 (46.6)	159 (64.6)	
Time since cancer diagnosis (months)					<0.001
<12	2092 (54.7)	1857 (59.6)	177 (38.1)	58 (23.6)	
>=12	1732 (45.3)	1257 (40.4)	287 (61.9)	188 (76.4)	
Primary tumor site					0.008
Colon	1767 (46.2)	1410 (45.3)	221 (47.6)	136 (55.3)	
Rectum	2057 (53.8)	1704 (54.7)	243 (52.4)	110 (44.7)	
Type of visited hospital					<0.001
Specialized cancer hospital	1794 (46.9)	1397 (44.9)	259 (55.8)	138 (56.1)	
General Hospital	2030 (53.1)	1717 (55.1)	205 (44.2)	108 (43.9)	
Clinical staging at initial diagnosis†					<0.001
Stage I/II	704 (19.1)	605 (20.1)	73 (16.9)	26 (11.2)	.
Stage III	1683 (45.7)	1431 (47.5)	159 (36.8)	93 (40.1)	.
Stage IV	1292 (35.1)	979 (32.5)	200 (46.3)	113 (48.7)	.
Metastasis at diagnosis†					<0.001
No metastasis	2375 (62.4)	2004 (64.7)	247 (53.3)	124 (50.4)	
With liver metastasis only	534 (14.0)	417 (13.5)	72 (15.6)	45 (18.3)	
With lung metastasis only	146 (3.8)	114 (3.7)	19 (4.1)	13 (5.3)	
With both liver and lung metastases	165 (4.3)	127 (4.1)	25 (5.4)	13 (5.3)	
Metastases in other sites or multiple metastases throughout the body	586 (15.4)	435 (14.0)	100 (21.6)	51 (20.7)	
Surgical treatment†					0.001
No	591 (15.5)	513 (16.5)	53 (11.4)	25 (10.2)	
Yes	3227 (84.5)	2595 (83.5)	411 (88.6)	221 (89.8)	
Chemotherapy†					<0.001
No	491 (12.9)	452 (14.5)	28 (6.0)	11 (4.5)	
Yes	3327 (87.1)	2656 (85.5)	436 (94.0)	235 (95.5)	
Radiotherapy†					0.438
No	2975 (77.9)	2414 (77.7)	372 (80.2)	189 (76.8)	
Yes	843 (22.1)	694 (22.3)	92 (19.8)	57 (23.2)	
Targeted therapy†					<0.001
No	2692 (70.5)	2359 (75.9)	249 (53.7)	84 (34.1)	
Yes	1126 (29.5)	749 (24.1)	215 (46.3)	162 (65.9)	
Involvement in treatment decision-making†					0.018
No	1459 (38.21)	1219 (39.20)	150 (32.47)	90 (36.59)	
Yes	2359 (61.79)	1891 (60.80)	312 (67.53)	156 (63.41)	

†The total number varies due to missing values.

†Less developed areas: Central, Northwest, Southwest, and Northeast; Developed areas: East, South, Northern.

TABLE 6 Multinomial analysis of factors affecting self-reported treatment efficacy (with poor efficacy as a reference).

Factor	Total number of cases, n(%)	Stable condition		Good efficacy	
		OR (95%CI)	*P*	OR (95%CI)	*P*
Patient occupation					
Government and public sector personnel	1617 (42.3)	1.66 (0.949,2.894)	0.2215	1.44 (1.044,1.999)	0.0025
Service workers, migrant workers, and individuals	1527 (39.9)	1.65 (0.983,2.772)	0.185	0.95 (0.708,1.284)	0.0453
Unemployment, layoffs, etc	680 (17.8)	1	—	1	—
Level of education†					
Elementary school and below	1120 (29.3)	2.18 (1.18,4.016)	0.0137	1.57 (1.067,2.323)	0.0360
Middle or high school	2084 (54.5)	1.47 (0.902,2.397)	0.983	1.31 (0.962,1.791)	0.6843
University and above	617 (16.1)	1	—	1	—
Average annual household income (Yuan)					
<50000	2204 (57.6)	0.59 (0.341,1.005)	0.0286	0.83 (0.579,1.198)	0.5391
50000~99999	1071 (28.0)	0.85 (0.508,1.409)	0.5965	0.82 (0.573,1.166)	0.3951
≥100000	549 (14.4)	1	—	1	—
Region					
Less developed region	1758 (46.0)	0.51 (0.36,0.731)	0.0002	0.78 (0.625,0.975)	0.0289
Developed region	2066 (54.0)	1	—	1	—
Time since cancer diagnosis (months)					
<12	2092 (54.7)	0.57 (0.384,0.836)	0.0042	1.94 (1.547,2.43)	<.0001
>=12	1732 (45.3)	1	—	1	—
Type of hospital visited					
Specialized cancer hospital	1794 (46.9)	1.04 (0.729,1.49)	0.8223	0.7 (0.558,0.881)	0.0024
General Hospital	2030 (53.1)	1	—	1	—
Clinical staging at initial diagnosis†					
Stage I/II	704 (19.1)	0.83 (0.402,1.733)	0.235	1.1 (0.695,1.732)	0.6437
Stage III	1683 (45.7)	1.39 (0.774,2.496)	0.0538	1.41 (0.961,2.078)	0.0275
Stage IV	1292 (35.1)	1	—	1	—
Surgical treatment†					
Yes	3227 (84.5)	0.87 (0.492,1.521)	0.6139	1.72 (1.225,2.414)	0.0017
No	591 (15.5)	1	—	1	—
Chemotherapy†					
Yes	3327 (87.1)	1.14 (0.526,2.489)	0.7341	1.69 (1.101,2.598)	0.0164
No	491 (12.9)	1	—	1	—
Targeted therapy†					
Yes	1126 (29.5)	0.49 (0.332,0.717)	0.0003	2.03 (1.585,2.593)	<.0001
No	2692 (70.5)	1	—	1	—
Involvement in treatment decision-making†					
Yes	2359 (61.8)	1.28 (0.900,1.810)	0.1711	1.33 (1.061,1.665)	0.0132
No	1459 (38.2)	1	—	1	—

†The total number varies due to missing values.
†Less developed areas: Central, Northwest, Southwest, and Northeast; Developed areas: East, South, Northern.

In this study, only 7.0% of patients were solely responsible for treatment decision-making, 47.0% of patients shared treatment decision-making with their family members, and 46.0% of patients had treatment decision-making by solely family members or doctors. These results are consistent with the results of previous studies conducted on Asian patients from Taiwan and the United States (35–37). There are also findings showing that patients are willing to be involved in treatment decision-making, but most patients prefer to make treatment decisions with or by their physicians (38–40). However, it also has been shown that patients in the United States and other developed countries are more willing to make treatment decisions (41, 42). This may be related to the traditional Chinese concept of family and the paternalistic style of doctors. Chinese patients have high trust in doctors, believe that "doctors know the best", and are willing to have their doctors make treatment decisions (43).

In this study, we found that gender, age at diagnosis, education level, family economic income, marital status, bearer of treatment expenses, type of hospital, and treatment method were independent factors affecting patient involvement in treatment decision-making. Males tended to be more likely to make treatment decisions by themselves, which reflects the dominance of males in the family. Younger patients, those with higher levels of education, and those with higher family income were more independent in making treatment decisions, which was similar to previous studies (44, 45), suggesting that younger and more educated patients are more likely to acquire disease-related information and to be more involved in treatment decision-making. Patients with wealthy families do not have to worry too much about the financial burden of treatment and are willing to have more personal control over their treatment decisions (46). Married patients are more involved in treatment decision-making than those in other marital statuses, which further reflects that Asians have a heavier family concept (37). For patients who paid for treatment costs by themselves and their spouses, family members were less likely to make treatment decisions, mainly because these patients had economic dominance. Compared with general hospitals, doctors from specialized cancer hospitals were more involved in treatment decision-making, which may be related to patients' higher trust in oncologists. It has been shown that the lack of knowledge of patients and the imbalance of the doctor-patient relationship are the main obstacles for patients to participate in treatment decision-making (47). Clinicians should timely provide information about diseases to patients from the perspective of patients, which has a great impact on patient involvement in treatment decision-making (48, 49). Good and efficient doctor-patient communication is a major factor in improving treatment decision-making satisfaction, treatment compliance, and improved treatment outcomes.

Patient-Reported Outcomes (PROs) refer to any outcomes directly reported by patients, including information related to health, life quality, and functional status (50). PROs may more accurately reflect the physical functioning and emotional well-being of an individual, which cannot be affected by physician interpretation and prejudice (51) and are superior predictors of survival compared with functional status (52). The application of PROs can reduce the symptom burden of CRC patients and improve patients' quality of life and survival. The evaluation of PRO is mainly through questionnaires (53), including short form-36, European Organization for Research and Treatment of Cancer, the quality of life questionnaire (EORTCQLQC30), and, the European Organization for Research and Treatment of colorectal cancer, the quality of life questionnaire (EORTCQLQ-CR38), etc. (54). In this study, we did not use scales to evaluate PROs. Instead, we used self-reported efficacy, i.e. patients' subjective feelings after treatment, which was divided into good efficacy, poor efficacy, and stable condition. A total of 3824 patients, mainly those receiving the first treatment, the second treatment, and the treatments following recurrence and metastasis, submitted self-reported efficacy assessments during treatment. With the increase in the number of treatment times, patients reported an increased number of unsatisfactory treatment outcomes, which is also in line with the progression of the disease. Generally, the patient's quality of life decreases with longer disease duration and advanced disease stages (55).

In this study, occupation, education level, average annual family income, economic level of the region, time since cancer diagnosis, hospital type, clinical stage at diagnosis, surgical treatment, chemotherapy, targeted therapy, and involvement in treatment decision-making were all significant factors affecting self-reported efficacy in patients with advanced CRC. Belachew. et al. found that higher education levels and economic income were associated with higher quality of life (56). McCombie et al. showed that CRC patients over the age of 80 years were always satisfied with the outcome of surgical treatment (57). Moreover, gender, ethnicity, medical insurance, tumor location, stage, metastasis, and other factors are all prognostic factors of CRC (58, 59). In addition, appropriate surgical treatment is essential to control tumor recurrence and metastasis, thus achieving improved survival rates (60). However, in this study, tumor location and metastasis were not independent prognostic factors, which may be related to the fact that all the study participants included in the study were with advanced CRC. In addition, patients who participated in treatment decision-making reported better self-reported treatment outcomes than patients who did not participate in treatment decision-making, possibly because patients who participated in treatment decision-making acquired more knowledge of tumors and had a better quality of life (61).

There are several limitations in this study. First, the role of doctors and nurses in patient involvement in treatment decision-making was not analyzed. Second, this is a cross-sectional study without long-term follow-up. The causal relationship between treatment effects and associated factors cannot be determined. Third, there are some missing values for some variables, which might cause some potential bias. Considering that the highest missing rate of a specific variable was lower than 5%, and the missing rates of most variables were less than 1%, we did not make further adjustments. Last but not least, the treatment effects were self-reported and were only evaluated based on subjective feelings, without using appropriate scales, which may lead to certain biases. In the follow-up work, we will collect more data and conduct a more in-depth analysis of the patient involvement in treatment decision-making and the self-reported efficacy of CRC patients.

In this study, we conducted a nationwide multi-center hospital-based survey of patients with advanced CRC and found that the involvement of patients in treatment decision-making was poor. The vast majority of treatment decisions were made jointly with family

members or by family members/physicians. Effective communication between physicians and patients should be further improved. Thus, patients can obtain timely information on CRC and then participate in treatment decision-making. The use of patient self-reported outcomes in clinical practice in China is in its infancy and lacks appropriate measurement tools, which should be further improved in the future.

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 study was reviewed and approved by the Medical Ethics Committee of Henan Cancer Hospital (No. 2019273). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: X-FG, H-FX, Y-LQ, LM, and RR. Administrative support: Y-LQ. Provision of study materials or patients: X-FG, H-FX, LL, Y-QY, XZ, X-HW, W-JW, L-BD, S-XD, H-LC, Y-QZ, Y-YL, J-XH, JC, Y-PF, C-YF, X-ML, J-CD, and LM. Collection and assembly of data: Y-QY, XZ, and H-FX. Data analysis and interpretation: X-FG, YL, and H-FX. Manuscript writing: X-FG, H-FX. Final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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High serum mannose in colorectal cancer: a novel biomarker of lymph node metastasis and poor prognosis

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Background: Lymph node status is an important prognostic indicator and it significantly influences treatment decisions for colorectal cancer (CRC). The objective of this study was to evaluate the ability of serum monosaccharides in predicting lymph node metastasis (LNM) and prognosis.

Methods: High performance anion exchange chromatography coupled with pulsed amperometric detector (HPAEC-PAD) was used to quantify serum monosaccharides from 252 CRC patients. Receiver operating characteristic (ROC) curves were used to evaluate predictive performance of parameters. Predictors of LNM were evaluated by univariate and multivariate analyses. The prognostic role of the factors was evaluated by survival analysis.

Results: The levels of serum mannose (Man) and galactose (Gal) were significantly increased in patients with LNM (p <0.0001, p =0.0017, respectively). The area under the curves (AUCs) of Man was 0.8140, which was higher than carcinoembryonic antigen (CEA) (AUC =0.6523). Univariate and multivariate analyses demonstrated histologic grade (G3) (odds ratio [OR] =2.60, p =0.043), histologic grade (mucin-producing subtype) (odds ratio [OR] =3.38, p =0.032), lymphovascular invasion (LVI) (OR =2.42, p <0.01), CEA (>5ng/ml) (OR =1.85, p =0.042) and high Man (OR =2.65, p =0.006) to be independent risk factors of LNM. The survival analysis showed that the high serum Man was independent risk factor for poor prognosis in CRC patients (HR=1.75, p =0.004).

Conclusions: The Man is superior to CEA in prediction of LNM for CRC patients. Man is expected to be a predictor for LNM in CRC. High serum Man is associated with poor prognosis of CRC patients.

KEYWORDS

colorectal cancer, mannose, lymph node metastasis, prognosis, biomarker

Introduction

The morbidity and mortality rates of CRC have been rising rapidly over the last decade. There were 1.33 million new cases and 694 thousand CRC-caused deaths in 2012, and the numbers had respectively risen to 1.88 million and 916 thousand by 2020 (1–3). In clinical practice, lymph node metastasis (LNM) is associated with poor prognosis, and it also influences treatment decisions (4). For instance, preoperative assessment of the likelihood of LNM could be used as a basis to advise neoadjuvant chemotherapy in CRC patients (4). In addition, in patients with early CRC (cT1), endoscopic therapy is feasible only when the possibility of LNM is negligible (5). However, up to now, it is still not accurate enough to predict LNM preoperatively (4). Some studies have postulated lymphovascular invasion (LVI) and poorly differentiated components as suggestive predictors of LNM (6, 7). However, these pathological data are generally not available until surgery. Besides these factors, biomarkers have also been investigated, and the combination of biomarkers and pathological parameters may increase the accuracy of LNM prediction (7).

The complexity of polysaccharide or glycan structures arises not only from non-template biosynthesis but also from different monosaccharides with multiple linkage positions (8). In fact, all human glycans consist of nine monosaccharides, including mannose (Man), sialic acid (SA), fucose (Fuc), xylose (Xyl), galactose (Gal), glucose (Glc), galactosamine (GalN), glucosamine (GlcN) and glucuronic acid (GlcA) (9). Glycan synthesis is the most complex post-translational modification of proteins. The various glycan structures significantly influenced biological functions of glycoprotein (10). Morever, glycans located on the surface of cells were actively involved in cellular events and they could impact the properties and behavior of cells (11). In previous study, alterations of glycosylation have been found in various cancers (12). Structural alteration in glycans has been recognized as biomarkers, which could be used in the tumor diagnosis, LNM prediction and prognosis assessment (13, 14). Although the tremendous ability of glycans on modulating glycoprotein function has long been recognized, the complexity of glycan structures and the diversity of glycosylation combinations have prevented the progress of glycan research (15). In response, our research group developed a method to obtain the composition of serum monosaccharides. The method could detect six monosaccharides at once, including Glc, Fuc, GlcN, GalN, Gal, and Man (8). In this study, we analyzed the relationship between serum monosaccharide levels and lymph node status. In addition, we analyzed the predictors of LNM in CRC patients. Further, based on the follow-up data, we assessed the risk factors for poor prognosis.

Materials and methods

Serum sample collection

From January 2019 to June 2020, a total of 252 fasting blood samples were collected. The serum samples were collected from CRC patients by laboratory physician in our hospital according to standardized procedure and doctor's prescriptions. There were 122 LNM-positive patients and 130 LNM-negative patients. The diagnosis of CRC and LNM were confirmed by endoscopy and postoperative pathology, as shown in Figure 1. Patients with history of prior tumor, radiotherapy, chemotherapy and type 2 diabetes mellitus (T2DM) were excluded. This study was designed on the basis of the Declaration of Helsinki of the World Medical Association. The research protocol was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL27534). And all the patients had signed informed consents.

Serum monosaccharides detection

The serum monosaccharide composition was analyzed as described in the previous report (8). In short, 2uL serum, 8uL deionized water and 10uL (6mol/L) HCl solution were added into the microwave degradation tube successively. Then the mixtures were hydrolysed in a microwave reactor (CEM, Germany) for 10min. The HCl was then removed by centrifugal drying (LABCONCO, Germany). Each pellet was dissolved in 150μL deionized water and then collected supernatant after centrifuging at 13,000 r/min for 10 min. Finally, the serum monosaccharides including Man, Fuc, Gal, GalN, Glc and GlcN were detected by high performance anion exchange chromatography coupled with pulsed amperometric detector (HPAEC-PAD) (Thermo, USA).

Data collection

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) treatment guidelines, the included patients later underwent colon/rectal resection with lymph node dissection, and the retrieved histologic slides were examined by two experienced pathologists individually.

Based on the most predominant histologic feature, tumors were classified as well, moderately, and poorly differentiated adenocarcinomas or signet ring cell type or mucinous carcinoma (6). According to American Joint Committee on Cancer (AJCC) TNM staging classification and Union for International Cancer Control (UICC), tumor invasion depth was divided into the following four grades: T1(tumor invasion did not exceed the submucosa), T2 (tumor invasion into muscularis propria), T3 (invasion depth reached subserosa), and T4(tumor invasion into the viscera peritoneum or adjacent structures or organs). D2-40 antibody was used to identified LVI (Dako, Denmark). Perineural invasion was diagnosed by detecting S100 protein.

Clinical and histopathological data of all patients were collected, including sex, age, body mass index (BMI), carcinoembryonic antigen (CEA) level, major tumor size, tumor location, histologic grade, depth of invasion, perineural invasion, LVI, and lymph node status.

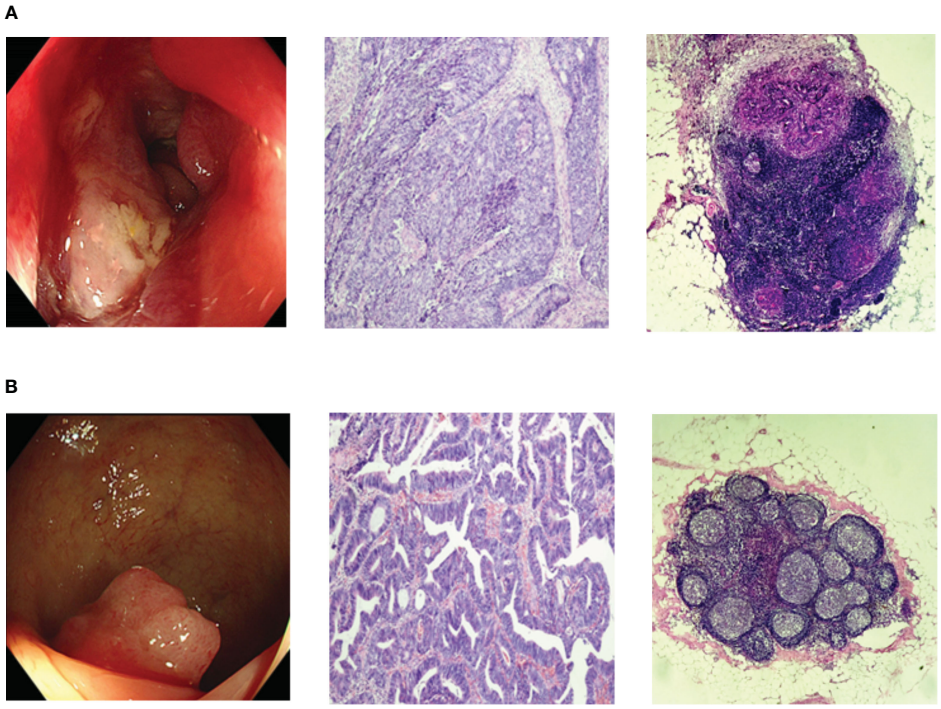

FIGURE 1
Representative endoscopic and histopathologic images. **(A)** Endoscopic and histopathologic images of LNM-positive CRC patients; **(B)** Endoscopic and histopathologic images of LNM-negative CRC patients;. CRC, colorectal cancer; LNM, lymph node metastasis.

Statistical analysis

All data were analyzed with SPSS statistical software (version 22.0) and GraphPad Prism 8.3. 0. T test was used to analyze quantitative data with normal distribution, while Mann-Whitney U test analyzed those without normal distribution. One-way ANOVA or Kruskal-Wallis test was used to analyze quantitative variables with three or more groups. Chi-square test or fisher exact test was used for univariate analysis. The significant variables in the univariate analysis were subsequently entered into a multivariate logistic regression analysis to acquire the independent risk factors for LNM. Log-rank test was performed for survival analysis. Prognostic factors were drawn from univariate and multivariate Cox proportional hazards models. Spearman correlation analysis assessed the relationship between the CEA and differentially expressed monosaccharides. Receiver operating characteristic (ROC) curves were used to evaluate the predictive performance of makers. All reported *p*-values were double-tailed, and *p*-value <0.05 was considered statistically significant.

Results

The expression of serum monosaccharides according to LNM status

A total of 252 serum samples were collected, including 122 LNM-positive patients and 130 LNM-negative patients. The optimized MAAH plus HPAEC-PAD method (8) was used to detect the levels of six hydrolyzed monosaccharides in the sera of CRC patients. The chromatogram of monosaccharides was shown in Figure 2A. Levels of Gal and Man increased significantly in CRC patients with LNM (p =0.0017, p <0.0001, respectively). However, there was no significant difference in levels of Fuc, GalN, GlcN and Glc between patients with LNM and those without LNM (Figures 2B–G).

ROC curve was used to evaluate the ability of factors to predict LNM. The area under the curve (AUC) of Gal was 0.5998 with a cut-off value of 2346 μmol/mL (Figure 3A). And the AUC of Man was 0.8140 with a cut-off value of 2663 μmol/ml (Figure 3B), whereas the AUC of CEA was 0.6523 (Figure 3C).

Clinicopathologic features of enrolled CRC patients

The prevalence of LNM in patients with tumor size≥2cm was 55.56% (52/90), which was higher than in patients with tumor size<2cm (43.21%, 70/162) (p =0.027). Regarding histologic grade, LNM occurred more frequently in patients with G3 (p =0.002) and mucin-producing subtype (p <0.001) than in those with G1 and G2. Regarding depth of invasion, 33.33% (16/48) of the T1/T2 patients were LNM-positive, while 51.96% (106/204) of the T3/T4 patients were LNM-positive (p =0.02). Patients with LVI are more prone to LNM than those without (p <0.001). No significant difference was observed in incidence of LNM due to perineural invasion. The incidence of LNM was significantly higher in patients with CEA >5ng/ml (p <0.001). According to the results in Figure 2, we

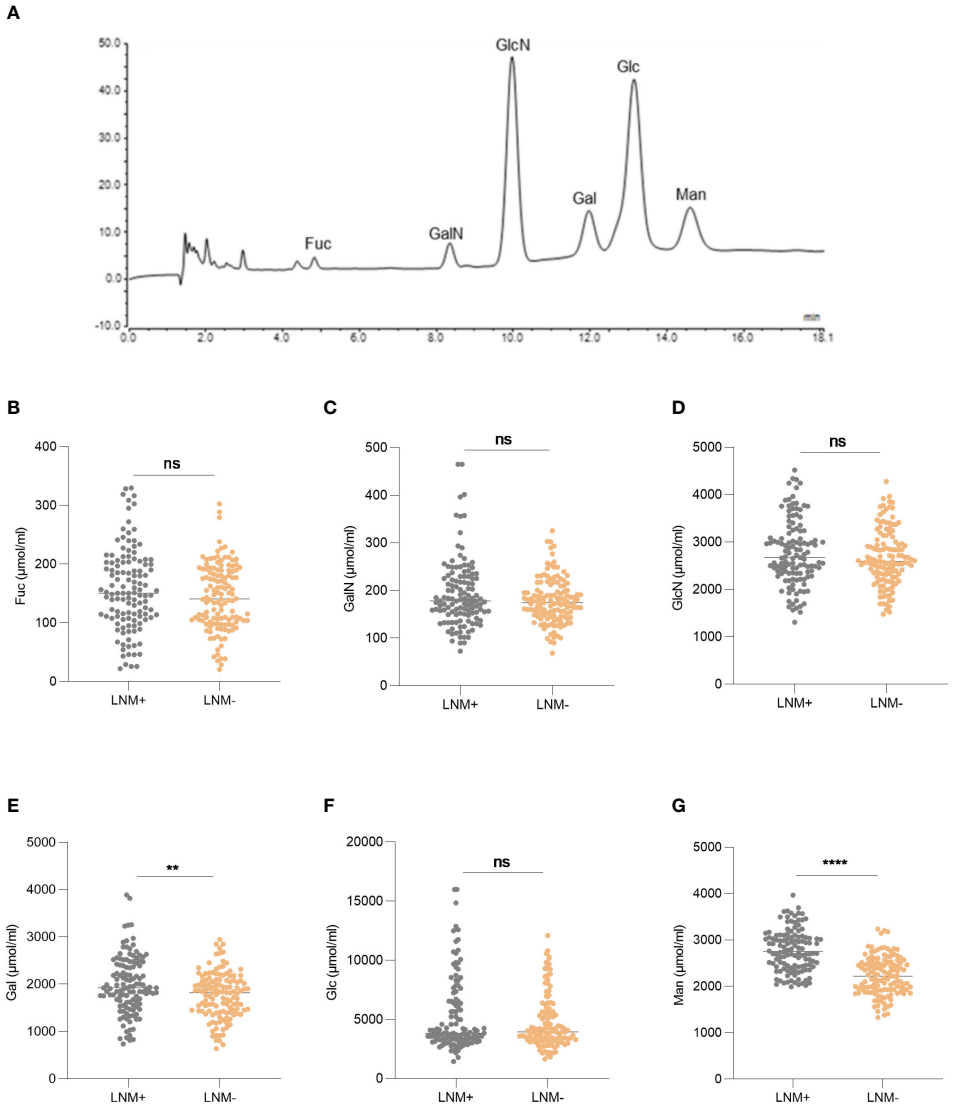

FIGURE 2
The expression of serum monosaccharides according to LNM status. **(A)** HPAEC-PAD chromatogram of monosaccharides. The expression of Fuc **(B)**, GalN **(C)**, GlcN **(D)**, Gal **(E)**, Glc **(F)**, Man **(G)** according to LNM status. LNM+: patients with lymph node metastasis; LNM-: patients without lymph node metastasis. LNM, lymph node metastasis; Fuc, fucose; GalN, galactosamine; GlcN, glucosamine; Gal, galactose; Glc, glucose; Man, mannose. ns, not significant, $^{**}p \leq 0.01$, $^{****}p \leq 0.0001$.

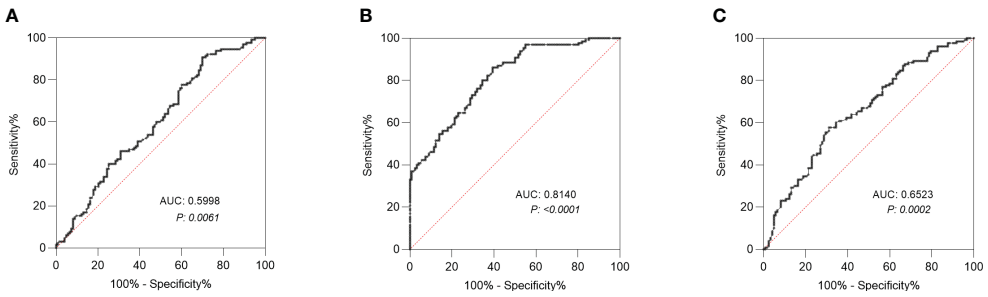

FIGURE 3
Receiver operating characteristic (ROC) curve analysis. **(A)** ROC curve analysis of Gal was conducted to differentiate CRC patients with LNM from those without LNM. **(B)** ROC curve analysis of Man was conducted to differentiate CRC patients with LNM from those without LNM. **(C)** ROC curve analysis of CEA was conducted to differentiate CRC patients with LNM from those without LNM. LNM, lymph node metastasis; Gal, galactose; Man, mannose. AUC, area under the curve; CEA, carcinoembryonic antigen.

screened two monosaccharides: Gal and Man. And the high expressions of Gal and Man were associated with the incidence of LNM (p <0.001, p <0.001, respectively). There was no significant difference with respect to gender, age, BMI, and tumor location between patients with LNM and those without LNM. The results were shown in detailed in Table 1.

Risk factors for LNM in CRC by univariate and multivariate analyses

The univariate analysis demonstrated that tumor size (≥ 2cm), histologic grade (G3), histologic grade (mucin-producing subtype), depth of invasion (T3-T4), LVI, high CEA, high Gal and high Man were associated with LNM. Subsequently, the stepwise logistic analysis showed that the independent risk factors for LNM in CRC were histologic grade (G3) (OR =2.60, p =0.043), histologic grade (mucin-producing subtype) (OR =3.38, p =0.032), LVI (2.42, p <0.01), CEA level(>0.5ng/ml) (OR =1.85, p =0.042) and Man (high) (OR =2.65, p =0.006). The results of multivariate analysis were listed in Table 2.

The performance of Man and Gal in predicting the progonosis of CRC patients

we obtained the survival status of CRC patients included in this study through hospitalization records inquiries and telephone follow-up. Survival analysis revealed that serum Gal and Man were markedly related to poor prognosis of CRC patients (p =0.016, p =0.0001, respectively) (Figures 4A, B). In addition, we evaluated the performance of clinical pathological factors and serum monosaccharides in predicting the progonosis of CRC patients. After the univariate and multivariate Cox regression analysis, we demonstrated that histologic grade (G3) (HR 1.61; p =0.035), histologic grade (mucin-producing subtype) (HR 1.77; p =0.024), depth of invasion (T3-T4) (HR 1.86; p =0.01), LVI (HR 2.22; p <0.001), and high serum Man (HR 1.75; p =0.004) were

TABLE 1 Univariate analysis of risk factors for lymph node metastasis in colorectal cancer.

	n	Node negative (–)	Node positive (+)	p value
Total	252	130	122	
Gender				0.363
female	94	45	49	
male	158	85	73	
Age				0.307
<60	81	38	43	
≥60	171	92	79	
BMI				0.681
≤28	201	105	96	
>28	51	25	26	
Location				0.421
colon	103	50	53	
rectum	149	80	69	
Tumor size				0.027
<2cm	162	92	70	
≥2cm	90	38	52	
Histologic grade				<0.001
G1, G2	198	116	81	reference
G3	30	9	22	0.002
mucin-producing subtype	24	5	19	<0.001
Depth of invasion				0.02
T1-T2	48	32	16	

(Continued)

TABLE 1 Continued

	n	Node negative (–)	Node positive (+)	*p* value
T3-T4	204	98	106	
LVI				<0.001
yes	102	30	72	
no	150	100	50	
Perineural invasion				0.112
yes	142	67	75	
no	110	63	47	
CEA (ng/ml)				<0.001
≥ 5	97	36	61	
< 5	155	94	61	
Gal				<0.001
low (<cutoff)	204	118	86	
high (≥cutoff)	48	12	36	
Man				<0.001
low (<cutoff)	167	101	59	
high (≥cutoff)	85	29	63	

The p value was calculated by Chi-square Test or Fisher exact test. Histologic grade: G1, well differentiated adenocarcinomas; G2, moderately differentiated adenocarcinomas; G3, poorly differentiated adenocarcinomas; mucin-producing subtype: signet ring cell type or mucinous carcinomas; LVI, lymphovascular invasion.

independent risk factors for poor prognosis. The detailed information was shown in Table 3.

Serum Man was elevated in early-stage CRC patients with LNM

To investigate the predictive ability of serum monosaccharides for LNM in early-stage CRC patients, we compared the levels of Gal and Man in T1/T2-stage CRC patients with and without LNM. The results showed that Gal level was not significantly different between the two groups. However, serum Man level was higher in LNM-positive patients (p <0.0001) (Figure 5).

In addition, we compared the levels of CEA and Man between T1N0 and T1N1 patients. The result showed there was no significant difference in CEA levels between the two groups (p =0.410); However, compared with T1N0 patients, serum Man levels were elevated in T1N1 patients (p =0.026) (Figure S1).

Association between serum monosaccharides and clinicopathologic parameters

The levels of Man and Gal were found to have no relationship with tumor location, size, and depth of invasion. Regarding

TABLE 2 Multivariate logistic regression analysis of lymph node metastasis in colorectal cancer.

	Odds ratio	95% CI	*p* value
Tumor size (≥2cm)	0.63	0.34-1.14	0.126
Histologic grade			0.020
G3	2.60	1.03-6.58	0.043
mucin-producing subtype	3.38	1.11-10.31	0.032
Depth of invasion (T3-T4)	1.25	0.59-2.68	0.56
LVI	2.42	1.28-4.57	<0.01
CEA (≥ 5 ng/ml)	1.85	1.02-3.34	0.042
Gal (high)	1.89	0.80-4.51	0.149
Man (high)	2.65	1.32-5.31	0.006

Histologic grade: G3, poorly differentiated adenocarcinomas; mucin-producing subtype, mucinous or signet ring cell type; LVI, lymphovascular invasion.

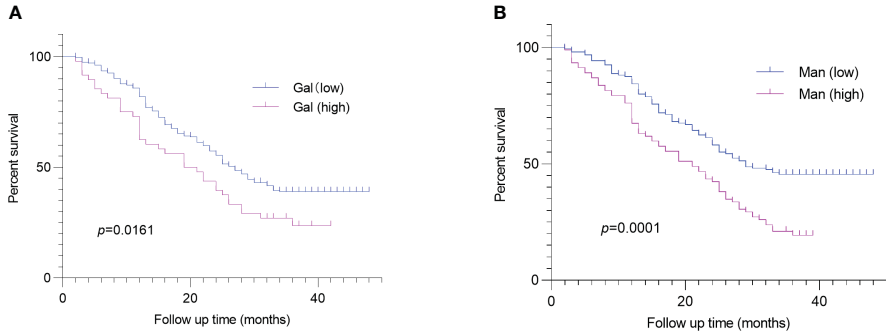

FIGURE 4
Log-rank analysis revealed that serum Gal **(A)** and Man **(B)** were associated with poor prognosis of CRC patients. CRC, colorectal cancer; Gal, galactose; Man, mannose.

histologic grade, the levels of Man were elevated in mucin-producting subtype (p =0.013). In addition, the levels of Man and Gal were not associated with parameters such as gender, age and BMI. However, in patients with high expression of CEA, the levels of Man (p =0.002) and Gal (p =0.018) were elevated. The detailed information was shown in Table S1.

The relationship was observed between serum Gal and CEA levels (p <0.0001; r =0.2626) (Figure 6A). And the serum Man level was positively correlated with the CEA level in CRC patients (p <0.0001; r =0.4208) (Figure 6B).

Discussion

Glycosylation, in simple terms, is the enzymatic process that glycans attach to lipids or proteins (16). The variability of glycan structures gives them great ability to modulate the biological functions of glycoproteins (10). Glycans are known to act in cell adhesion, migration and intracellular signal transduction (17), and they are correlated with tumor invasion and metastasis (18). Alterations in protein glycosylation have been identified as hallmarks in tumorigenesis and progression (16). The glycan structure also altered during disease progression (19, 20), and some previous reports have demonstrated that glycans could be used as biomarkers in cancer diagnosis and metastasis (14, 21). However, it is difficult to detect glycans due to their abundant varieties and complex structures. It is well known that there are nine donors in mammals supplying polysaccharides for glycosylation, including Fuc, GalN, GlcN, Gal, Glc, Man, GlcA, Xyl and SA (9). Our research group has developed a high-throughput and easily generalized method to obtain circulating monosaccharides based on chromatography (8). To the best of our knowledge, this is the first study to demonstrate that the

TABLE 3 Univariate and multivariate Cox-regression analysis of the factors affecting prognosis in colorectal cancer.

	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
Gender (female)	1.22	0.88-1.69	0.214			
Age (≥60)	1.03	0.75-1.40	0.868			
BMI (>28)	0.76	0.52-1.10	0.172			
Location (rectum)	1.22	0.89-1.68	0.208			
Tumor size (≥2cm)	1.11	0.81-1.52	0.524			
Histologic grade			<0.001			0.017
Histologic grade (G3)	1.91	1.23-2.97	0.004	1.61	1.03-2.51	0.035
Histologic grade (mucin-producing subtype)	2.53	1.58-4.05	<0.001	1.77	1.08-2.89	0.024
Depth of invasion (T3-T4)	2.22	1.55-3.19	0.0005	1.86	1.16-3.00	0.01
LVI	2.21	1.54-3.20	<0.001	2.22	1.60-3.07	<0.001
Perineural	1.34	0.97-1.86	0.090			
CEA (>5ng/ml)	1.362	1.00-1.857	0.048	1.02	0.73-1.43	0.912
Gal (high)	1.56	1.02-2.39	0.016	0.89	0.57-1.38	0.603
Man (high)	1.89	1.35-2.64	<0.001	1.75	1.20-2.56	0.004

Histologic grade: G3, poorly differentiated adenocarcinomas; mucin-producing subtype, mucinous or signet ring cell type; LVI, lymphovascular invasion.

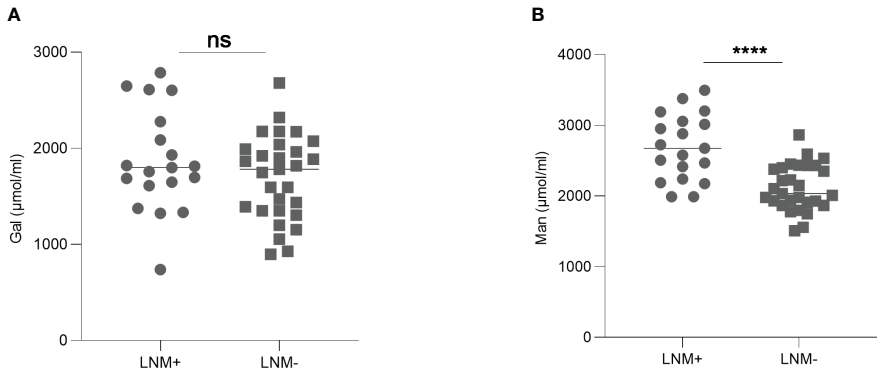

FIGURE 5
The levels of Gal **(A)** and Man **(B)** in early-stage CRC patients with or without LNM. Gal, galactose; Man, mannose; CRC, colorectal cancer; LNM, lymph node metastasis; ns, not significant; ****$p \leq 0.0001$.

level of serum Man can be used as predictor of LNM and poor prognosis in CRC.

Our results showed that, among six serum monosaccharides, the Man level was elevated in LNM-positive CRC patients. Further, this study revealed that high serum Man was associated with adverse outcomes of CRC, and it was the independent risk factors for poor prognosis. The previous study found that abnormal high-mannose on tumor cell surface could enhance the capability of cell adhesion, further promoting tumor invasion and metastasis (13). Lyndsey et al. (22). found that the serum Man level in esophageal cancer patients was higher than that in the healthy, and it was higher in advanced patients than in early patients, which was consistent with our results. In previous studies, increased high-mannose glycans have been found in tumor tissues (21, 23), cell lines (24), and serum (14) of CRC patients. However, why high-mannose N-glycans elevated in cancer remains uncertain. This may be due to the accumulation of precursors caused by incomplete synthesis of N-glycans (25). Ganapati et al. found that aberrant α-mannosidase IA and glycosyltransferases lead to the formation of high-mannose glycans in prostate cancer cells (26). In addition, Fanny et al. indicated that in early-stage CRC patients, high-mannose N-glycans were correlated with malignant progression of disease, as it could promote cell proliferation (21). Mariana et al. (16). demonstrated that CRC cells could use the increased aberrant N-glycans to escape immune surveillance. Besides CRC, high-mannose N-glycan levels also elevated in papillary thyroid microcarcinoma (27), prostate cancer (28) and breast cancer (13, 25), and they were frequently increased in cancer metastasis.

Moreover, our results showed that serum Gal level was higher in CRC patients with LNM than in those without LNM. Xu et al. (29). found that Gal level was higher in CRC carcinomas than in normal control mucosa and precancerous lesions. However, Marcelo et al. (14). showed decreased galactosylation in serum of CRC patients. In addition, fucosylation level was altered in CRC (14, 24), but there was no difference in Fuc level between patients with LNM and those without LNM in our study. One possible explanation was that the serum degraded monosaccharides were affected by various glycans from tissues, cells, glycoproteins, etc. Therefore, the variations of partial glycosylation may not be consistent with changes in total monosaccharide levels. This still needs further exploration.

CEA is the most frequently used marker for CRC screening, diagnosis and monitoring. We compared the performance of CEA and serum monosaccharides in prediction of LNM. The ROC curve analysis showed that the predictive performance of Man for LNM was better than CEA. In our study, we also found that the serum Man level in CRC patients was positively correlated with CEA. As a glycoprotein, the glycan chains of CEA were variable, which were mainly composed of Man, Fuc, SA, Gal and N-acetylglucosamine (30). Zhao et al. (31).

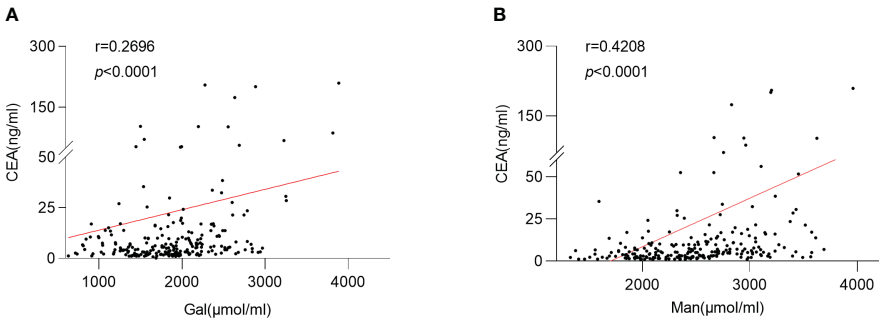

FIGURE 6
Relationship between serum monosaccharides and CEA. **(A)** Correlation between the serum Gal and CEA; **(B)** Correlation between the serum Man and CEA; Gal, galactose; Man, mannose; CEA, carcinoembryonic antigen.

demonstrated stage-dependent alterations of CEA glycosylation patterns in CRC. In specifically, mannose level increased in tumor-associated CEA.

With regard to the analysis of clinicopathologic factors, the results of this study suggested that independent risk factors for LNM in CRC included poorer histologic grade, LVI and CEA; in addition, histologic grade (G3), histologic grade (mucin-producing subtype), depth of invasion(T3-T4), and LVI were associated with poor prognosis. The above results were consistent with previous studies (32–35). The consensus molecular subtypes (CMS) of colorectal cancer indicated that the metabolic subtype (CMS3) potentially associated with Man metabolism and mucinous differentiation (36). Therefore, the poorly differentiated tumors were separated into distinct categories: G3 and mucin-producing subtypes. In this study, the levels of serum Man were elevated in CRC patients with mucin-producing subtype, which is consistent with previous research (36).

In the latest CRC treatment guidelines (5), the JSCCR noted that indication for endoscopic resection was intramucosal carcinoma or slight submucosal carcinoma with little possibility of LNM. Therefore, the evaluation of LNM in early CRC is valuable to guide clinical treatment. Our results showed that serum Man level was higher in early CRC patients with LNM. In addition, compared to T1N0 patients, the levels of Man were elevated in T1N1 patients, while no significant difference was observed in CEA levels between the two groups. This suggested that Man would be a promising marker for predicting LNM in early-stage CRC. However, due to the small sample size of early-stage patients, the analysis is not detailed. Subsequent accurate stratified analysis will be necessary in the future. Furthermore, no external validation was conducted in this study. Nevertheless, the samples we collected were screened using rigorous inclusion and exclusion criteria, suggesting that our findings might be reliable and reproducible.

Conclusions

The Man is superior to CEA in LNM prediction for CRC patients, and it is the independent risk factor for LNM. Serum Man level was associated with poor prognosis of patients with CRC. Man is expected to be a marker for LNM and prognosis in CRC 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 authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. 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

XW: participated in the research design, conducted experiments, and drafted the paper. HL: involved in clinical data collection. XC: designed and supervised the study. ZT: designed, supervised thes study, and wrote the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary materials

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1213952/full#supplementary-material

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Integration of single-cell RNA sequencing and bulk RNA transcriptome sequencing reveals a heterogeneous immune landscape and pivotal cell subpopulations associated with colorectal cancer prognosis

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Introduction: Colorectal cancer (CRC) is a highly heterogeneous cancer. The molecular and cellular characteristics differ between the colon and rectal cancer type due to the differences in their anatomical location and pathological properties. With the advent of single-cell sequencing, it has become possible to analyze inter- and intra-tumoral tissue heterogeneities.

Methods: A comprehensive CRC immune atlas, comprising 62,398 immune cells, was re-structured into 33 immune cell clusters at the single-cell level. Further, the immune cell lineage heterogeneity of colon, rectal, and paracancerous tissues was explored. Simultaneously, we characterized the TAM phenotypes and analyzed the transcriptomic factor regulatory network of each macrophage subset using SCENIC. In addition, monocle2 was used to elucidate the B cell developmental trajectory. The crosstalk between immune cells was explored using CellChat and the patterns of incoming and outgoing signals within the overall immune cell population were identified. Afterwards, the bulk RNA-sequencing data from The Cancer Genome Atlas (TCGA) were combined and the relative infiltration abundance of the identified subpopulations was analyzed using CIBERSORT. Moreover, cell composition patterns could be classified into five tumor microenvironment (TME) subtypes by employing a consistent non-negative matrix algorithm. Finally, the co-expression and interaction between SPP1+TAMs and Treg cells in the tumor microenvironment were analyzed by multiplex immunohistochemistry.

Results: In the T cell lineage, we found that CXCL13+T cells were more widely distributed in colorectal cancer tissues, and the proportion of infiltration was increased. In addition, Th17 was found accounted for the highest proportion in CD39+CD101+PD1+T cells. Mover, Ma1-SPP1 showed the characteristics of M2

phenotypes and displayed an increased proportion in tumor tissues, which may promote angiogenesis. Plasma cells (PCs) displayed a significantly heterogeneous distribution in tumor as well as normal tissues. Specifically, the IgA+ PC population could be shown to be decreased in colorectal tumor tissues whereas the IgG+ PC one was enriched. In addition, information flow mediated by SPP1 and CD44, regulate signaling pathways of tumor progression. Among the five TME subtypes, the TME-1 subtype displayed a markedly reduced proportion of T-cell infiltration with the highest proportion of macrophages which was correlated to the worst prognosis. Finally, the co-expression and interaction between SPP1+TAMs and Treg cells were observed in the CD44 enriched region.

Discussion: The heterogeneity distribution and phenotype of immune cells were analyzed in colon cancer and rectal cancer at the single-cell level. Further, the prognostic role of major tumor-infiltrating lymphocytes and TME subtypes in CRC was evaluated by integrating bulk RNA. These findings provide novel insight into the immunotherapy of CRC.

KEYWORDS

single cell, immune landscape, colorectal cancer, tumor-associated macrophages, Treg, plasma B cell

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in the digestive system and the third main cause of mortality related to malignant tumors worldwide (1, 2). CRC often generically refers to colon cancer and rectal cancer, but in fact, it is a tumor with high heterogeneity. Of note, the specificity of the proximal to distal intestinal development creates different microbial communities and gene and protein expression patterns among different regions in the intestine during development, resulting in various physiological functions (3). Consequently, colon and rectal cancers exhibit differences in pathological features, treatment regimens, and prognostic outcomes (4–6). Fortunately, the emergence of single-cell sequencing has enabled the analysis of inter- and intra-tumor heterogeneity (7, 8). Yet, no study has been conducted to elucidate the heterogeneity of immune cell subpopulations in the colon and rectal cancers with single-cell sequencing.

Breakthroughs in immunotherapy have been achieved in cancer treatments (9). Nevertheless, immunotherapy is not beneficial for all tumor patients, as the response to it largely depends on the characteristics of the tumor microenvironment (TME) (10). The efficacy of immunotherapy is remarkably affected by the intricate interaction between cytotoxic T cells and natural killer (NK) cells that play an important role in immune surveillance, as well as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) that dominate the immunosuppressive microenvironment (11, 12). In addition, the TME can be reprogrammed by the interconversion of T cells between the pre-exhausted and exhausted states and macrophages between the M1 and M2 phenotypes (13, 14).

Likewise, the prognosis of tumor patients and their responses to immunotherapy can be directly affected by the infiltration status and phenotypic heterogeneity of tumor-infiltrating immune cells, especially T cells, in solid tumor tissues (15). T cell dysregulation within tumors is progressive and dynamically process from pre-exhausted to terminal exhausted, which is considered an important factor affecting the efficacy of immunotherapy in CRC patients (16). Early dysfunctional T cells could regain effector function and reprogrammed into effector T cells through immunotherapy, which becomes a breakthrough to reverse the exhaustion of T cells, while late dysfunctional T cells cannot be saved due to their resistance to therapeutic reprogramming (17). PD1 expression increases with the progression of T cell exhaustion, in addition to the co-expression of CD38 and cd101 in late dysfunctional T cells may reflect fixed dysregulation of $CD8^{+}$T cells, which indicates an adverse response to anti-PD1 immunotherapy (18). Whereas the co-expression of CD39 and CD103 has been suggested to be a marker of tumor antigen-specific TILs in solid tumors, in some researches including CRC, $CD103^{+}CD39^{+}$T cells have been suggested to be an immune marker to predict patient prognosis as well as response to ICB therapy (19–21). Therefore, identification of T cell heterogeneous phenotype could provide an aid for achieving effective patient stratification in immunotherapy.

Macrophages are highly heterogeneous cells, among which tumor-associated macrophages (TAMs) are important immune cells in TME (22). TAMs can promote tumorigenesis and metastasis and exert immunosuppressive effects through pro-angiogenesis, starvation of cytotoxic CD8+T cells, and recruitment of Tregs (23). Furthermore, TAM targeting has recently emerged as a hot spot in tumor immunotherapy. For

instance, a prior study validated that CSF1R inhibitors could reduce TAMs in the TME and promote macrophage repolarization to M1, thus showing tremendous potential for clinical application (24). However, the specific heterogeneity of TAMs and the ambiguous time course of macrophage recruitment and polarization pose certain obstacles to TAM-targeted therapy (25). As key antigen-presenting cells (APCs), the two conventional subsets, cDC1 and cDC2, are responsible for the presentation of tumor-associated antigens to CD8+ T cells and CD4+ T cells, respectively (26, 27). Additionally, the two immunosuppressive APCs, plasmacytoid dendritic cells (pDCs) and novel mature LAMP3+ DCs, exist in the TME of various solid tumors and have attracted increasing attention (28–30). B cells, a major component of the TME, are also emerging as a key player in the anti-tumor immune response, whose function and distribution are highly dependent on tertiary lymphoid structures (TLSs) (31). Specifically, germinal center B cell clones in mature TLSs differentiate into plasma cells (PCs) that can produce IgG or IgA antibodies against tumor-related antigens (32). Importantly, B cells and TLSs have recently been demonstrated as the key to the clinical outcome of immunotherapy in tumor patients (33–36). Therefore, a deeper understanding of the immune cell landscape in the colon and rectal cancers and non-cancerous tissues can lay an essential theoretical foundation for achieving precision in immunotherapy for these diseases.

The large-scale single-cell CRC transcriptome database, created by integrating two published single-cell databases (GSE132465 and GSE146771) and describing an elaborate molecular signature of immune cells and the heterogeneity of TME in the colon and rectal cancers, was thoroughly investigated (37, 38). Importantly, our study also analyzed the crosstalk between immune cells with CellChat and identified patterns of incoming and outgoing signals of the overall immune cell population. Finally, we determined five TME immune cell infiltration patterns in CRC patients, and their relationships with CRC progression were investigated. Our research provides new insights into the immune microenvironment of CRC and provides new potential targets for CRC immunotherapy.

Materials and methods

Single-cell data processing and quality control

Firstly, 10x Genomics single-cell data were obtained from the SMC dataset of GSE132465 and the 10x Genomics dataset of GSE146771. Because CD45+ cells were isolated by fluorescence-activated cell sorting in advance, the 10x Genomics data of GSE146771 contained only the data of immune cells. Since only immune cells in tissues were analyzed in our study, blood cells in the GSE146771 dataset were removed and immune cells were extracted from the SMC dataset, followed by the merging of data from these two datasets using merge function. Then, 27 colon cancer tissues, 6 rectal cancer tissues, and 18 adjacent tissues were grouped according to the anatomical location provided in the clinical information table of the datasets for subsequent analyses. The single-cell RNA-sequencing data were created for Seurat objects with the Seurat package (4.1.0). Low-quality cells with unique feature counts > 6000 or < 300 or mitochondrial counts > 15%, as well as ribosomes < 3% and erythrocytes < 0.1%, were filtered, with 62,398cells remained after quality control.

Unsupervised dimensionality reduction

A total of 62,398 immune cells were identified and classified into four major immune cell clusters (T cells, NK cells, B cells, and myeloid cells). These subpopulations were re-clustered into immune cell lineages. Specifically, the original metadata were normalized using the NormalizeData function, and the FindVariableFeatures function was used to select 2,000 hypervariable genes. Next, the data were scaled using the ScaleData function before the PCA dimension reduction. Next, the harmony function was used to remove the batch effect from the data. The FindClusters and cluster functions were used for cell reclustering. The resolution from 0.1 to 1 was used to obtain better sub-clusters. Potential marker genes were determined using the FindAllMarkers function and subjected to t-distributed Stochastic Neighbor Embedding (t-SNE) analyses. Typical marker genes were used to annotate cell clusters into known cell lineages.

Pseudotime trajectory analysis

Monocle2 (version 2.20.0) was used for pseudotime analyses to determine the differentiation trajectory of cell development. After the UMI matrix was read from the Seurat object, the newCellDataSet function was utilized to create the object. Genes with mean expression > 0.1 were selected in the trajectory analysis, followed by dimension reduction with the DDRTree method and cell sorting with the orderCells function.

SCENIC analysis

SCENIC (1.2.4) was used to analyze the enrichment of key transcriptomic factors in macrophage clusters. The motif Hg38 was selected as the SCENIC dataset, and 1500 cells were randomly selected to construct a co-expressed gene model. Next, the potential target genes of transcription factors were identified with GENIE3. DNA-motif enrichment analyses were performed with RcisTarget (1.14.0) to identify direct binding sites (regulons). The activity of each regulon in each cell was assessed with AUCell (1.16.0), followed by the calculation of the area under the receiver operating characteristic curve (AUC) and the integration of the expression rank of all genes in the regulon. The RegulonAUC matrix was imported into Seurat for the cluster analysis and visualization of single-cell data.

Cell–cell communication analysis using CellChat

The intercellular communication between immune cell subsets in colon and rectal cancers was predicted with the Cellchat package (1.1.3) based on the analysis of ligand-receptor interactions. With the normalized Seurat data as the Cellchat object, CellChatDB.human was selected as the receptor-ligand interaction database. The communication probabilities were calculated with the computeCommunProb function to demonstrate cell interactions in terms of both the number and weight of interactions. The extractEnrichedLR function was utilized to extract all of the important interacting L-R pairs and related signaling genes of a given signaling pathway to present cell-cell communication mediated by a single L-R pair. In addition, global communication patterns and signal networks were analyzed with the CellChat adopted pattern recognition method based on non-negative matrix factorization (NMF).

Gene set variation analysis pathway enrichment analysis

Hallmarks gene sets were downloaded from the Molecular Signatures Database (MSigdb). Afterwards, GSVA enrichment analyses were performed for cell subsets with the GSVA package (version 1.40.1). Additionally, the AverageExpression function was used to calculate the average gene expression in all cells of each subpopulation. The R package CluserProfiler (V4.0.5) was used for the pathway enrichment analysis of specific gene sets, with Adj.p.val < 0.05 considered significantly enriched pathways. Then, the key pathways were selected for visualization.

Scoring of macrophage M1 and M2

The score of the macrophage subgroups M1 and M2 phenotypes referred to the average normalized expression of the characteristic genes related to classically activated M1 macrophages (SOCS1, NOS2, TNF, CXCL9, CXCL10, CXCL11, CD86, IL1A, IL1B, IL6, CCL5, IRF5, IRF1, and CCR7) and alternatively activated M2 macrophages (IL4R, CCL4, CCL18, CCL22, MARCO, VEGFA, CTSA, CTSB, TGFB1, MMP9, CLEC7A, MSR1, IRF4, CD163, TGM2, and MRC1).

Distribution and proportion of CD39 +CD101+PD1+T cells in CRC

If the cells conformed to the condition that the gene expression of CD39, CD101, or PD1 was > 0, they were defined as positive for the target gene. If the simultaneous expression of two or three target genes was > 0 at the same time, the cells were defined as double- or triple-positive. Only cells that simultaneously met the requirement of the expression of CD39, CD101 or PD1 being 0 were counted as triple-negative cells. The proportion of cells meeting these conditions was counted, and t-SNE was used to visualize the distribution of cells with different phenotypes.

Cell subtype deconvolution based on bulk RNA-sequencing data and tumor microenvironment classification

The gene expression matrix was generated based on single-cell RNA (scRNA) sequencing (seq) data to characterize cell clusters. The CIBERSORT deconvolution algorithm was used to assess the relative infiltration abundance of each cell cluster in the colon adenocarcinoma (COAD; 480 tumor samples and 41 normal samples) and rectum adenocarcinoma (READ; 167 tumor samples and 10 normal samples) cohort from The Cancer Genome Atlas (TCGA). Then, the difference in the obtained relative infiltration abundance between tumor and normal tissues was calculated with the Wilcoxon test. The ConsensusClusterPlus package (1.58.0) (39) was utilized to determine the optimal K value and identify the cellular subtypes.

Clinical sample collection

Approved by the Ethics Committee of the General Hospital of the Northern Theatre Command, PLA, China, we collected 9 tumor cases and adjacent normal tissues from 9 patients with the pathological diagnosis of CRC during surgical resection. All patients were diagnosed with primary colorectal tumors and were treatment Naïve. They ranged in age from 31 to 67, with a median age of 58. The clinical characteristics of these patients, including age, gender, pathological classification and stage, are shown in Table S1. The tissues were embedded in paraffin and sectioned at 4 μ M for subsequent immunofluorescence assay.

The multiplex immunohistochemistry

We performed multiple immunohistochemical staining according to the kit manufacturer' s instruction (Wuhan Powerful Biotechnology Co., LTD). In brief, after multiple rounds of repeated antigen repair, incubation of primary antibody, HRP labeling of secondary antibody and amplification of TSA fluorescence signal, a paraffin section was marked with multiple target fluorescence labeling, and finally DAPI was used to re-stain the nucleus. Spectral imaging was performed with a multi-spectral tissue imaging system (FI3, Nikon, Japan), followed by Image scanning and analysis using caseviewer and Image J. The antibodies used in the experiment were as follows IgA (Abcam, ab124716), IgG (Abcam, ab109489), CD163 (Abcam, ab182422), CD44 (Abcam, ab6124), SPP1 (Osteopontin) (Abcam, ab214050), pan Cytokeratin (Abcam, ab7753), Foxp3 (Abcam, ab215206).

Statistical analysis

Statistical analysis was performed with R 4.2.3, SPSS v26, and Prism 8.0. Data with normal distribution were compared by the 2-tailed Student's t-test, and data with abnormal distribution were compared by Wilcoxon's rank-sum test. The Kruskal-Wallis test, a nonparametric test, was utilized for comparisons among three or more independent groups. Survival was analyzed with the Kaplan-Meier method and log-rank test.

Results

Single-cell profiling of immunogenomic landscape in the microenvironment of CRC

10x scRNA-seq data were obtained from GSE132465 and GSE146771 datasets, including 18 adjacent normal samples (10 from GSE132465 and 8 from GSE146771), 27 colon tumor samples (20 from GSE132465 and 7 from GSE146771), and 6 rectal tumor samples (3 from GSE132465 and 3 from GSE146771). The clinical information of all patients is detailed in Table S2. A schematic chat of the experimental design was showed in Figure 1A. These two datasets were integrated by removing the batch effect of samples, and the obtained major cell types were derived from different patients with low patient specificity. After quality control and filtration, 62,398 immune cells were retained for unsupervised clustering, including 24,698 cells from adjacent normal tissues, 30,579 cells from colon cancer tissues, and 7,121 cells from rectal cancer tissues. 10 major immune cell subpopulations, including $CD8^+$ T cells, $CD4^+$ T cells, NK cells, B cells, plasma cells, cycling cells, macrophages, monocytes, dendritic cells (DCs), and mast cells, were successfully identified according to their typical marker genes using the T-distributed randomly adjacent embedding (t-SNE) dimension reduction method. Cells stemming from different datasets and tissues were classified and color-coded. All cellular subgroups were evenly distributed resulting in no obvious patient- or disease-specific pattern (Figure 1B). The typical marker genes for each cluster were visualized using t-SNE plots and the top5 genes were displayed using the bubble plot (Figures 1C, E). T lymphocytes are the main tumor-infiltrating immune cells in the TME of CRC however, the proportion of total T lymphoid lineage cells did not display differences between tissues. We found that the B lineage had a decreased proportion in CRC samples compared to normal tissues, conversely, myeloid cells had a higher proportion in tumor tissues (Figure 1D). Taken together, we performed an unsupervised re-clustering of major immune cell subpopulations to comprehensively explore the heterogeneity of the colorectal cancer microenvironment.

Characterization of the heterogeneity of T and NK cell subtypes in CRC

After the unsupervised clustering, the obtained 32,879 T cells were classified into five $CD4^+$ clusters ($CD4^+$ Naïve, $CD4^+$ Tem, Tfh, Th17, and Treg) and five $CD8^+$ clusters ($CD8^+$ Tem-KLRD1, $CD8^+$ Tem-GZMK, Trm, MAIT and $CD8^+$ Tex) (Figure 2A). Naïve $CD4^+$ T cell cluster exhibited the high expression of Naïve T cell marker genes CCR7, TCF7, and SELL. However, no Naïve $CD8^+$ T cells were identified. Additionally, a subpopulation of Memory $CD4^+$ T cells was identified, which was characterized by the expression of ANXA1, GPR183, and IL7R (Supplementary Figure 1A). No cytotoxic genes and exhaustion marker genes were found to be highly expressed in the $CD4^+$ Tem cluster (Figure 2I). According to the phenotypes of effector molecules, two effector memory $CD8^+$T cells were identified: $CD8^+$Tem-GZMK with high expression effector molecule GZMK, and the $CD8^+$ Tem-KLRD1 cluster was characterized by the high expression of the NK cell inhibitory receptor KLRD1 Meanwhile, GZMK was almost not expressed in the $CD8^+$ Tem-KLRD1 cluster, and the effector molecules NKG7, GZMA and IFNG were highly expressed in both subclusters with higher expression in the $CD8^+$Tem-GZMK cluster, suggesting a predominance of cytotoxicity (Supplementary Figure 1C, Figure 2I).

The $CD8^+$ Tex cluster exhibited the high expression of exhaustion markers including HAVCR2, PDCD1, CTLA4, and LAG3. The majority of effector molecules such as GNLY, GZMK, GZMA and NKG7 were also expressed in the $CD8^+$ Tex cluster. Furthermore, co-expression of CD38/CD101 is a marker of terminal exhaustion T cells. In this study, CD38 and CD101 were expressed at higher levels in the $CD8^+$ Tex cluster, suggesting that the $CD8^+$ Tex cluster was in a state of terminal exhaustion (Figure 2I). Likewise, the proliferation- and cell cycle-related genes MKI67, STMN1, and TOP2A were also upregulated in the $CD8^+$ Tex cluster, indicating that certain $CD8^+$ Tex cells were in a proliferative state (Figure 2B). In fact, prior studies have confirmed exhausted $CD8^+$ T cells as the highly proliferating cell population in the TME at a specific stage (40, 41). In addition, the Treg cluster characteristically expressed the marker genes FOXP3 and IL2RA while highly expressed the T cell co-stimulatory factors TNFRSF4, TNFRSF18, TNFRSF9, CD27, and ICOS, especially TNFRSF9, which is a known activation marker for antigen-specific Tregs. Of note, the Treg cluster had higher expression of CTLA4 and TIGIT than any other exhausted T cell clusters (Figure 2I). Therefore, it could be concluded that the Treg cluster might play a pivotal role in the immunosuppression of CRC due to its higher infiltration level in tumor tissues and lower infiltration level in normal tissues.

A unique class of unconventional mucosal associated invariant (MAIT) cells with a profile of the marker genes KLRB1 (CD161), NCR3, RORA, and SLC4A10 and the inhibitory NK cell receptors KLRG1, KLRB1, and IL4I1 (a tumor-derived tryptophan catabolic enzyme that promotes tumor invasion) exists in the intestinal mucosal tissues. Likewise, the MAIT cluster was also noted to characteristically overexpress CEBPD, a transcription factor associated with a variety of malignancies (Supplementary Figure 2C). Intriguingly, the MAIT cluster maintained the activity of cytotoxic effectors. Meanwhile, PDCD1, CTLA4, HAVCR2, and LAG3 were differentially expressed, among which LAG3 was the most significantly expressed, but CD38 and CD101 were not expressed in this cluster (Figure 2I). Therefore, we speculated that the MAIT cluster might be a kind of T cell in an exhausted state but might be in a pre-exhausted state compared with the $CD8^+$ Tex cluster.

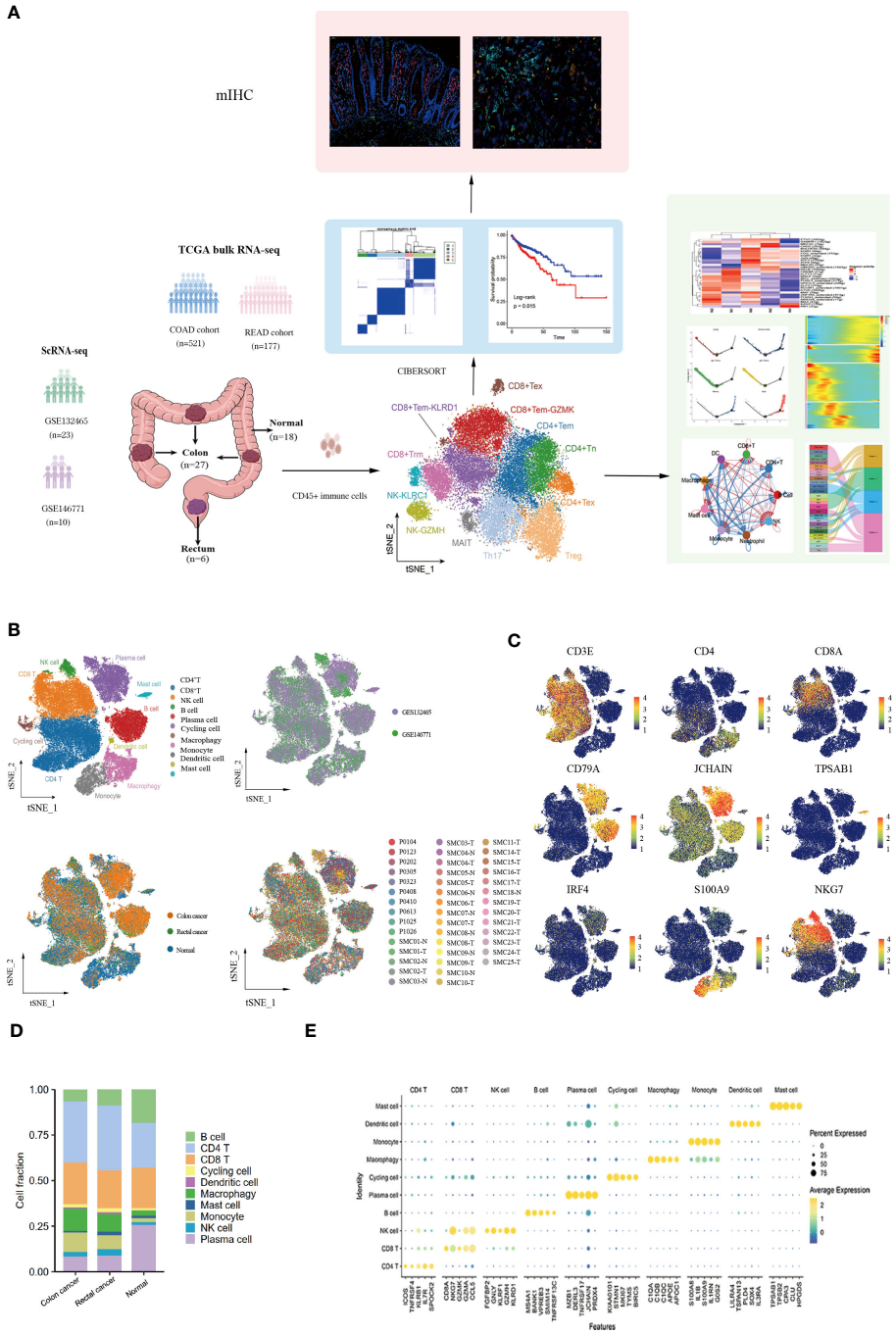

FIGURE 1
Landscape of immune cells in the microenvironment of colon cancer, rectal cancer, and adjacent normal tissues at the single-cell transcription level. **(A)**Schematic diagram explaining the workflow of the experimental design. **(B)** t-SNE (t-distributed Stochastic Neighbor Embedding) plot of 62,398 high-quality immune cells showing the major immune cell type clusters in the tumor microenvironment (TME) of colorectal cancer (CRC) and adjacent normal tissues, color-coded by dataset, tissue types, and patients. **(C)** t-SNE plots showing the expression levels of representative marker genes for major immune cell clusters, color-coded by gene expression levels. **(D)** Stacked bar plots showing the cell fractions of major immune cell types in colon cancer, rectal cancer, and adjacent normal samples. **(E)** Bubble plot showing the average expression level of the top 5 marker genes for the 10 major immune cell clusters.

A $CD8^+$ T cell cluster characterized by high expression of ITGAE (CD103) and CD69 represented tissue-resident memory T (Trm) cells, which permanently reside in tissues instead of returning to the blood circulation and can mediate rapid immune responses. Trm cells exert an immunosurveillance effect, which has been implicated in preventing the development of solid tumors. In the Trm cluster, the cytotoxic factors GZMA, GZMB, NKG7, and GNLY were upregulated. Trm cells have been verified to still maintain the ability to produce cytotoxic molecules and effector cytokines despite the high expression of the immune checkpoints HAVCR2, LAG3, and TIGIT in these cells, suggesting that $CD103^+$ Trm is more resistant to exhaustion than circulating T cells. Unlike

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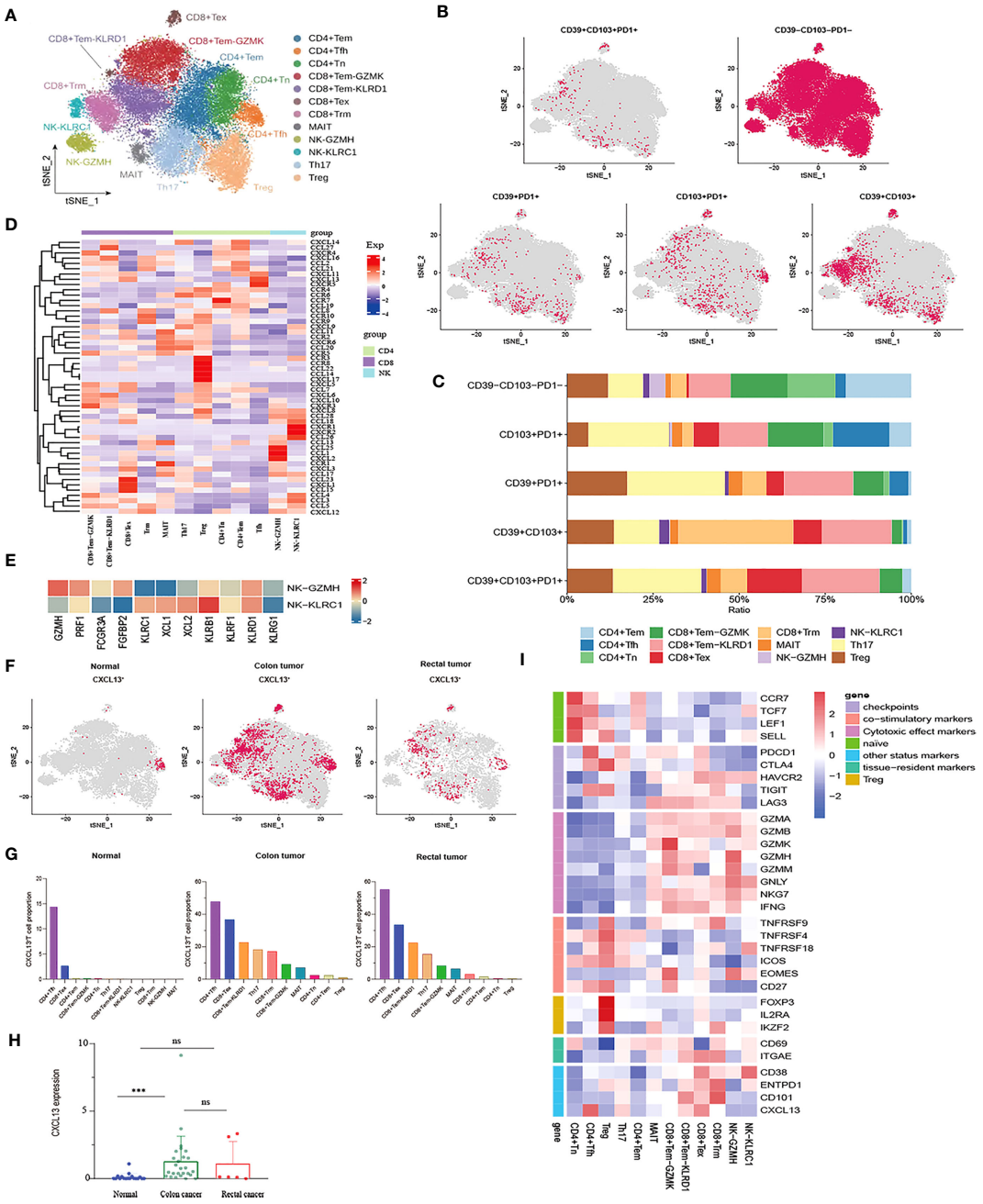

FIGURE 2
Characterization of phenotypes of T cells and NK cells in colon cancer, rectal cancer and adjacent normal tissues. **(A)** t-SNE plot of a total of 32,879 T cells re-clustered into 10 clusters and 1,898 NK cells re-clustered into 2 clusters using color-coded by cell type. **(B)** t-SNE projections showing the expression and distribution of phenotypic marker genres CD39, CD103, and PD1 in T andNK clusters. Each dot represents a cell defined as positive expression of marker genes. **(C)** Stacked bar plots displaying the percentages of each cluster from T and NK subpopulations with different CD39, CD103, and PD1phenotypes. **(D)** Heatmap showing the expression profile of canonical chemokines and chemokine receptors of T and NK clusters. **(E)** Heatmap demonstrating the expression characteristics of special functional genes in two NK subgroups with different phenotypes **(F)** t-SNE projections of CXCL13 expression distribution in normal, colon and rectal tissues. **(G)** Box plot comparing the expression levels of CXCL13 in T andNK lineage among calculated using Kruskal-Wallis test, ***p< 0.001, ns p > 0.05. **(H)** Fractions of CXCL13$^+$ cells among T andNK subpopulations in different tissues from scRNA-seq datasets. **(I)** Heatmap of the relative expression of function related genes, including naïve, cytotoxic, exhaustion, co-stimulatory and resident in T andNK cell subsets.

CD8$^+$ Tex, Trm cells can restore immune function when re-exposed to appropriate antigens. Moreover, ENTPD1 (CD39) was higher expression in the Trm cluster, demonstrating that Trm cells were reactive tumor-infiltrating lymphocytes (TILs) distinct from bystander T cells (Figure 2I).

CD39, CD103, and PD-1 have been independently considered markers of tumor-reactive CD8$^+$ TILs (20). Co-expression of PD-1, CD103, and CD39 is crucial for stratifying patients receiving immunotherapy. It is generally believed that CD39, CD103, and PD-1 are co-expressed, and triple-positive TILs may be related to

improved response rates and prognostic outcomes (42, 43). Nevertheless, our study found that PD1$^+$CD39$^+$CD103$^+$ T cells were rarely observed in CRC and that these small numbers of triple-positive cells were mainly distributed in the Th17 and CD8$^+$Tem-KLRD1 subsets. Similarly, compared with other T cell subpopulations, Th17 and CD8+ Tem-KLRD1 cells accounted for a higher proportion of PD1$^+$CD103$^+$ T and CD39$^+$PD1$^+$ T cells, and CD8$^+$Trm accounted for the highest proportion of CD39$^+$CD103$^+$ T cells (Figures 2B, C). Different phenotypes of Th17 cells, especially CD39$^+$CD101$^+$PD1$^+$ Th17 cells, may be critical for the prediction of tumor-reactive TILs; however, such studies are currently lacking. We also found that PD1 was poorly expressed in tissue-resident T cells, whereas HAVCR2 was highly expressed (Figure 2I). Therefore, we speculate that this type of TRM might respond better to anti-TIM3 treatment.

The 1,898 NK cells were mainly divided into two clusters: the NK-KLRC1 cluster expressing the inhibitory receptors KLRC (NKG2A) and KLBR1; the NK-GZMH cluster expressing the inhibitory receptors KLRD1, as well as cytotoxic molecules GZMH and PRF1. Meanwhile, the NK-GZMH cluster had a high level of the exhaustion markers HAVCR2 and LAG3, while the NK-KLRC1 cluster expressed HAVCR2 and CD38, indicating that both NK cell clusters were representative of a certain degree of exhaustion (Figure 2I). Furthermore, CD16 and FGFBP2 (CD14) were highly expressed in the NK-KLRC1 cluster and, conversely, poorly expressed in the NK-GZMH cluster (Figure 2E). It is widely recognized that most NK cells in the blood have the characteristics of CD16$^+$ FGFBP2$^+$ (CD14$^+$), so it is hypothesized that the NK-KLRC1 cluster infiltrated in tissues is derived from NK cells in the blood. Meanwhile, chemokines were identified to show different expression levels between the two NK clusters, among which XCL1 and XCL2 were the main chemokines expressed in the less cytotoxic NK-KLRC1 cluster (Figure 2E). Importantly, these two chemokines are extensively accepted to recruit XCR1$^+$ cross-presenting DCs into the tumor to cause tumor-driving inflammation, thus changing a “cold tumor” into a “hot tumor”.

Cluster analysis was performed on the expression patterns of major chemokines and receptors of T and natural killer (NK) cell subgroups in the tumor microenvironment of colorectal cancer. The results indicated that the CD8$^+$Tex subgroup highly expressed chemokines that promoted angiogenesis and participated in the migration of inhibitory immune cells, such as CCL15, CXCL1, and CXCL12. In addition to the well-known chemokine receptor CCR4, the Treg cell subset also higher expression CCL22, CCL14, CXCL17, CCR3, and CCR8. Chemokines CCL24, CCL1, and CXC12 were highly expressed in the NK-GZMH subgroup, while chemokine CCL26 and chemokine receptors CXCR1 and CXCR2 were highly expressed in the NK-KLRC1 subgroup. The CD8$^+$Tem GZMK subgroup highly expressed CXCR3, and the chemokines CXCL19, CXCL10, and CXCL11 interacted with the immune cells of CXCR3$^+$ to recruit cells with anti-angiogenesis function. The follicular helper T (Tfh) cell subgroup higher expression chemokines CXCL11, CXCL13, and CXCR5 (Figure 2D). The CXCL13-CXCR5 axis can induce tumorigenicity or anti-tumor immune response in the tumor microenvironment by recruiting multiple lymphocyte populations. On the one hand, the CXCL13 signal plays a leading role in the recruitment of B cells and the formation of tertiary lymphoid structures, activating the immune response of some tumors (44); on the other hand, CXCL13 is critical for driving the occurrence, development, and metastasis of malignant tumor (45). We analyzed the expression and distribution of CXCL13 in the tumor microenvironment of CRC (Figure 2F). Compared with that in normal tissues, the expression of CXCL13 in colon cancer tissues was significantly increased, but there was no significant difference in rectal cancer tissues (Figure 2H). The distribution of CXCL13$^+$ T cells in normal, colon, and rectal cancer tissues had significant heterogeneity. In normal tissues, CXCL13$^+$ T cells were mainly distributed in CD4$^+$ Tfh and CD8$^+$ Tex subgroups. However, CXCL13$^+$ T cells showed a wider distribution in cancer tissues. In addition to CD4$^+$ Tfh and CD8$^+$ Tex subsets, CXCL13$^+$ T cells also had a high proportion in Th17 and CD8$^+$ Tem subsets in cancer tissues (Figure 2G). We speculated that the differential expression of CXCL13 in different cell subsets may play distinct roles in tumor progression and immune promotion.

Landscape of the heterogeneity and diversity of myeloid cell in the TME of CRC

A total of 10,514 macrophages underwent unsupervised re-clustering into five macrophage clusters (3,748), four monocyte clusters (4,925), three DC clusters (1,025), mast cell cluster (1,025) and neutrophils (95) (Figure 3A). The Ma0 subgroup was characterized by SEPP1 expression, in which the complement pathway-related genes such as C1QA, C1QB, and C1QC were prominently expressed and the orphan nuclear receptors (NR4A1, NR4A2, and NR3A3) that mediate macrophage-induced inflammation were up-regulated. Furthermore, the abundant expression of MHC II molecules in this cluster indicated that SEPP1$^+$ TAM possessed a strong ability of antigen presentation (Figure 3E). Among the hallmark gene sets for Gene Set Variation Analysis (GSVA), TGFβ and KRAS signaling pathways were found to be enriched mainly in the Ma0 subgroup (Figure 3F).

The Ma1 cluster characteristically expressed SPP1, as well as high expression of marco which can promote M2 macrophage polarization, meanwhile CXCL5, which promotes tumor metastasis, was also highly expressed in this subpopulation. Likewise, metallothionein including MT2A, MT1E, and MT1F was abundantly expressed in this cluster, therefore assuming a crucial role in the formation, progression, and drug resistance of tumors. In addition, S100A proteins were also upregulated in the Ma1 subgroup (Figure 3E, Supplementary Figure 2A). Ma1 cells were involved in angiogenesis, epithelial mesenchymal transformation and inflammation-related signaling pathways (Figure 3F) Ma2 had higher APOE expression than other macrophage subtypes (Figure 3E, Supplementary Figure 2A), which was mainly related to lipid metabolism and reactive oxygen species (Figure 3F). Ma3 exhibited T cell gene profile with highly expressive of T cell signature genes, which were associated with interferon-α and interferon-γ response pathways (Supplementary Figure 2A, Figure 3F). Ma4 was with the characteristic high expression of the proliferation-related genes KIAA0101, TOP2A and MKI67 and the

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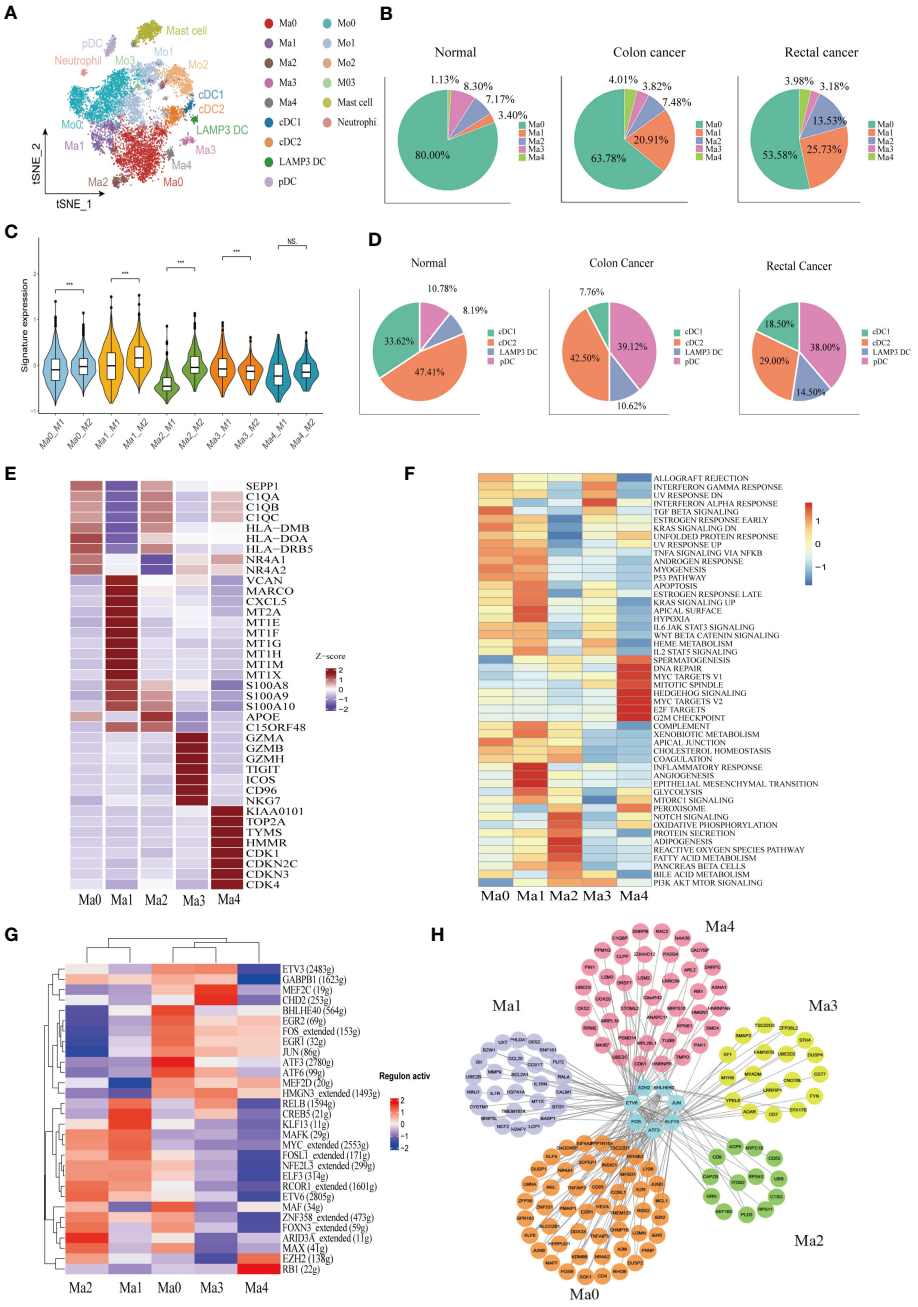

FIGURE 3
Identification of the heterogeneity of myeloid cells in colon cancer, rectal cancer, and adjacent normal tissues. **(A)** t-SNE plot of 10,514 myeloid cells re-clustered into 15 clusters. **(B)** Pie chart presenting the proportion of five different phenotypes macrophage in the whole macrophage lineage. **(C)** Violin plot comparing the scores of M1 and M2 macrophage clusters by wilcox. test, ***p < 0.001, ns p > 0.05. **(D)** Pie chart presenting the proportion of four different dendritic cell (DC) subtypes in the whole DC lineage. **(E)** Heatmap showing the key differentially expressed genes (DEGs) of each macrophage cluster. **(F)** Heatmap showing the enriched pathways from hallmark gene sets in macrophage clusters using gene set variation analysis (GSVA). **(G)** Heatmap of the top 30 regulators with the highest area under curve (AUC) scores showing the activity of transcription factors (TFs) in macrophage clusters using single-cell regulatory network inference and clustering (SCENIC). **(H)** Protein-protein interaction (PPI) networks of prominent TF-target genes in 5 macrophage clusters.

abundant expression of the cell cycle-related genes (CDK1, CDKN2C, CDKN3, and CDK4) (Figure 3E. The results of GSVA demonstrated that the cluster was located mainly in DNA repair, MYC and cell cycle related signaling pathways (Figure 3F). Macrophage clusters were scored based on the average expression of M1 and M2-like signature genes. The results showed that Ma0, Ma1, and Ma2 tended to be M2-like phenotypes and Ma3 cluster was inclined to the M1-like phenotypes, while Ma4 had no significant difference in the two phenotypes (Figure 3C).

Analysis of the proportion of each macrophage subgroup showed that Ma0 had the largest proportion, and Ma0 was the dominant macrophage subgroup in both normal and CRC tissues.

In normal paracancerous tissues, Ma3 was the main macrophage subgroup, except for Ma0; however, in CRC tissues, Ma1 was the dominant subgroup, except for Ma0, and Ma3 accounted for the lowest proportion (Figure 3B). The proportions of macrophage subgroups in myeloid cells from various tissues were further analyzed. Compared to normal tissues, colon cancer tissues had a significantly increased proportion of Ma1 and Ma4 but only a slightly increased proportion of Ma2. There were no significant differences in the proportions of Ma0 and Ma3 in the various tissues. However, there was no significant difference in the proportion of macrophages in various rectal cancer subtypes compared to that in colon cancer or normal tissues. (Supplementary Figure 2I). Therefore, we speculate that Ma1 is a major tumor-associated macrophage with immunosuppressive effects in colon cancer.

SCENIC was used to analyze the key transcription factors (TFs) that may regulate macrophages, followed by identification of the top 30 TFs ranked by the relative activity scores of regulons. The results showed that two important TAM-related transcription factors, BHLHE40 and ATF3, were highly expressed at Ma0. BHLHE40 promotes the expression of proinflammatory genes in macrophages (46), while ATF3 negatively regulates macrophages (47). FOS and JUN proto-oncogenes were also upregulated in the Ma0 cell subsets. CREB5 and KLF13, which influence macrophage polarization, were highly expressed in the Ma1 cluster. The Kruppel-like Factor (KLF) family is vital for regulating macrophage-mediated inflammation (48). For example, KLF13 knockdown downregulates the expression of M1 macrophage-related factors induced by lipopolysaccharides (49). In addition, ARID3A, a gene involved in the maturation of macrophages and the promotion of M2 macrophage polarization (50), was highly expressed in the Ma2 cluster (Figure 3G). A protein–protein interaction (PPI) network was constructed for key regulatory transcription factors and core target genes of the macrophage subgroups. The results showed that the number of interactions between transcription factors and target genes in Ma0 was the largest and that the target genes were jointly regulated by multiple TFs (Figure 3H).

Monocytes were further re-clustered into four clusters as per CD14 and CD16 expression: Mo0 ($CD14^{++}CD16^{-}$), Mo1 ($CD14^{+}CD16^{+}$), Mo2 ($CD14^{+}CD16^{-}$), and Mo3 ($CD14^{+}CD16^{+}$) (Supplementary Figure 2C). Mo0 stimulated the release of cytokines and chemokines such as IL6, IL1A, CXCL1, CXCL5, and CCL20, which can induce monocyte recruitment to tumor. In addition, high expression of INHBA is thought to promote the proliferation of colon cancer cells (51). Mo1 had different gene expression patterns from Mo0, and some chemokines, CXCL9, CXCL10 and CXCL11, were significantly increased in this subgroup. In addition, IFN induction genes IFIT2 and IFIT3 are highly expressed. We also found significant upregulation of IDO1 expression in this subpopulation. Mo2 subgroup expressed macrophage characteristic genes, such as complement pathway related genes C1QA, C1QB, C1QC, and lipid metabolism related genes APOE and APOC1(Supplementary Figure 2D).

Dendritic cells (DCs) were re-clustered into four clusters according to the characteristic marker genes, including cDC1 (CLEC9A and BATF3), cDC2 (CLEC10A, CD1C, and FCER1A), pDC (CLECA4, IL3RA, and LILRA4), and $LAMP3^{+}$ DC (CCR7 and LAMP3) (Supplementary Figure 2B). We identified a mature DC cell, LAMP3 $^{+}$DC, in CRC, which is believed to play a role in tumor cell migration in a variety of cancers. $LAMP3^{+}$DC highly expresses chemokine CCL19 and its receptor CCR7, which may recruit other immune cells to migrate to tumor tissues through the CCL19-CCR7 axis. In addition, IDO1 was found to be significantly higher expression in $LAMP3^{+}$DC (Supplementary Figure 2G). GSVA results indicated that the $LAMP3^{+}$ DC cluster was related to IL2, IL6, and interferon signaling pathways (Supplementary Figure 2F). Plasmacytoid dendritic cells (pDCs) comprise a subset of dendritic cells characterized by the ability to participate in inflammatory responses and exert immunosuppressive actions. However, we found that GZMB was abundantly expressed in the pDC subgroup (Supplementary Figure 2G). Consistently, previous studiesalso confirmed that pDCs were the main source of GZMB. The high expression of GZMB in pDCs may be induced by interleukin. The cytotoxicity function of this derived GZMB is inferior to its immune regulation. Hence, it does not directly induce apoptosis of target cells, but the proliferation of T cells can be inhibited in a GZMB-dependent manner (52, 53). The pDC cluster correlated to DNA repair, KRAS, mTOR, and CRC signaling pathways (Supplementary Figure 2F). The proportion of the pDC subgroup was increased significantly in cancer tissues, while the proportion of cDC1 in colon cancer DC cells was significantly reduced (Figure 3D). The analysis of DC proportion in various tissues showed that the proportion of pDCs in colon cancer and rectal cancer tissues was increased to a certain extent compared with that in normal tissues ($p < 0.05$), while the proportion of cDC1 in colon cancer tissues was decreased significantly ($p < 0.001$). However, there was no significant difference in $LAMP3^{+}$ DC proportion among groups ($p > 0.05$) (Supplementary Figure 2I).

Identification of landscape of B lymphocytes and developmental trajectory states of B lineage of CRC

A total of 17,107 B cells were determined and then clustered with unsupervised clustering into six clusters, Naïve B cell cluster (6,849), germinal center B cell cluster (671), two plasma cell clusters IgA^{+} plasma cell cluster (8,190) and IgG^{+} plasma cell cluster (1,118), one memory B cell cluster (131), and one cycling B cell cluster (148) (Figure 4A). We found that the infiltration of plasma cells (PCs) was significantly heterogeneous among different tissues. Compared with normal tissues, the infiltration abundance of IgA^{+} PCs in CRC decreased. In contrast, the proportion of IgG^{+} PC was elevated significantly in colon cancer tissues compared to normal tissues but not statistically significant increase in the rectal cancer group (Supplementary Figure 3A). Meanwhile, analysis of B cell DEGs among different tissues revealed that IgG-related gene (IGHG1-4) was highly expressed in colon cancer (Supplementary Figure 3B). The results of immunofluorescence also verified that IgA was mainly enriched in the mucosal layer of normal tissue, while IgG was more abundant in the intermuscular stroma of normal tissue. The average expression level of IgA in normal tissue was higher

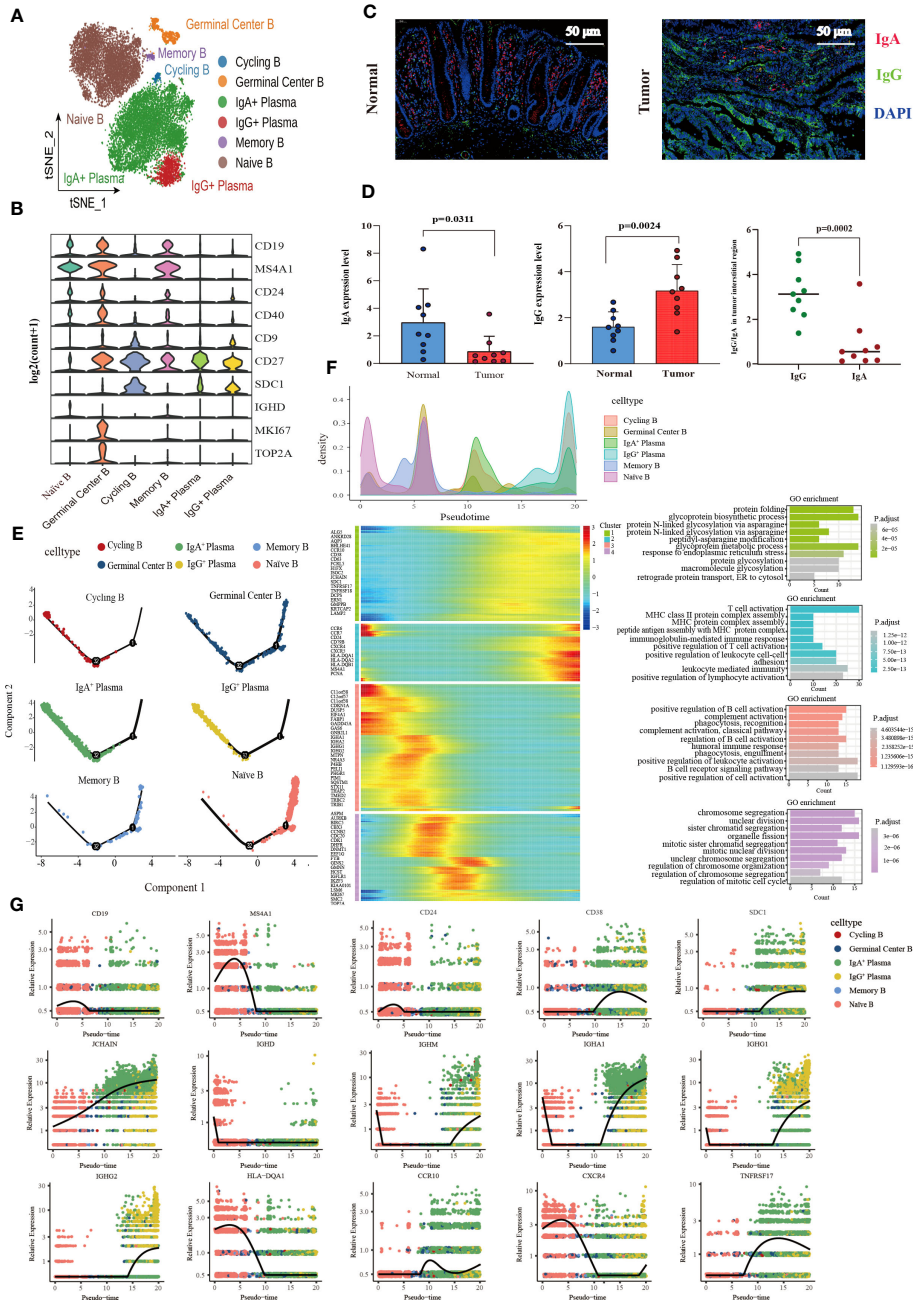

FIGURE 4
Characterization of the landscape of B lymphocytes and developmental trajectories of B lineage in CRC. **(A)** t-SNE projections of 17,107 B cells re-clustered into 6 major clusters. **(B)** Violin plot of relative expression of key characteristic genes in B lineage clusters. **(C)** Representative images of fluorescence staining showing the expression and distribution of IgA and IgG in normal intestinal tissue (left) and CRC tissue (right), respectively. Red representing IgA, green representing IgG, and blue representing DAPI, scale bar=50μm. **(D)** Statistical analysis results of immunofluorescence staining indicating the average expression of IgA decreased in CRC tissues compared with normal intestinal epithelium (left), whereas the average expression of IgG increased (middle), and the expression of IgG higher than that of IgA in tumor stroma (left). **(E)** Developmental trajectories of B lineage inferred using monocle2, each cell subtype marked with a different color. **(F)** Cell density variation of B cell subtypes during the pseudotime (top), pseudo-heatmap of the representative DEGs in differentiation branches (left bottom), Gene Ontology (GO) functional enrichment analysis of DEGs re-clustered into 4 clusters (right bottom). **(G)** Pseudo-scatter plots showing the expression variation and distribution of some specific genes during the pseudotime, color-coded by cell types.

than that of IgG. On the contrary, in cancer tissues, IgG enrichment was observed, but not IgA (Figure 4C, D).

In terms of molecular phenotype, PCs and Cycling B were featured by low expression of CD19 and MS4A1 (CD20). In additional, PCs showed $CD138^{+}CD27^{+}CD38^{+}$ phenotype. CD24 was poorly expressed in the IgA^{+} PCs, while it expressed in the IgG^{+} plasma cluster (Supplementary Figure 3C). Cycling B cell cluster was named according to previous studies (54), which exhibited the characteristics of both B and T cells and the upregulation of the effector molecules of T cells including KLRB1, ANXA1, NKG7,

GZMA and IL7R. Furthermore, the memory B cell cluster also expressed T cell signature genes and effector molecules, with a similar high expression gene pattern to the cycling B cell cluster. Interestingly, these two clusters were noticeably different regarding B cell signature genes. The memory B cell cluster had the high expression of CD19 and MS4A1 (CD20) and FCER2 (CD23) and the low expression of CD38, SDC1 (CD138), and IgA (IGHA1 and IGHA2) and IgM (IGHM) related genes, which was contrary to the cycling B cell cluster. More importantly, IGHM expression was significantly higher in the cycling B cell cluster than in other clusters, indicating that cycling B cells were immature B cell (Supplementary Figure 3D). Additionally, both the Naïve B and Germinal Center B cell clusters were characterized by the high expression of CD19, MS4A1 (CD20), CD24, and CD40 and the low expression of CD27, and SDC1 (CD138). The germinal center B cell cluster characteristically expressed the high level of the proliferation-related genes MKI67 and TOP2A (Figure 4B).

The pseudotime trajectory analysis of B cell clusters was performed with Monocle2 to elucidate the B cell developmental trajectory, as well as the distribution of branches and the cell density of each cluster. Among these clusters, naïve B cells were located at the beginning of the branch and subsequently differentiated to memory B cells. Germinal center B cells were distributed throughout the trajectory and eventually differentiated to IgA^+ PCs, IgG^+ PCs and Cycling B cells at the end of the trajectory (Figure 4E). A total of 459 differential genes were yielded through the pseudotime trajectory analysis and allocated to 4 clusters based on gene classification with similar patterns. As reflected by the results of GO enrichment analyses, genes in Cluster 1 were mainly enriched in the signaling pathways that modulate protein biosynthesis, genes in Cluster 2 and 3 majorly in the signaling pathways involved in the immune response process, and genes in Cluster 4 primarily related to the signaling pathways implicated in cell cycle processes (Figure 4F). The pseudotime dynamic changes of key genes during the development of B cells were analyzed. The results revealed that CD19, MS4A1 and CD24 were mainly expressed in Naïve B cells at the early stage of development and gradually decreased with the development of B cells, while CD38 was mainly expressed in PCs at the late stage of development and increased first and then decreased with time. In addition, CD138 was also expressed in PCs, and its expression gradually increased with time. Immunoglobulin-related genes were rearranged during B cell development. IGHD was mainly expressed in the early development of B cells and gradually disappeared with the activation of B cells. JCHAIN was distributed throughout the development of B cells, and its expression gradually increased with time. It is generally believed that the differentiation from B cells to PCs undergoes a process of switching from IgM to IgG. However, we found that IGHM expression rapidly decreased and disappeared at the early stage of B cell development, and then gradually increased in the late development of B cells. MHC II molecules were highly expressed at the early stage of B cell development and eventually disappeared during the development of PCs. During the development of B cells, the expression of CCR10 changed from low to high, and the expression of CXCR4 decreased gradually. TNFRSF17, a marker of B lymphocyte maturation, was mainly expressed in mature B cells and PCs, which played a vital role in B cell maturation and autoimmune response (Figure 4G).

Evaluation of the infiltration abundance and prognostic value of the major cell subpopulations

A gene matrix was obtained from the scRNA-seq data to characterize the 33 immune cells. In addition, the bulk RNA-seq data from TCGA-COAD and READ cohorts were deconvoluted using CIBERSORT to calculate the relative abundance of each sample. The data showed that in the COAD cohort, the infiltration abundance of $CD8^+$Tex, cDC2, IgG^+PC, Ma1, Ma4, Mo1and pDC clusters in tumor tissues was higher than that in normal tissues. Conversely, higher infiltration abundance levels of $CD4^+$Tem, $CD4^+$Tfh, $CD4^+$Tn, $CD8^+$Tem-KLRD1, $CD8^+$Trm, IgA^+PCs, Ma3, mast cells, Mo0, Mo3, and Naïve B were found in normal samples ($p < 0.05$) (Figure 5A). In the READ cohort, the Ma3, Ma4, Mo0, neutrophil, NK-KLRC1, and Treg clusters showed higher infiltration abundance in tumor tissues; however, the expression levels of $CD4^+$Tfh, $CD8^+$Tex, $CD8^+$Trm, germinal center B cells, Ma1, Ma2, MAIT, memory B, Mo3, and pDC clusters were higher in normal tissues than those in tumor tissues ($p < 0.05$) (Figure 5B). Next, we investigated the relationship between the infiltration abundance and overall survival (OS) with CRC. Our findings indicated that in the COAD cohort, the Ma2-APOE cluster was associated with a poor prognosis in colon cancer, whereas the cDC1, $CD8^+$Trm, and $CD4^+$Tn clusters were associated with a good prognosis. In the READ cohort, IgA^+ plasma cell infiltration may predict a favorable prognosis for rectal cancer (Figure 5C)

Identification of five TME subtypes characterized by immune cells deconvolution in CRC and their prognostic significance

We used the CIBERSORT deconvolution algorithm to infer the composition of 33 of the immune cell subtypes in the bulk RNA sequence data from the TCGA-COAD and READ cohorts. A total of 623 CRC patients from TCGA cohorts were clustered into five different TME subtypes (TME 1-5) by consensus clustering method and the relationship between the different subtypes and clinical characteristics (including: age, sex, TNM, stage and tissue location) was illustrated by heatmap (Figures 6A, B). Further, the overall survival of CRC patients from TCGA cohort was assessed by Kaplan-Meier survival analysis, which confirmed significant differences in the prognosis of CRC patients with the five TME subtypes. Notably, the TME-1 subtype represented a significantly reduced proportion of T-cell infiltration and the highest proportion of macrophages, which had the worst prognosis (Figures 6C-E). Although the TME-4 subtype had the highest proportion of T cell infiltration, it mainly showed $CD8^+$Tex subtype, lacking infiltration of cytotoxic T cells, and therefore had a poor prognosis (Figures 6A, C, E, F).

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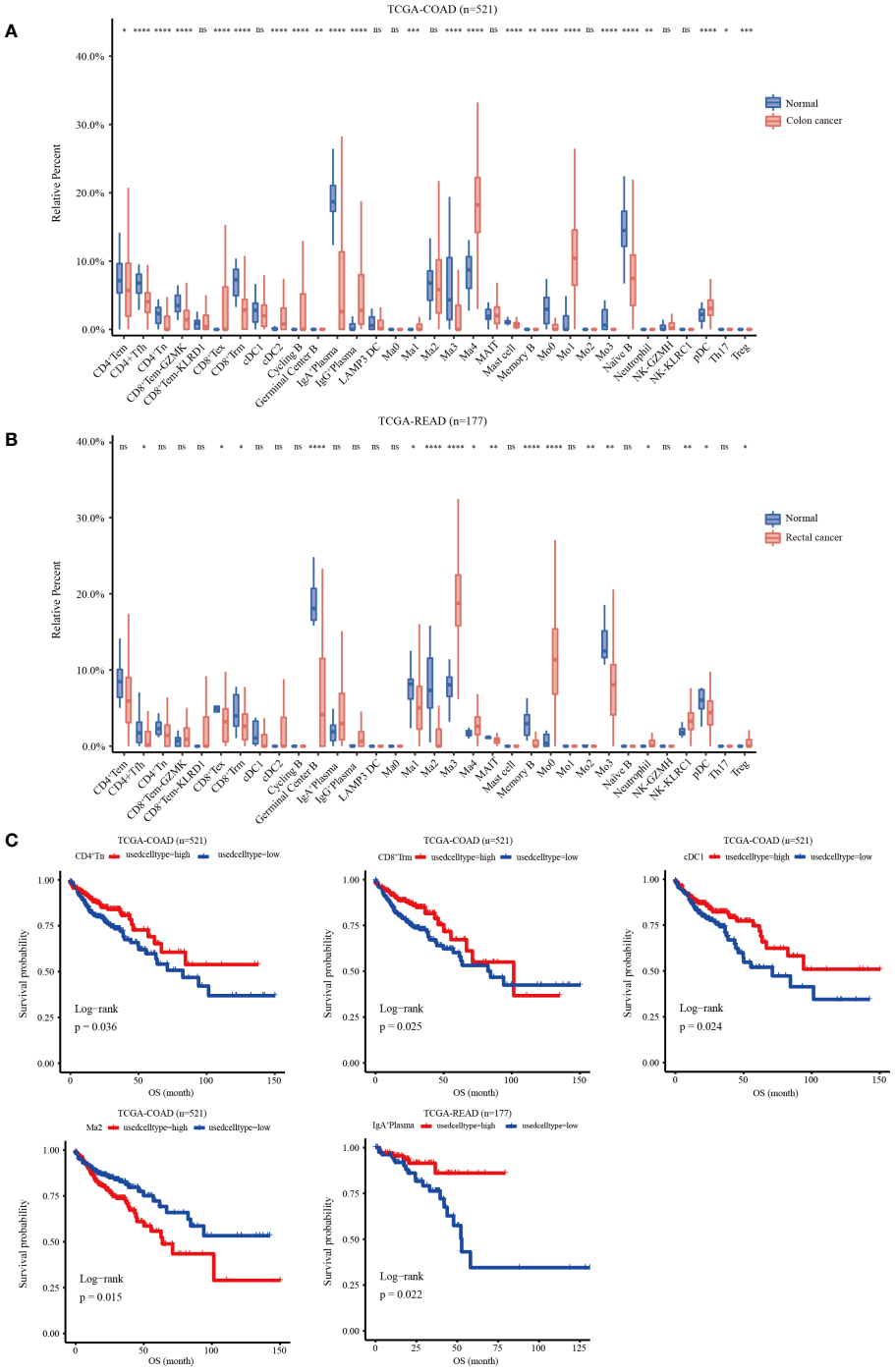

FIGURE 5
Relative infiltration abundance and prognostic significance of 33 immune cell subpopulations revealed by CIBERSORT deconvolution algorithm. **(A)** Relative infiltration abundance of 33 immune cell subpopulations identified by ScRNA-seq data in 480 colon cancer tissues and 41 adjacent tissues from the COAD cohort. **(B)** Relative infiltration abundance of 33 immune cell subpopulations identified by single-cell data in 167 colon cancer tissues and 10 adjacent tissues from the READ cohort, *p < 0.05, **p< 0.01, ***p< 0.001, ****p< 0.0001, and ns p > 0.05. **(C)** Kaplan-Meier overall survival curves of 460 patients in the TCGA-COAD cohort and 172 patients in the TCGA-READ cohort divided into the high infiltration group and low infiltration group, *p < 0.05.

CellChat analysis of immune cell communication in CRC

CellChat was used to comprehensively assess immune cell interactions between colon or rectal cancer tissues and normal tissues in terms of the number and weight of cell communications (Figure 7A, Supplementary Figures 4A, B). In terms of incoming signals, the interaction number of macrophages increased significantly, the interaction weight of DC signals was elevated most substantially, and the interaction number and weight of

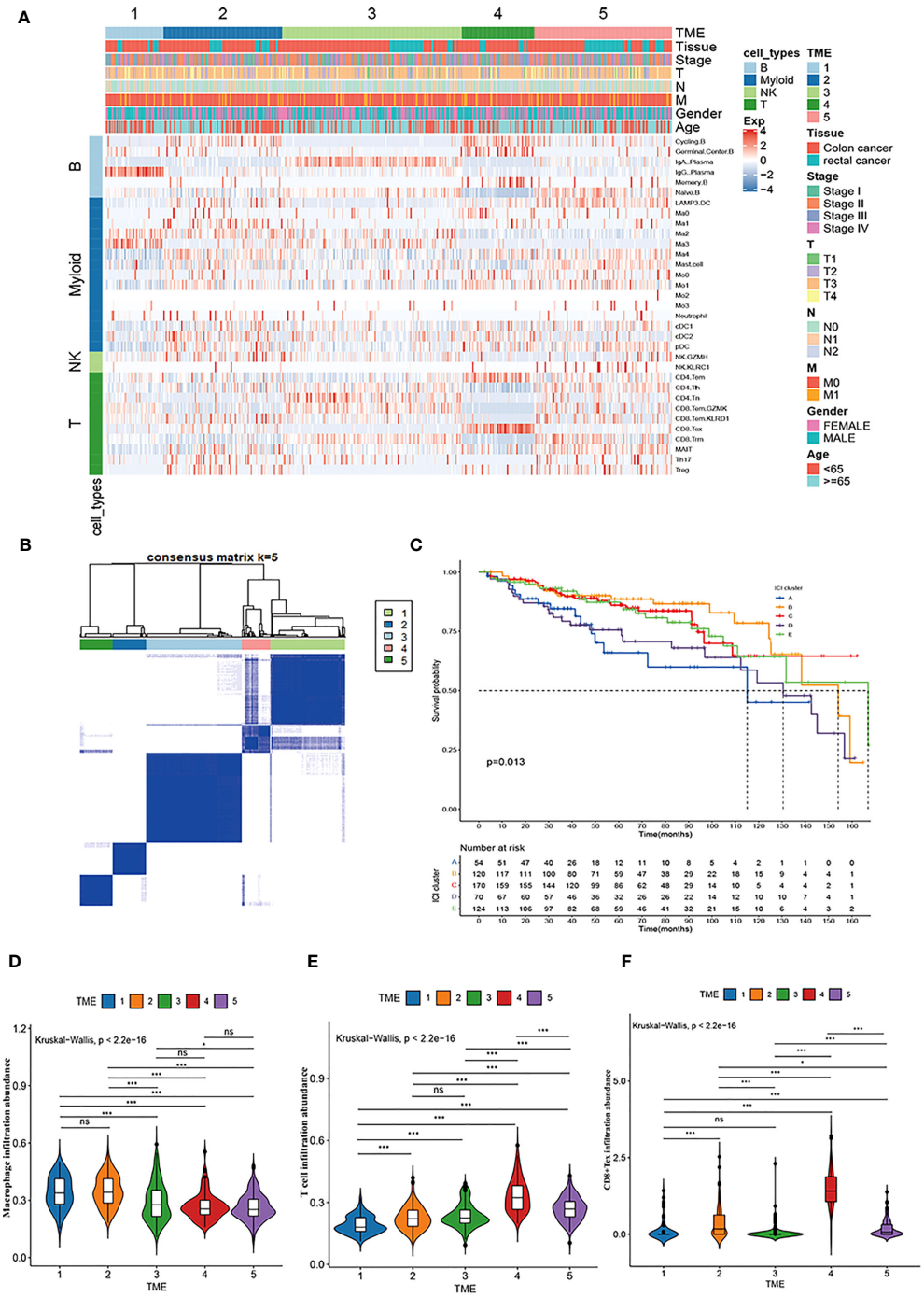

FIGURE 6
Immune cell characteristics and prognostic significance of TME subtypes in CRC. **(A)** Heatmap showing unsupervised clustering of 5 TME subtypes of immune patterns in the TCGA cohort, with the rows representing the 33 immune subpopulations identified by the ScRNA-seq data set, and the columns representing 647 CRC patients from the TCGA-COAD and READ cohorts; hierarchical clustering according to TME subtype, histological site, disease stage, tumor-node-metastasis (TNM) stage, and age. **(B)** Consensus matrix heatmap representing the consensus matrix with k=5 by consensus clustering; the range of value from 0 to 1 implying the probability in the same cluster with the color scaling from white to dark blue. **(C)** Kaplan-Meier overall survival curves of 5 TME subtypes in TCGA-COAD and READ cohorts. **(D-F)** Violin plot showing the representative immune cell abundance of 5 TME subtypes, including macrophages **(D)**, T cells **(E)**, and $CD8^+$ Tex cells **(F)**, compared by Kruskal-Wallis test.

monocytes decreased most significantly in colon cancer tissues when compared with normal tissues. Regarding outgoing signals, the number and weight of communication between monocytes and DCs were prominently increased, whereas the number and weight of communication between monocytes and neutrophils were most significantly reduced (Supplementary Figure 4C). Compared with those in normal tissues, the number of incoming signals of macrophages and DCs increased, but the weight of macrophages decreased and the number and weight of monocytes decreased most significantly in rectal cancer tissues. For the outgoing signals,

macrophages and DCs both showed increases in interaction quantity and weight, while monocytes and neutrophils both had significantly decreased interaction number and weight (Supplementary Figure 4D). Further, the difference in the interaction between colon and rectal cancer tissues was analyzed, the results of which suggested elevated incoming signals from NK cells but diminished incoming signals from macrophages and outgoing signals from monocytes in rectal cancer tissues as compared to colon cancer tissues (Figure 7B). In conclusion, the interaction between myeloid cells and other cells was significantly changed in both the comparison between normal tissues and cancer tissues and the comparison between colon cancer and rectal cancer.

Importantly, CellChat further uncovered the patterns of incoming and outgoing signals. At the outgoing end of the signaling pathway, immune cell subsets acted as secretory cells to send signals principally through four patterns. Specifically, T and NK cells drove CD99, CD45, and ADGRE5, as well as INF-II and interleukin signaling pathways, mainly through Pattern 2. The major B cell subsets cDC1 and pDC mediated CD22, GAS, and ICOS signaling pathways primarily through Pattern 4. Myeloid cell clusters drove MHC II, SPP1, BAFF, CXCL, CD86, and PD-L1 signaling pathways through Pattern 1. Additionally, Ma1, Mo0, Mo3, and neutrophils jointly promoted ICAM, TNF, FN1, and other pathways through Pattern 3 (Figure 7C). More importantly, T, B, and myeloid cells were dominated by Pattern 4, Pattern 3, and Pattern 2, respectively, when immune cell subsets served as the targeted cells at the incoming end of the signaling pathway. Pattern 1 corresponded to the incoming signals from numerous immune cells, which were mainly driven by ADGRE5 and SELPLG signaling pathways (Figure 7D).

All communication probabilities in the information network were summarized to compare the difference in overall information flow between colon and rectal cancers. The results unraveled that CCL5, THBS, SPP1, ICAM, and TNF signaling pathways were more abundant in colon cancer (red), whereas SELPLG, LIGHT, CSF, and BAFF signaling pathways were more abundant in rectal cancer (green) (Figure 7E). The visualization results of heat maps revealed an elevation in the overall information flow from $CD8^+$ T cell, DC, and macrophage clusters in both colon and rectal cancer tissues, the most significant increase in the information flow from macrophages in colon cancer tissues, and a dominant increase in the information flow from $CD8^+$ T cells in rectal cancer tissues (Figure 7F).

As macrophages are key to cell communication in CRC and are heterogeneous in communication across tissues, the probability of ligand-receptor communication between macrophages and other immune cells was further compared between colon and rectal cancer tissues. The results depicted that macrophages were critical for regulating cell-cell communication in CRC and that tissue variation existed in communication patterns. SPP1-CD44 (L-R) was highly active in the communication between macrophages and other cells and more active in colon cancer tissues than in rectal cancer tissues throughout intercellular information interaction as it mediated the immunosuppression and progression of CRC. Because the ligand MIF is a chemokine-like inflammatory mediator, its multi-subunit receptor complexes CD74-CXCR4 and CD74-CD44 can orchestrate inflammatory pathways. Our findings manifested that CD74-CXCR4 and CD74-CD44 were highly activated in the signal flow from macrophages to B and T lymphocytes (Figure 7G). The Ma1 subgroup exerted the strongest effect on these receptor-ligand pairs (Supplementary Figure 4E). Therefore, this result supported our previous inference that Ma1 was a kind of M2-like TAMs.

Multiplex immunohistochemistry description the interaction between $SPP1^+$TAM and Treg in the TME of CRC

To validate the cell communication results based on Cellchat analysis, mIHC technology was used to verify the cell population interactions mediated by the high active L-R interaction. The previous prediction of L-R interactions found that SPP1-CD44 interation revealed strong effects on the interaction between macrophages and Treg subgroups (Supplementary Figure 4E), so we analyzed the co-localization of $SPP1^+$TAM and Treg in the TME of CRC. Consistent with our prediction, the prevalence of $SPP1^+$TAMs co-localizing with $Foxp3^+$Tregs and the proximity of their spatial locations within the CD44 enriched regions, led us to hypothesize that the crosstalk between $SPP1^+$TAMs and $Foxp3^+$Tregs increases the immunosuppressive effect, which is most likely mediated by SPP1-CD44 (Figures 8A-D, Supplementary Figures 5A, B).

Discussion

The inter- and intratumoral heterogeneities of immune cell tumors directly affect the prognosis of patients and their response to immunotherapy. In this study, two CRC 10xGenomics scRNA-seq datasets were integrated, including 33 patients and 6,2398 immune cells re-clustered into 33 immune cell clusters, to characterize the immune cell landscape of CRC and comprehensively analyze the phenotypic and molecular differences and intercellular communication between immune cells in CRC at single-cell resolution. In addition, the heterogeneity of colon cancer, rectal cancer, and normal adjacent tissues in the immune microenvironment and their differences in cell-interaction patterns were compared. Furthermore, we combined bulk RNA-seq data from TCGA cohorts to evaluate the prognostic value of these pivotal immune cell subpopulations. In addition, according to the characteristics of immune infiltration, patients with CRC were divided into five TME subtypes with different prognostic characteristics.

TAMs are the most important myeloid cells in the immunosuppressive microenvironment of tumors (38, 55). In the present study, the diversity and complexity of myeloid cells were investigated. Five macrophage phenotypes and four different subtypes of DCs were identified. More importantly, we observed a heterogeneous distribution of myeloid cells in CRC and normal adjacent tissues. We found an important Ma1-SPP1 macrophage that exhibited M2-like phenotypes, which potentially promoted angiogenesis and increased infiltration abundance in tumor tissues. Therefore, we speculate that Ma1-SPP1 may be an important TAM. Interestingly, however, when we compared the

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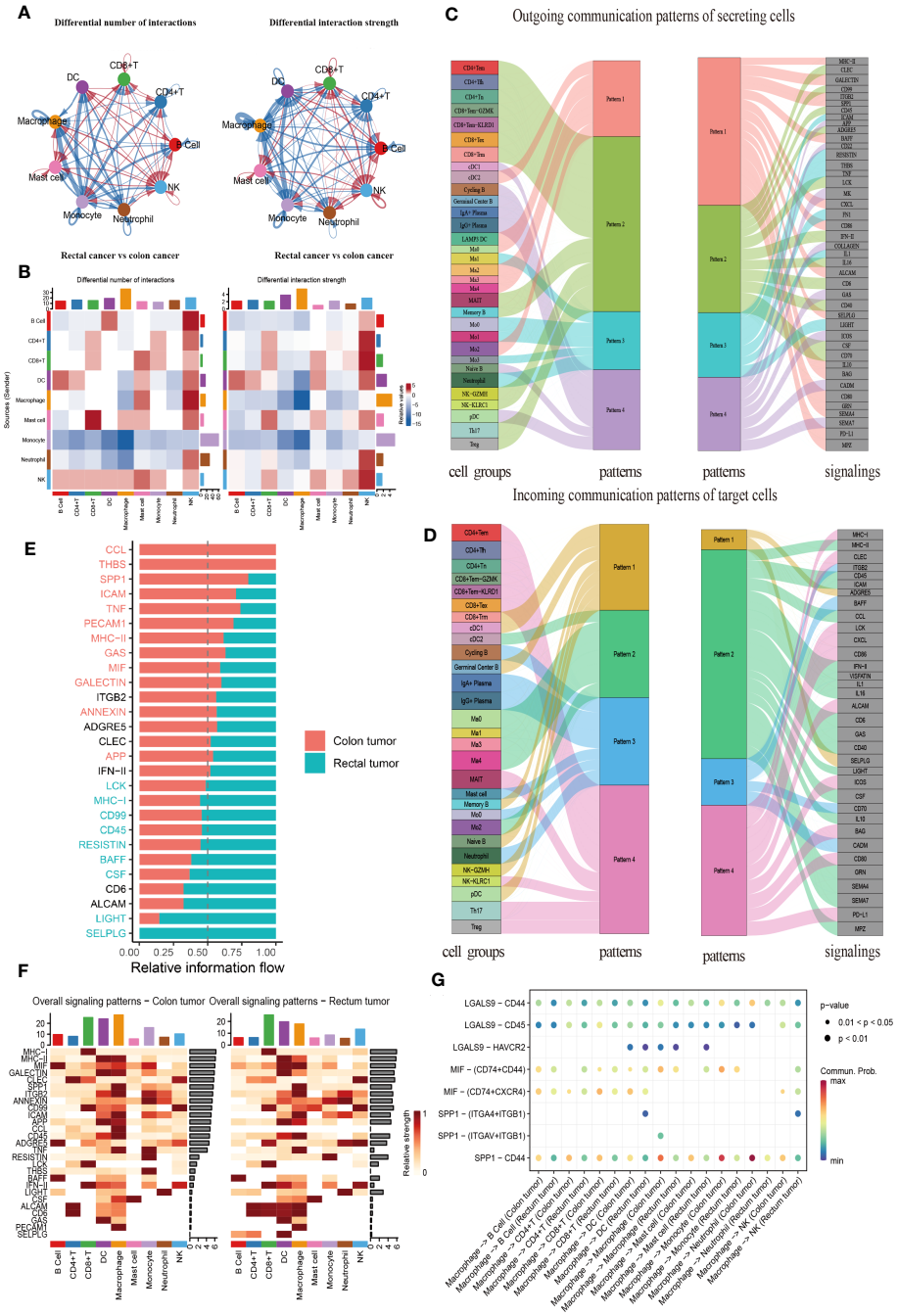

FIGURE 7
CellChat analysis of the crosstalk between immune cells in colon cancer or rectal cancer. **(A)** Comparisons of overall changes in cell-cell communication between rectal cancer and colon cancer, including the differential number of interactions (left) and differential interaction strength (right) between immune cells of rectal cancer compared with colon cancer, with the blue line representing reduced communication in rectal cancer compared to colon cancer, while the red line representing increased communication in rectal cancer compared to colon cancer. **(B)** Heatmaps showing the interaction number (left) and interaction strength (right) between colon cancer and rectal cancer, with the top color bar representing the sum of the column values displayed in incoming signals and the right color bar representing the sum of outgoing signals, red or blue indicating increased or decreased signal of colon cancer compared with normal control. **(C)** Outgoing signal pattern of immune cells acting as secretory cells, and the pattern corresponding to signaling pathways. **(D)** Incoming signal pattern of immune cells acting as target cells, and the pattern corresponding to signaling pathways; the thickness of the flow indicating the contribution to each pattern. **(E)** Differences in the overall signaling pathway between colon cancer and rectal cancer, with the ranking indicating the importance of the pathways; red indicating the signaling pathways enriched in colon cancer, green representing the signaling pathways enriched in rectal cancer, and black representing no difference in signaling pathway enrichment in colon cancer and rectal cancer. **(F)** Heatmaps of the overall signaling pathway of each immune cell subpopulation mediated by individual signaling pathway in colon cancer (left) and rectal cancer (right). **(G)** Communication probabilities of important ligand-receptor pairs from macrophages to individual immune cells in colon and rectal cancers, with the dot color reflecting the communication probability, blank indicating the communication probability zero, and dot size representing the p value.

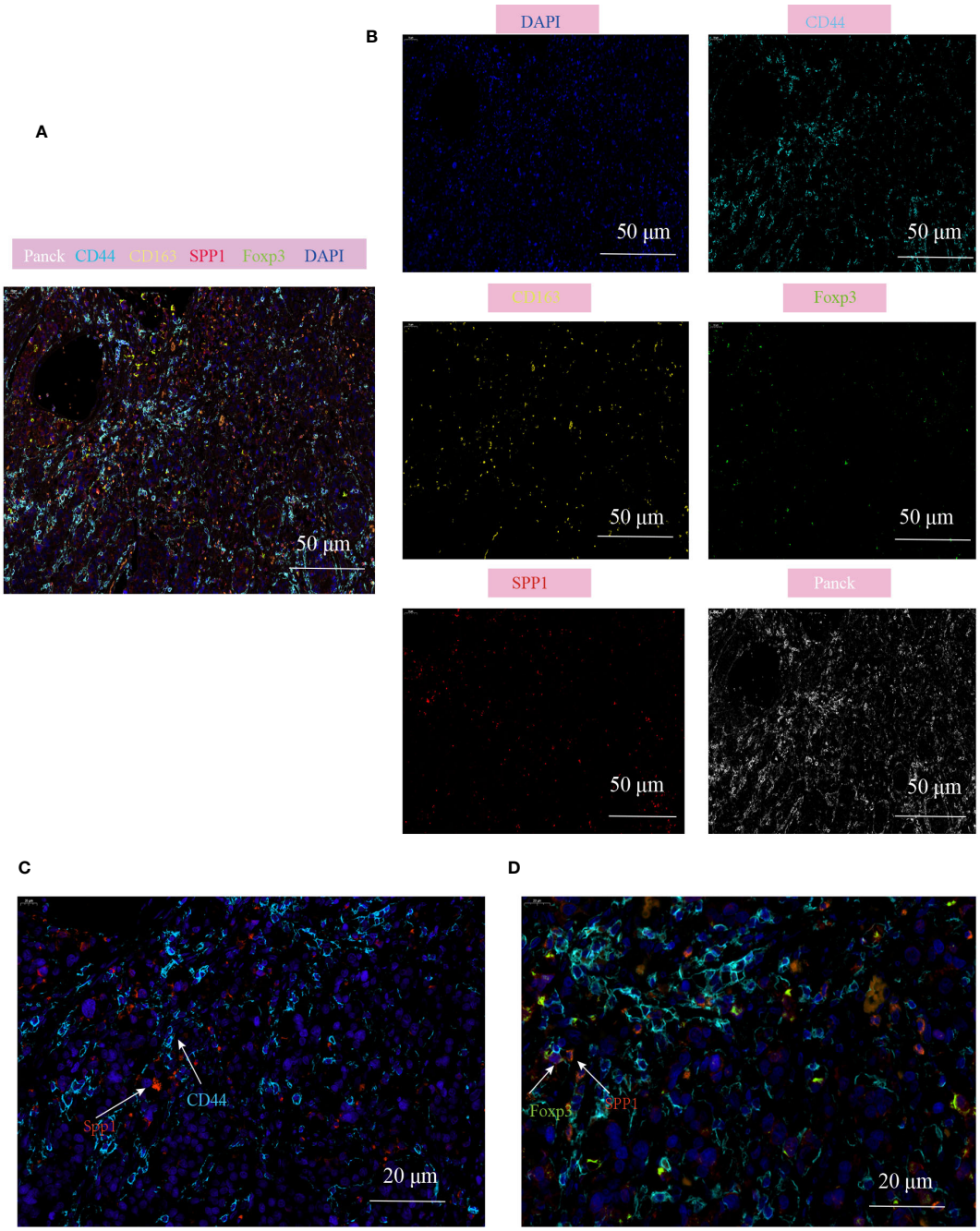

FIGURE 8
Multiplex immunofluorescence showing the interaction between SPP1^{+}TAM and Foxp3^{+}Treg in the TME of CRC. **(A, B)** Multiplex immunofluorescence images demonstrating the localization of different cell populations in CRC, using typical marker genes including Panck (white), CD44 (cyan), CD163 (yellow), SPP1(red), Foxp3 (green), DAPI (blue), scale bar=50μm; **(C)** Representative images of SPP1-CD44 mediated co-localization of cell populations in CRC patients, scale bar=20μm; **(D)** Representative images of interaction of SPP1^{+}TAM and Foxp3^{+}Treg cells in the CD44 enriched regions, scale bar=20μm.

inter-tissue heterogeneity based on our analysis of the single-cell dataset, the proportion of Ma1-SPP1 macrophages in colon cancer tissue was higher than that in normal tissue, whereas the increase in rectal cancer was not statistically significant. In addition, we did not observe significant differences in the abundance of infiltrating macrophage subsets between colon and rectal cancers.

Importantly, we found that myeloid cells play an important role in cell–cell communication. In different pathological tissues, myeloid cells show differences in the strength of their interaction and signaling pathways with other cells. This difference may have a more significant impact on the tumor microenvironment than on the abundance of infiltration. Specifically, the interaction of macrophages with DCs and other immune clusters increased in CRC tissues, whereas monocyte communication decreased. Compared to colon cancer, the communication signals of macrophages and monocytes are decreased in the TME of

patients with rectal cancer. Among these, the SPP1 signaling pathway, a characteristic gene of the Ma1 subgroup, is highly active in colon cancer, whereas the SELPLG and LIGHT signaling pathways are highly active in rectal cancer. Interestingly, we observed a high probability of SPP1-CD44 mediated information flow in the cell–cell communication between Ma1 macrophages and Tregs. We hypothesized that SPP1-CD44 information flow mediates intercellular crosstalk between TAMs and Tregs, which enhances the immunosuppressive microenvironment of CRC. Furthermore, through mIHC, we confirmed the spatial co-localization of $SPP1^{+}$TAMs and Tregs, and this cell–cell interaction was more prominent in CD44 enriched areas. Although we were able to identify SPP1 as a ligand of TAMs that interacts with CD44 high-expressing cells, we could not confirm whether CD44 was directly involved in intercellular crosstalk as a receptor for Tregs or whether other $CD44^{+}$cell populations acted as a bridge to increase Treg infiltration due to the low cell specificity of CD44.

cDC1s are the main APC cells responsible for antigen cross-presentation, and the priming of $CD8^{+}$T cells is crucial for antitumor responses (26). Recruitment and expansion of cDC1 in the TME were associated with increased $CD8^{+}$T cell infiltration and a good prognosis and exhibited a better clinical response to ICI. A study of Notch-regulated dendritic cells inhibiting the development of inflammation-associated CRC revealed a direct relationship between Notch2 signaling and infiltrating cDC1s as well as an association between the inhibition of cDC1 signaling and poor prognosis in human CRC. The study indicated that decreased intratumoral cDC1s and circulating cDC1s in patients with CRC are related to disease stage, whereas suppressed cDC1 gene signature expression in human CRC is associated with a poor prognosis (56). In addition, another study found that colorectal tumors can be further sensitized to immune checkpoint therapy using a combination of low-dose chemotherapy and oncolytic HSV-1 in a mouse model of dMMR CRC, mainly through the mechanism of making tumors sensitive to immunotherapy by promoting high levels of cDC1 infiltration in tumors after treatment, and the therapeutic effect depends on the presence of cDC1s (57). Our study observed a significant reduction in the abundance of cDC1 infiltration in colon cancer in the scRNA-seq cohort, and high infiltration of cDC1 was found to be correlated with good outcomes in TCGA-COAD cohort. Therefore, our findings support cDC1 as a potential biomarker for predicting OS in patients with CRC.

The enrichment of PCs in tumors significantly correlates with the aggregation of tertiary lymphoid structures (TLSs) (58). PCs produced in situ in tumor TLSs can generate antibodies against specific tumor-related antigens, which exert anti-tumor or tumor-promoting effects in different TMEs (59, 60). The enrichment of PCs in some tumors also serves as a prognostic indicator for PD-L1 inhibitor therapy (31, 61). After reclustering the single-cell data of CRC, we identified PCs with IgA^{+} PC and IgG^{+} PC phenotypes, presenting a significantly heterogeneous distribution in the tumor and normal tissues. Specifically, IgA^{+} PCs are decreased in colorectal tumor tissues, whereas IgG^{+} PCs are enriched in tumor cells. IgA^{+} PCs are usually believed to be abundantly produced by the intestinal mucosa and can migrate to target tissues (62). Therefore, IgA^{+} PCs have been detected in the microenvironments of multiple tumors. However, the role of IgA^{+} PCs in tumor development and progression has not been unanimously determined (63, 64). In CRC, IgA^{+} PCs inhibit the activation of cytotoxic $CD8^{+}$ T cells, leading to a poor prognosis (54). In contrast, another study reported that IgA^{+} PCs are significantly associated with the long-term survival of patients with rectal cancer (65). By analyzing the clinical data of colon adenocarcinoma (COAD) and rectum adenocarcinoma (READ) from the Cancer Genome Atlas (TCGA) database, we found that the infiltration of IgA^{+} PCs was associated with a prolonged OS of patients with rectal cancer. Hence, the enrichment of IgA^{+} PCs may contribute to the prognosis of rectal cancer; however, no correlation was observed between the enrichment of IgA^{+} PCs and the prognosis of colon cancer. Accumulating evidence suggests that IgG antibodies produced by IgG^{+}PCs can enhance the T cell response (66). In addition, IgG antigens can directly induce antibody-dependent cellular cytotoxicity (ADCC) via Fc receptor activation (67). Nevertheless, in complement-rich tumors, IgG antibodies activate the complement cascade, thus producing anaphylatoxins and promoting inflammation and angiogenesis (32). We found that IgG^{+} PCs were enriched in colon cancer tissues; however, whether IgG^{+} PC enrichment was indicative of a better prognosis was not determined. However, the role of IgG^{+} PCs in the TME requires further experimental verification.

CD103 is recognized as a marker of Trm cells, and it is generally believed that Trm cells express high levels of PD-1, TIGIT, and CD39 (68). The co-expression of CD103 and CD39 has been confirmed to be a marker for the identification of tumor-reactive $CD8^{+}$TIL in human solid cancers (20, 69). Notably, Duhen et al. confirmed that the percentage of $CD103^{+}CD39^{+}CD8^{+}$ TILs was high in MSI-high colon cancer with high mutational burden, which showed the highest response rates to immunotherapy. In contrast, the percentage of $CD103^{+}CD39^{+}CD8^{+}$ TILs was low in patients with microsatellite-stable colon cancer and colorectal liver metastasis, who tended to respond poorly to immunotherapy (69). Some studies have suggested that triple-positive TIL exhibit a strong activation/exhaustion phenotype and have a superior prognostic impact compared to TIL expressing other combinations of these markers (20). Interestingly, we found that the abundance of $PD1^{+}CD39^{+}CD103^{+}$TILs was extremely low in CRC, whereas a few triple-positive cells were mainly distributed in the Th17 and $CD8^{+}$Tem-KLRD1 subpopulations. Double-positive cells accounted for a high proportion, and $CD8^{+}$Trm was the predominant subpopulation of $CD39^{+}CD103^{+}$T cells. The expression of PD-1 was not upregulated in $CD8^{+}$Trm; however, the expression of HAVCR2 was significantly upregulated. Highly infiltrated $CD8^{+}$Trms were associated with prolonged OS in CRC but not with the prognosis of rectal cancer. Therefore, we believe that $CD39^{+}CD101^{+}CD8^{+}$Trm could better predict the tumor reactivity of $CD8^{+}$TIL in colon cancer.

In conclusion, this study comprehensively analyzed the immune cell atlas of human CRC at the single-

cell level. Specifically, the heterogeneity distribution and phenotype of immune cells were deeply analyzed in colon cancer and rectal cancer, followed by the characterization of the pathway enrichment, cell communication, and transcription factors of each immune cell subset. Further, the prognostic role of major TILs and TME subtypes in CRC was evaluated by integrating bulk RNA transcriptome data. These findings provide novel insight into the immunotherapy of CRC.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found within the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of General Hospital of Northern Theater Command. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QZ conceived and designed the study. YL performed single cell bioinformatics analysis, and YL, QZ processed statistical analysis. CZ, XW helped provide clinical sample collection and histopathological experiments. MH and YL helped review the paper and provided key data explanations. ZQ wrote the manuscript according to the opinions of all the authors. All authors have read and approved the manuscript.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1184167/full#supplementary-material

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Risk factors for lateral pelvic lymph node metastasis in patients with lower rectal cancer: a systematic review and meta-analysis

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Background and objective: Lateral pelvic lymph node (LPLN) metastasis is one of the prominent reasons for local recurrence (LR) in patients with rectal cancer (RC). The evaluation criteria of lateral lymph node dissection (LLND) for patients in eastern (mainly in Japan) and western countries have been controversial. The aim of this study was to analyse the risk factors for LPLN metastasis in order to guide surgical methods.

Methods: We searched relevant databases (Embase (Ovid), Medline (Ovid), PubMed, Cochrane Library, and Web of Science) for articles published between 1 January 2000 and 05 October 2022 to evaluate the risk factors for LPLN metastasis in patients with RC in this meta-analysis.

Results: A total of 24 articles with 5843 patients were included in this study. The overall results showed that female sex, age <60 years, pretherapeutic CEA level >5 ng/ml, clinical T4 stage (cT4), clinical M1 stage (cM1), distance of the tumour from the anal verge (AV) <50 mm, tumour centre located below the peritoneal reflection (Rb), short axis (SA) of LPLN ≥8 mm before nCRT, short axis (SA) of LPLN ≥5 mm after nCRT, border irregularity of LPLN, tumour size ≥50 mm, pathological T3-4 stage (pT3-4), pathological N2 stage (pN2), mesorectal lymph node metastasis (MLNM), lymphatic invasion (LI), venous invasion (VI), CRM (+) and poor differentiation were significant risk factors for LPLN metastasis (P <0.05).

Conclusion: This study summarized almost all potential risk factors of LPLN metastasis and expected to provide effective treatment strategies for patients with LRC. According to the risk factors of lateral lymph node metastasis, we can adopt different comprehensive treatment strategies. High-risk patients can

perform lateral lymph node dissection to effectively reduce local recurrence; In low-risk patients, we can avoid overtreatment, reduce complications and trauma caused by lateral lymph node dissection, and maximize patient survival and quality of life.

KEYWORDS

rectal cancer, lateral pelvic lymph node metastasis, risk factors, meta-analysis, LPLN

1 Introduction

Colorectal cancer (CRC) is the third most common malignant tumour in the world. In 2020, it was ranked as the fourth leading cause of cancer death, second to lung cancer (1), and its burden is estimated to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030 (2).

Local recurrence (LR) of RC is still a serious clinical problem that is related to low survival and high incidence rates. It diffuses through the superior lymphatic drainage of the inferior mesenteric artery as well as the lateral lymphatic drainage of the internal iliac artery outside the rectum (3, 4). Lateral pelvic lymph node (LPLN) metastasis is considered the main cause of LR in patients with low rectal cancer (LRC) (5–7). Several studies verified that the incidence of LPLN metastasis in patients with LRC was approximately 15% (8), while the incidence of stages T3 and T4 exceeded 20% (9, 10). Klusters M et al. assumed that lymph and tumour cells wound flow into the LPLN system when the tumour is crushed during surgical resection. In addition, the LPLN system was left untouched during standard TME, and partial damage during rapid dissection of the lateral ligament led to lateral positive lymphatic residue. Finally, lymph converged in the presacral area and flowed into serum, which might have led to local tumour recurrence (11). It is urgent to find the relevant risk factors for LPLN metastasis. However, recent studies have shown that lateral recurrence has become the most common recurrence mode, accounting for up to 50%~82.7%. Lateral recurrence after rectal cancer surgery has been heavily discussed and is a barrier to prevention and treatment of colorectal surgery (6).

However, there has been no meta-analysis to clarify the risk factors for LPLN metastasis in patients with LRC to date. We included all significantly relevant articles to compile this meta-analysis to further guide the treatment of rectal cancer patients with suspected LPLN metastasis. It can guide us to identify which patients with rectal cancer need lateral lymph node dissection to reduce the risk of local recurrence.

Abbreviations: AV, anal verge; CIs, confidence intervals; cM1, clinical M1 stage; cN, clinical N stage; CRC, Colorectal cancer; ESGAR, the European Society of Gastrointestinal and Abdominal Radiology; LI, lymphatic invasion; LLND, lateral lymph node dissection; LPLN, Lateral pelvic lymph node; LR, local recurrence; LRC, low rectal cancer; MeSH, Medical Subject Headings; MLNM, mesorectal lymph node metastasis; MRA, middle rectal artery; MRI-EMVI, extramural venous invasion on MRI; NOS, Newcastle Ottawa Scale; ORs, Odds ratios; OSNA, one-step nucleic acid amplification; pN, pN stage; pN2, pathological N2 stage; pT3-4, pathological T3-4 stage; R1, positive circumferential margin; Rb, below the peritoneal reflection; RC, rectal cancer; SA, short axis; VI, venous invasion.

2 Materials and methods

2.1 Literature search

Studies published up to 05 October 2022 were identified by searching Embase (Ovid), Medline (Ovid), PubMed, Cochrane Library, and Web of Science. No regional restriction was imposed. Articles were confined to human studies published in English. The search algorithms consisted of Medical Subject Headings (MeSH) and free text terms, including the following: “Rectal cancer”, “Lateral pelvic lymph node metastasis”, and “risk factor”. Eligible literature was identified by reading the included relevant articles.

2.2 Article selection

Inclusion criteria: (1) participants: rectal cancer patients with clinically suspected LPLN metastasis; (2) intervention: pathological examination confirmed positive metastasis of LPLN; (3) comparison: pathological examination confirmed negative metastasis of LPLN; (4) outcome measures: report at least one of the endpoints listed in Table 1; (5) study design: randomized controlled trials, prospective or retrospective cohort and case-control studies. Studies were excluded if: (1) they were reviews, case reports, conference articles or unrelated studies (the article did not contain rectal cancer, lymphatic metastasis, or risk factor analysis); (2) the metastatic lymph node was not LPLN; and (3) no outcome measures of interest were reported.

2.3 Outcomes of interest

We tried to screen all comparable data of the included articles as fully as possible. When a certain indicator contains data with more than 2 articles, it is considered as “Outcomes of Interest”. The

indicators were as follows: Sex, age, pretherapeutic CEA level (ng/ml), border irregularity of LPLN, mixed signal intensity of LPLN, short axis of LPLN before CRT (mm), short axis of LPLN after CRT (mm), distance of the tumour from the AV (50 mm or 40 mm), tumour location, tumour size (mm), cT, cN, cM, pT, pN, LI, MLNM, VI, PI, CRM and differentiation.

2.4 Data extraction and outcome measures

Two authors (ZDX and TL) independently screened all the included studies and extracted the relevant data. Divergence of views was resolved through discussion between the authors. When consensus could not be reached, the third author (RMN) was

TABLE 1 Main characteristics of the selected studies.

Reference	Journal	Country	N	LPLN (+) rate	Age	Operation method	Outcome
Abe 2022 (12)	World Journal of Surgical Oncology	Japan	67	26.9%	LPLN(+): 66.5 (47-83) LPLN(-): 65 (33-78)	laparoscopy/open	1, 3, 10a, 12, 13, 14, 15, 17
Dev 2018 (13)	Indian Journal of Surgical Oncology	India	43	20.9%	/	/	1, 4, 7a, 9, 10a, 10b, 11a, 13, 17
E. Agger 2021 (14)	International Journal of Colorectal Disease	Sweden	344	8.7%	/	/	1, 3, 10a, 10c, 14
Fujita 2009 (15)	International Journal of Colorectal Disease	Japan	210	22.4%	/	/	1, 2, 4, 8, 9, 10a, 11a, 12, 13, 14, 15, 17
Hiyoshi 2019 (16)	International Journal of Clinical Oncology	Japan	78	11.5%	62.8 (19–80)	laparoscopy/open	1, 3, 4, 8, 10c, 13, 17
Ishibe 2020 (17)	International Journal of Colorectal Disease	Japan	458	15.5%	63 (28–86)	open	1, 4, 7b, 9, 13, 17
Iwasa 2021 (18)	International Journal of Colorectal Disease	Japan	102	19.6%	64 (30–82)	/	3, 4, 7a, 8, 10c, 16
Kawai 2021 (19)	Disease Of The Colon & Rectum	Japan	279	9.3%	64 (32–86)	/	1, 2, 6a, 7b, 10a, 10c
Kim 2007 (6)	Annals of Surgical Oncology	Korea	366	6.6%	57 (27–83)	/	1, 4, 6b, 7a, 9, 10a, 16, 17
Kim 2018 (20)	PLOS ONE	Korea	57	40.4%	57 (50–67)	/	1, 4, 5a, 5b, 6a, 6b, 7a, 9, 10a, 11a, 11b, 12, 14, 15, 17
Komori 2018 (21)	European Journal of Surgical Oncology	Japan	328	7.3%	/	/	1, 2, 6a, 7a, 8, 9, 11b, 17
Lim 2013 (22)	International Journal of Colorectal Disease	Korea	67	40.0%	/	/	1, 8, 10a, 10b, 11a, 11b, 12, 15, 16, 17
Malakorn 2019 (23)	Disease Of The Colon & Rectum	America	64	51.6%	/	/	1, 6b, 11a, 11b, 12, 15
Nakanish 2020 (24)	Annls Surg Oncology	Japan	247	28.7%	60 (49–67)	/	1, 4, 10a, 11a, 17
Ogawa 2016 (25)	International Journal of Colorectal Disease	Japan	394	21.3%	64 (16–87)	/	1, 10c, 11a, 13, 17
Oh 2014 (26)	Annls Surg Oncology	Korea	66	33.3%	58.5 (31-82)	laparoscopy/open	1, 9, 10a, 10b
Park 2018 (27)	journal of surgical research	Korea	99	32.3%	/	/	1, 4, 6b, 7a, 10a, 17
Sekido 2019 (28)	Surgery Today	Japan	60	20.0%	60 (19–77)	/	1, 2, 6b, 7b, 10a, 17
Sugihara 2006 (7)	Dis Colon Rectum	Japan	1977	6.5%	/	/	1, 8, 11a, 12, 13, 14, 17
Wang 2019 (29)	Colorectal Disease	China	76	17.1%	54.33 ± 10.03	laparoscopy/open	1, 2, 4, 6b, 7a, 17

(Continued)

TABLE 1 Continued

Reference	Journal	Country	N	LPLN (+) rate	Age	Operation method	Outcome
Wang 2020 (30)	Journal of Gastrointestinal Surgery	Japan	215	18.6%	/	laparoscopy/open	1, 3, 4, 11a, 11b, 14, 17
Wu 2007 (31)	World Journal of Gastroenterology	China	96	14.6%	65 (25-86)	/	1, 2, 4, 9, 12, 14, 17
Yang 2021 (32)	Techniques in Coloproctology	China	77	28.6%	54 (25–89)	laparoscopy/open	1, 2, 3, 4, 6a, 7a, 10a, 10b, 11a, 11b, 17
Zhou 2021 (33)	BMC Surgery	China	73	20.5%	55.8 ± 10.4	laparoscopy/open	1, 2, 4, 5a, 7a, 11a, 12, 14, 15, 17

LPLN, lateral pelvic lymph node; Outcome: 1 gender, 2 age, 3 preoperative therapy, 4 pre-therapy CEA (ng/ml), 5a border irregularity of LPLN, 5b mixed signal intensity of LPLN, 6a Short axis before CRT (mm), 6b Short diameter after CRT (mm), 7a distance of the tumor from the anal verge (50mm), 7b distance of the tumor from the anal verge (40mm), 8 tumor location, 9 tumor size (mm), 10a cT, 10b cN, 10c cM, 11a pT, 11b pN, 12 lymphatic invasion, 13 MLNM: mesorectal lymph node metastasis, 14 venous invasion, 15 perineural invasion, 16 CRM, 17 differentiation.

consulted, and a discussion ensued until a consensus was reached. The following relevant information was extracted from all the included studies: reference, journal, country, number of patients, LPLN (+) rate, age, operation method and endpoints.

2.5 Study quality assessment

The quality of the enrolled studies was evaluated by two authors independently using the Newcastle Ottawa Scale (NOS), with a maximum of nine points per study (34). Studies with a score <6 were considered low-quality studies and excluded. For this systematic review, we adhered to the Meta-analysis of Observational Studies guidelines and the Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (35).

2.6 Statistical analysis

We used RevMan 5.4 software from the Cochrane Collaboration for all statistical analyses. Odds ratios (ORs) with 95% confidence intervals (CIs) were assessed to analyse dichotomous variables. p of Q test >0.1 and I^2 < 50% illustrated a lack of heterogeneity, and in this case, the pooled estimate was calculated by a fixed effects model. Otherwise, when p of Q test <0.1 or I^2 >50%, a random effects model was adopted. A leave-one-out sensitivity analysis was performed by excluding one study back and forth to confirm that our results were not driven by any single trial. Publication bias was assessed by visual inspection of the symmetry of a funnel plot. The level of significance was defined as p <0.05 (test for heterogeneity was set at p <0.1).

3 Results

3.1 Study selection and characteristics

The flow chart for the inclusion of articles is shown in Figure 1. A total of 24 studies were eventually included in the quantitative synthesis by screening databases through search strategies in advance (6, 7, 12–33). The baseline characteristics and lymph details of the studies are displayed in Table 1. A total of 24 retrospective articles with 5843 patients were included in this study, of which the LPLN-positive rate was between 6.5% and 51.6%. Most articles were reported in East Asia (12 in Japan, 5 in Korea, 4 in China and 1 in India), but 2 were reported in Western countries (1 in Sweden and the other in America). The NOS scores of the studies are displayed in Figure 2, and all studies scored 6 points or higher.

3.2 Outcomes of baseline characteristics

The outcomes are summarized in Figures 3A, B. For all outcomes, low statistical heterogeneity existed between the studies, and the fixed effects model was used. The pooled results showed a significantly higher risk of LPLN metastasis in females (OR: 1.28, 95% CI: 1.09-1.50, I^2 = 18%, P =0.003) and age <60 years (OR: 1.41, 95% CI: 1.01-1.97, I^2 = 5%, P =0.04).

3.3 Preoperative examination results

3.3.1 Pretherapy CEA level (ng/ml)

The outcome is listed in Figure 3C. No statistical heterogeneity existed between the studies; thus, the fixed effects model was used. Graphics demonstrated that a pretherapeutic CEA level >5 ng/ml was strongly associated with LPLN metastasis (OR: 1.55, 95% CI: 1.23-1.94, I^2 = 0%, P =0.0002).

3.3.2 Tumour border and signal characteristics on MRI

The outcomes are listed in Figures 3D and S1. Pooled results revealed a significantly higher risk of LPLN metastasis with border irregularity on MRI (OR: 4.84, 95% CI: 2.09-11.21, I^2 = 0%, P =0.0002). Regarding tumour signal characteristics, the random effects model was used due to obvious statistical heterogeneity, photographs seemed to not affect LPLN metastasis (OR: 3.98, 95% CI: 0.77-20.56, I^2 = 76%, P =0.10).

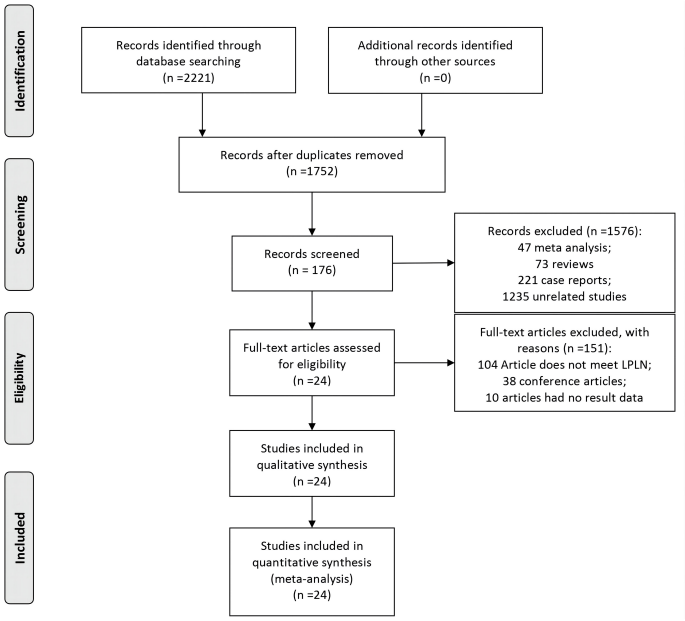

FIGURE 1
Inclusion and exclusion criteria chart.

3.3.3 SA of LPLN on MRI/CT (mm)

The outcomes are summarized in Figures 4A and S2. The fixed effects model was used because no statistical heterogeneity existed in the SA of LPLN ≥5 mm after nCRT, while the random effects model was used because obvious statistical heterogeneity existed in the SA of LPLN ≥8 mm before nCRT. Overall, the results showed that both SA of LPLN ≥5 mm after nCRT (OR: 17.93, 95% CI: 10.02-32.07, I^2 = 0%, P <0.00001) and SA of LPLN ≥8 mm before nCRT (OR: 9.33, 95% CI: 3.51-24.83, I^2 = 68%, P <0.00001) proved to be hazard factors for LPLN metastasis.

3.3.4 Tumour location and size

The outcomes are summarized in Figures 4B–D and 5A. The fixed effects model was used owing to low statistical heterogeneity. Overall, the results showed a significantly higher risk of LPLN metastasis in the distance of the tumour from the AV <50 mm (OR: 1.65, 95% CI: 1.17-2.31, I^2 = 0%, P =0.004) or ≤40 mm (OR: 2.72, 95% CI: 1.74-4.26, I^2 = 0%, P <0.0001), tumour centre located Rb (OR: 4.95, 95% CI: 3.18-7.71, I^2 = 0%, P <0.00001), and tumour size ≥50 mm (OR: 1.65, 95% CI: 1.23-2.21, I^2 = 39%, P =0.0009).

3.3.5 cTNM stage

The outcomes are summarized in Figures 5B, C and S3. The fixed effects model was used owing to low statistical heterogeneity. Pooled results revealed that both cT4 (OR: 1.56, 95% CI: 1.16-2.09, I^2 = 15%, P =0.003) and cM1 (OR: 3.64, 95% CI: 2.31-5.73, I^2 = 32%, P <0.00001) were hazard factors for LPLN metastasis. However, cN2-3 did not seem to affect LPLN metastasis (OR: 1.09, 95% CI: 0.61-1.93, I^2 = 0%, P =0.77).

3.4 Postoperative examination results

3.4.1 pTN stage

The outcomes are summarized in Figures S4, 5. The random effects model was used because obvious statistical heterogeneity existed in pT stage, while the fixed effects model was used because no statistical heterogeneity existed in pN stage. Overall, the results showed that both pT3-4 (OR: 2.81, 95% CI: 1.83-4.30, I^2 = 59%, P <0.00001) and pN2 (OR: 7.61, 95% CI: 4.88-11.85, I^2 = 0%, P <0.00001) were conspicuous hazard factors for LPLN metastasis.

3.4.2 Invasion

The outcomes are summarized in Figures 5D, 6A, B and S6. Regarding LI, MLNM and VI, the fixed effects model was used owing to low statistical heterogeneity. Overall, the results showed a significantly higher risk of LPLN metastasis in LI (OR: 4.02, 95% CI: 2.98-5.43, I^2 = 0%, P <0.00001), MLNM (OR: 6.20, 95% CI: 4.73-8.13, I^2 = 0%, P <0.00001) and VI (OR: 2.52, 95% CI: 1.93-3.29, I^2 = 18%, P <0.00001). While the random effects model was used because obvious statistical heterogeneity existed in the PI, photographs seemed to not affect LPLN metastasis (OR: 1.45, 95% CI: 0.86-2.45, I^2 = 56%, P =0.17).

3.4.3 Differentiation and CRM

The outcomes are summarized in Figures 6C, D. The fixed effects model was used owing to low statistical heterogeneity. Overall, the results showed a significantly higher risk of LPLN metastasis in poor differentiation (OR: 3.34, 95% CI: 2.62-4.26, I^2 = 22%, P <0.00001) and R1 (OR: 2.90, 95% CI: 1.13-7.40, I^2 = 7%,

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Reference	Selection	Comparability	Outcome	Score
Abe 2022	***	*	***	7
Dev 2018	***	**	***	8
E. Agger 2021	***	**	***	8
Fujita 2009	***	**	***	8
Hiyoshi 2019	***	**	***	8
Ishibe 2020	***	**	**	7
Iwasa 2021	***	**	***	8
Kawai 2021	***	*	**	6
Kim 2007	***	**	***	8
Kim 2018	***	**	***	8
Komori 2018	***	**	***	8
Lim 2013	***	**	**	7
Malakorn 2019	**	**	**	6
Nakanish 2020	***	**	***	8
Ogawa 2016	***	**	**	7
Oh 2014	***	**	***	8
Park 2018	***	**	**	7
Sekido 2019	***	**	***	8
Sugihara 2006	**	**	**	6
Wang 2019	***	**	***	8
Wang 2020	***	**	***	8
Wu 2007	***	**	***	8
Yang 2021	***	**	***	8
Zhou 2021	***	**	***	8

FIGURE 2
The NOS scores of studies. The * represent the various scores of the NOS scale.

P =0.03). The total valuable variables as possible risk factors for LPLN metastasis were summarized in Figure 7. The funnel plot of publication bias which included various indicators were listed in Figure 8.

4 Discussion

Surgical treatment is the main treatment for rectal cancer, in which radical resection and regional lymph node dissection are the key to success. The special drainage characteristics of rectal cancer lymph nodes determine the extent of lymph node dissection. The rectal lymphatic drainage area is distributed along the medial space of the obturator foramen of the internal iliac artery, and once metastasis occurs, it will spread upwards, laterally and downwards. It is worth noting that lateral lymph node metastasis is a metastatic pathway of low rectal cancer. Chemoradiotherapy has a poor effect and affects the prognosis of patients with rectal cancer. Previous literature has reported that LPLN metastasis is the main cause of LR in patients with LRC. Postoperative LR is a serious complication in patients with LRC that leads to pain, ureteral and intestinal obstruction, fistula and inflammation and significantly reduces the quality of life of patients. The prevention of LR is crucial because of the poor treatment effect when LR develops (36). Lateral lymph node metastasis is a common problem in the diagnosis and treatment of low rectal cancer, but there is still controversy between Eastern and Western scholars on whether TME should be combined with lateral lymph node dissection for middle and low rectal cancer (37). The studies and literature of Japanese scholars have confirmed that the effect of lateral lymph node dissection is affirmative, which can significantly reduce the local recurrence rate and significantly improve the 5-year survival rate. At present, lateral lymph node dissection has become a standard procedure in Japan. However, this procedure is not widely accepted in Western countries. The treatment for advanced rectal cancer in Europe and America is preoperative

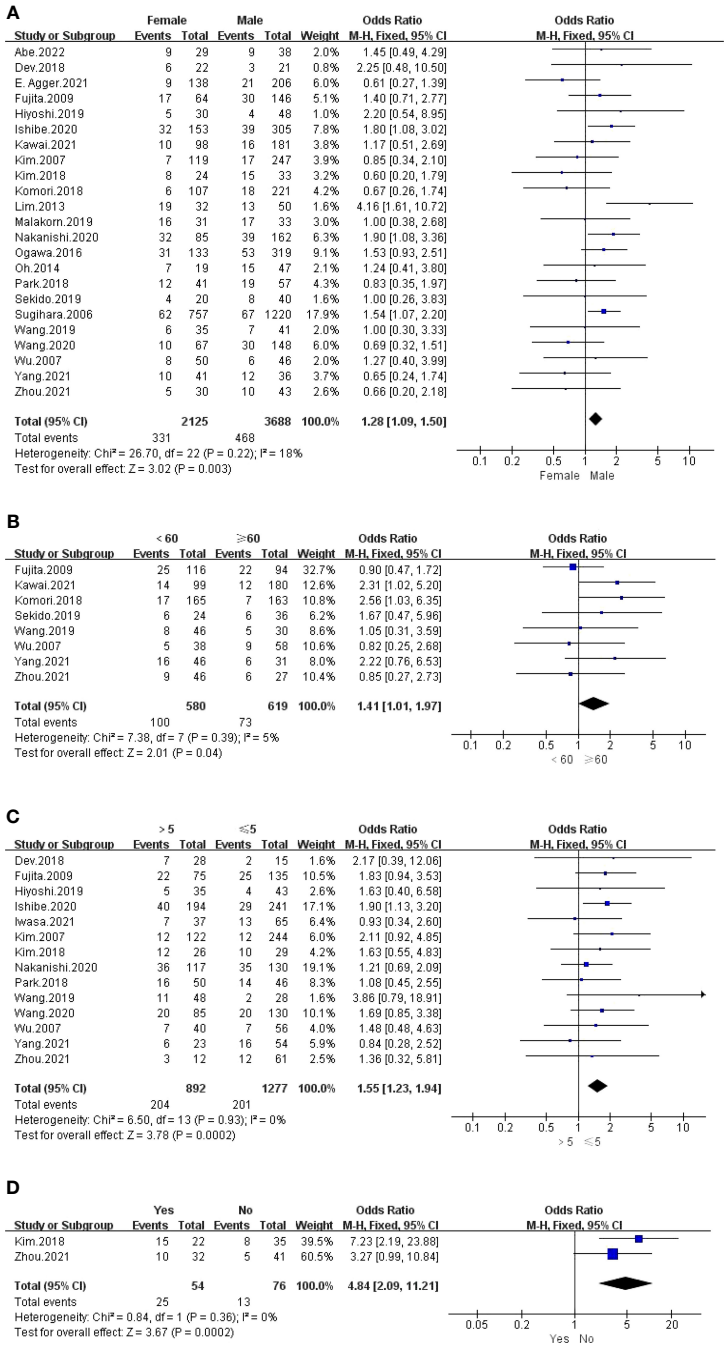

FIGURE 3
(A). Gender; **(B)** Age; **(C)** Pre-therapy CEA level; **(D)** Border irregularity of LPLN.

neoadjuvant chemoradiotherapy (nCRT)+TME as a standard treatment strategy based on the explanation that LPLN is considered to be a systemic disease as well as unresectable by the TME procedure alone (38). In addition, several studies have authenticated that nCRT can reduce the rate of local recurrence (39, 40). However, Ogura et al. refuted that it is still a problem with the treatment of nCRT before TME and cleared the lower proportion of local recurrence when TME was combined with LLND (41).

In recent years, on account of recognition of local disease rather than a systemic disease about LPLN (8, 42, 43), the Japanese Society for Cancer of the Colon and Rectum recommends the LLND procedure for advanced LRC, especially located below the peritoneal reflection (Rb), which is able to reduce the rate of LPLN metastasis (44), but complications such as longer operation time, higher blood loss and sexual dysfunction occur sequentially (8, 45–47). Consequently, the TME+LLND group was compared with the TME+nCRT group, and Kusters et al. found that the local

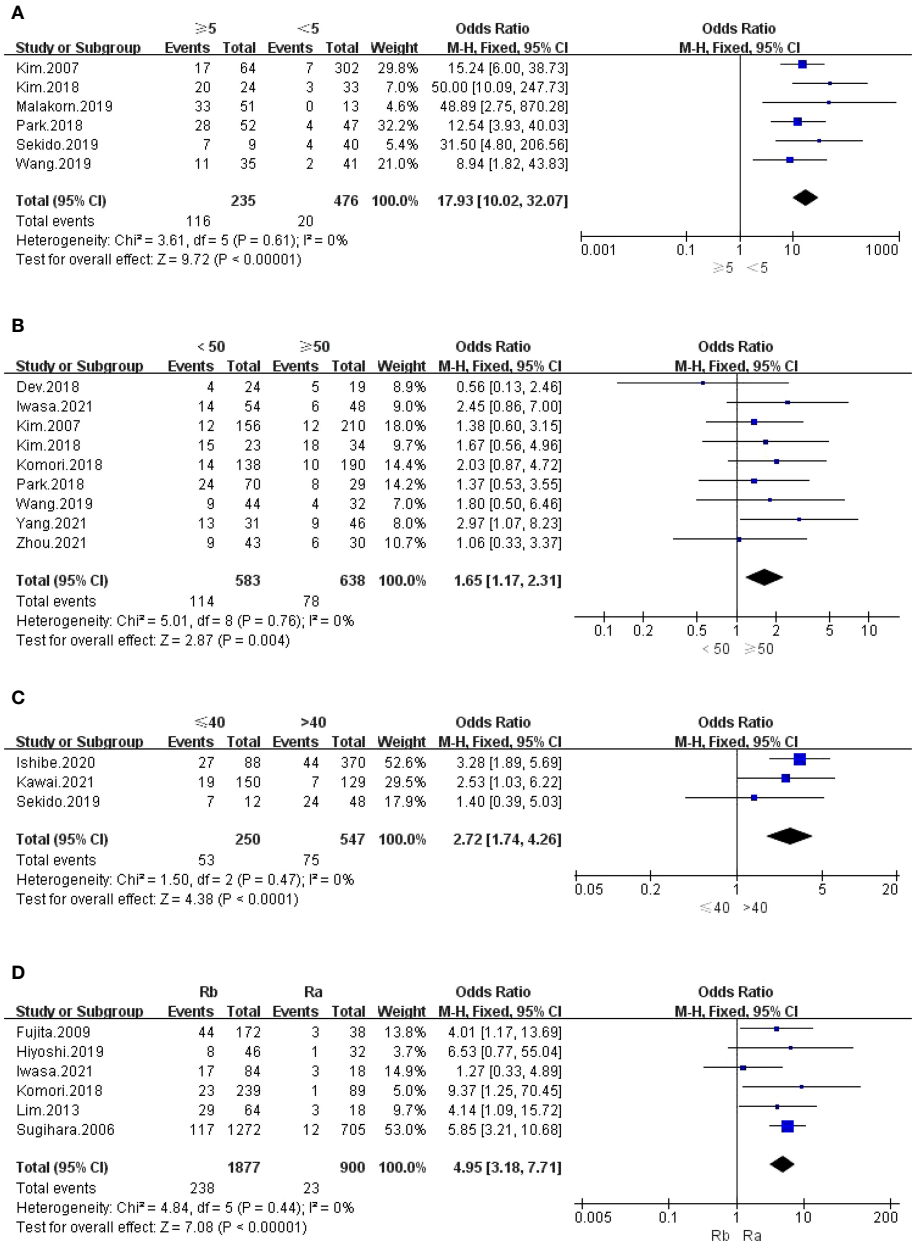

FIGURE 4
(A) LPLN ≥5mm after nCRT; **(B)** Distance of the tumor from the AV <50mm; **(C)** Distance of the tumor from the AV ≤40mm; **(D)** Tumor center located Rb.

recurrence rate in both groups was lower than that of the TME alone group, although there was no significant difference (48). In contrast, J.S. Williamson et al. supported the point of views that LLND, especially internal iliac lymph node metastasis, should be considered a resectable local disease and that enlarged lymph nodes that do not respond to nCRT should be surgically dissected (49).

We performed a meta-analysis to identify the risk factors for LPLN metastasis and to provide a more scientific and accurate evaluation index for lateral lymph node dissection. Our results showed that female sex, age <60 years, pretherapeutic CEA level >5 ng/ml, cT4, cM1, distance of the tumour from the AV <50 mm, tumour centre located Rb, SA of LPLN ≥8 mm before nCRT, SA of LPLN ≥5 mm after nCRT, border irregularity of LPLN, tumour size ≥50 mm, pT3-4, pN2, MLNM, LI, VI, CRM (+) and poor differentiation were risk factors for LPLN metastasis.

Similar to previous studies (42, 50, 51), our results showed that female sex was independently associated with LPLN metastasis, potentially owing to the anatomical difference between the male and female pelvis (52). Age <60 years was risk factor as well, because younger patients had the higher basal metabolic rate, and the faster the tumor progression, the higher rate of LPLN metastasis. In addition, a pretherapeutic CEA level >5 ng/ml was associated with LPLN metastasis as well.Elevated CEA levels often indicate a later tumour stage and a greater risk of lateral lymph node metastasis. Similarly, tumour size ≥50 mm was related to LPLN metastasis because the larger the tumour diameter, the greater the

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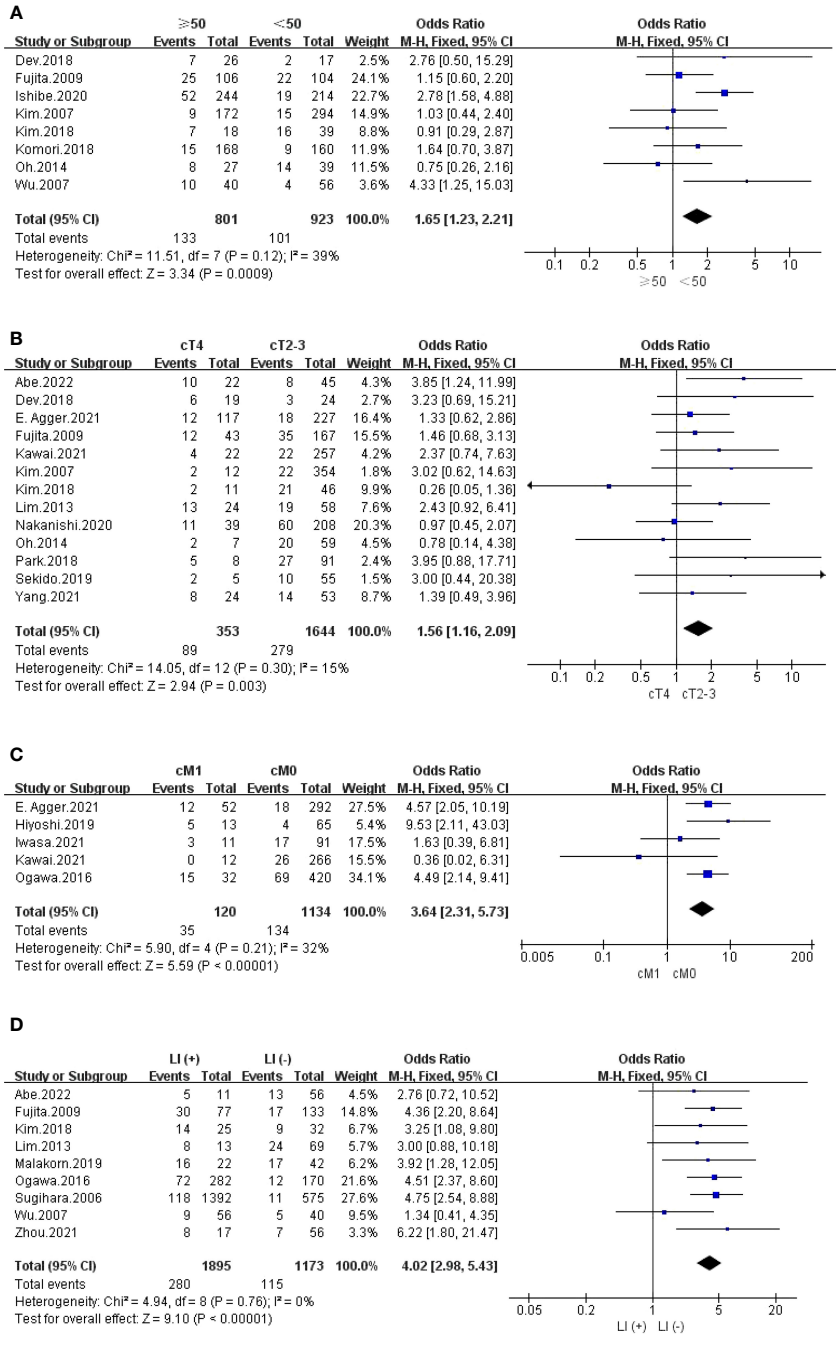

FIGURE 5
(A) Tumor size ≥50 mm; **(B)** cT4; **(C)** cM1; **(D)** LI.

depth of invasion, and the higher the probability of LPLN metastasis. Additionally, lower tumour location was also related to LPLN metastasis; however, no accurate standard was determined. Nine studies used AV =50 mm, while three studies used 40 mm as the critical level. The other 6 studies used peritoneal reentry as the cut-off. Anatomically, compared with the tumour centre located at the Ra, the lymphatic drainage of the tumour centre located at the Rb was more complex (53), In addition, the internal iliac and obturator lymph nodes were the most common LPLN metastasis pathways, which were located at the Rb (54, 55). The lower the tumour location, the more drainage to the lateral lymph node region, and thus the higher the probability of LPLN metastasis.

Several studies showed that there was no significant difference between the sensitivity and specificity of CT and MRI in the diagnosis of LPLN metastasis (21, 23). A SA of the LPLN ≥8 mm before CRT was a significant risk factor for LPLN metastasis; however, there was no standard for the selection of cut-off for lymph node diameter. Some studies increased the cut-off to 7 mm (25, 31, 41), which could fully delaminate transverse local recurrence (41). Fujita et al. even advanced the cut-off to 5 mm

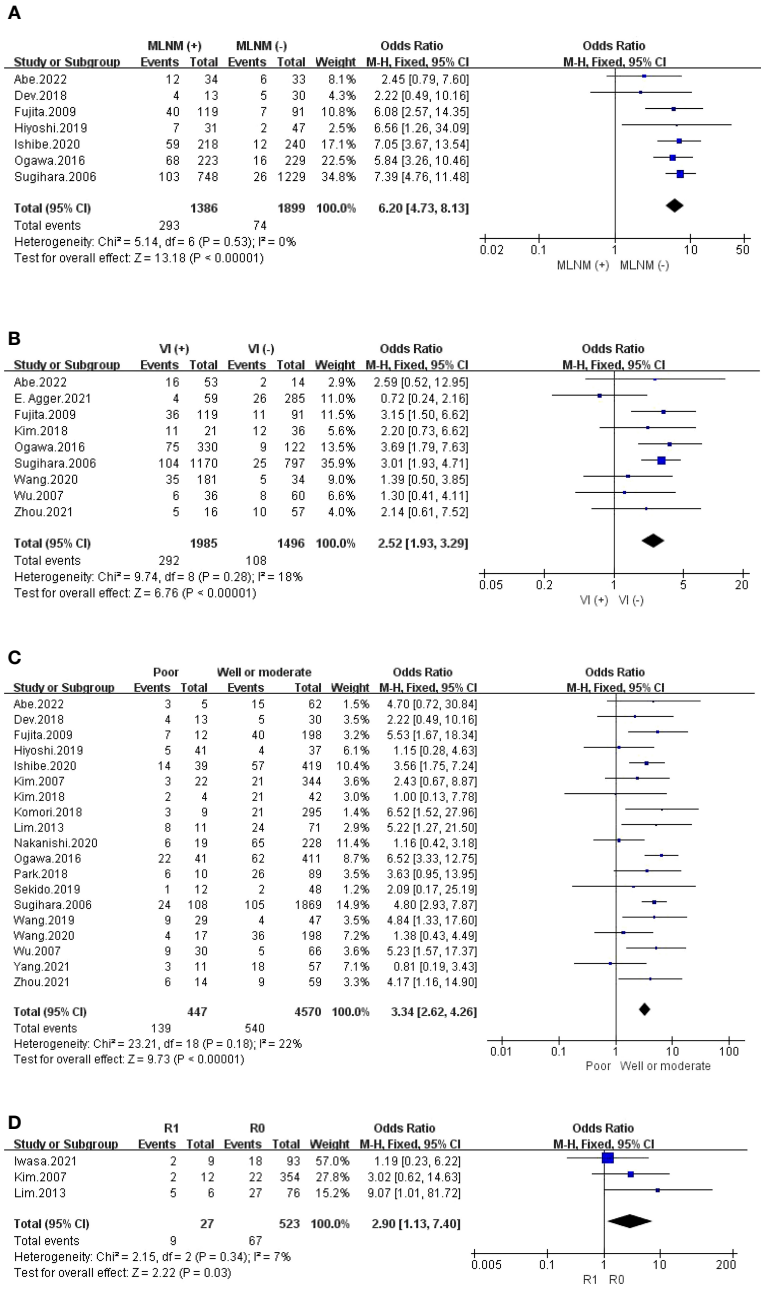

FIGURE 6
(A) MINM; **(B)** VI; **(C)** Differentiation; **(D)** CRM.

(23, 29). More researchers predicted the risk of LPLN metastasis through the ROC curve area, and the size of the lymph node corresponding to the largest area was selected as the cut-off (26, 27, 32, 52). Although the standard is not unified, most studies set the critical value of lymph node size before nCRT as 8 mm. The results of our data analysis support that a pre-CRT SA of LPLN ≥8 mm is a significant risk factor for LPLN metastasis. Similarly, our results also showed that the SA of LPLN ≥5 mm after nCRT was significantly related to LPLN metastasis. Most of the included articles suggested 5 mm as the cut-off, except that Kawai et al. suggested 8 mm (17) and Zhou et al. suggested 7 mm (15), because 100% sensitivity was observed for a size ≥ 5 mm after nCRT to predict LPLN metastasis (18). Therefore, a SA ≥5 mm in the remaining LPLN after nCRT should be one of the clear signals of LPLN metastasis. In general, both before and after nCRT, our results showed that LPLN enlargement was significantly related to LPLN metastasis. In addition to lymph node enlargement, the specific imaging features of lymph node metastasis are also very important. Notably, the morphology of lymph nodes on MRI showing irregular boundaries and mixed signal intensity is often suggestive of LPLN metastasis, and our analysis of results also demonstrates that the irregular boundaries of LPLN is risk factor for lateral lymph node metastasis, which is consistent with previous research results (56). Some studies even found that it could improve

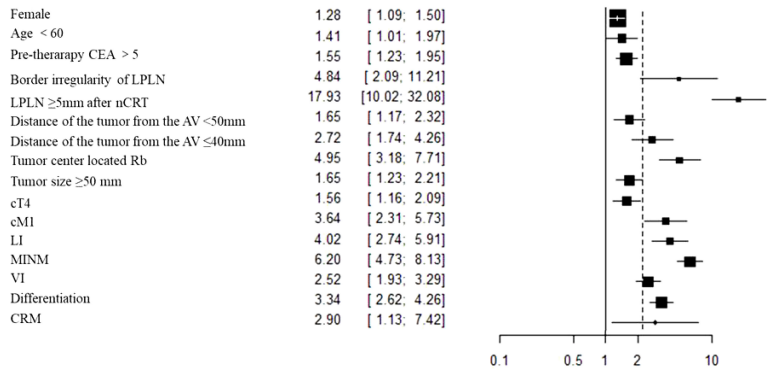

FIGURE 7
The total valuable variables as possible risk factors for LPLN metastasis.

the prediction ability of MRI for LPLN metastasis in place of lymph node size (57). Regarding the depth of cancer invasion, Wang et al. considered it an important indicator for LPLN metastasis assessed by preoperative diagnostic imaging (28). Our results showed that patients with cT4 stage were more likely to have LPLN metastasis than those with cT2-3 stage; equally, patients with cM1 stage were more prone to have LPLN metastasis than patients with cM0. Rectal lymphatic vessels arise from the lamina propria of the rectal mucosa in anatomy; thus, the percentage of lymph node metastasis is approximately 8-15% in patients with early RC (58, 59). When the tumour invades the submucosa, cancer cells have more opportunity to spread through the lymphatic vessels, leading to LPLN metastasis. In addition, the deeper the infiltration, the higher the probability of LPLN metastasis. The overall study shows that the risk of LPLN metastasis is closely related to the clinical stage of the tumour, and the later the clinical stage of the tumour, the higher the risk of LPLN metastasis.

Current studies have shown that lymphatic, venous and perineural invasions are risk factors for LR of RC, with 1 recurrence confirmed by histopathological examination in every 4 to 5 patients (60, 61). Our results showed that LI (including MLNM) and VI were strong predictors of LPLN metastasis. It is clear that LI (including MLNM) and VI indicate a later stage of the tumor and an increased risk of lateral lymph node metastasis. In addition, compared with well or moderate differentiation, our results showed that poor differentiation was a risk factor for LPLN metastasis. It is obvious that poorly differentiated carcinoma has stronger invasive and metastatic abilities and is more likely to have distant metastasis, so poorly differentiated RC is more likely to have lateral lymph node metastasis. Echoing previous reports, compared with tubular and papillary adenocarcinoma, mucinous and signet ring adenocarcinoma that did not respond to radiotherapy had a higher probability of LPLN metastasis (3, 7, 62). In addition, we also analysed whether a positive circumferential margin was a risk factor for LPLN metastasis. The results showed that a positive circumferential margin (R1) was also a risk factor for LPLN metastasis. It was obvious that RC patients with R1 were often in a later clinical stage and more likely to develop lateral lymph node metastasis.

Currently, more methods of predicting LPLN metastasis are being developed. However, it is necessary to explore better techniques to help surgeons make more accurate judgements. Dev et al. proposed a risk stratification nomogram based on important predictors of LPLN metastasis to comprehensively evaluate and guide treatment (20). Miyake et al. used a novel one-step nucleic acid amplification (OSNA) assay to calculate LPLN metastasis targeting lymph node micrometastasis with 100% sensitivity and 86% specificity, which was significantly higher than that of CT and MRI (63). Iwasa et al. proved that the presence of the middle rectal artery (MRA) assessed by ceMRI could accurately predict bilateral LPLN metastasis (including micrometastasis) (25). Abe et al. proved that extramural venous invasion on MRI (MRI-EMVI) was independently related to LPLN metastasis and proposed that it could more accurately predict LPLN metastasis combined with lymph node size (12). As we mentioned above, treatments for LPLN metastasis of LRC differ between eastern and western countries. We supported that combining the advantages of both treatments, developing strengths and avoiding weaknesses, may achieve an unprecedented effect. We recommend patients with the following risk factors: Age <60 years, female, elevated CEA level, large tumor volume, low distance from anal margin, enlarged lymph nodes with irregular enhancement (especially SA of LPLN ≥8 mm before nCRT, SA of LPLN ≥5 mm after nCRT), pT 3 - 4, pN 2 can be given priority to comprehensive treatment including lateral lymph node dissection. Other low-risk factors can be carefully performed lateral lymph node dissection to avoid complications and trauma caused by lateral lymph node dissection. There were some limitations in our study. First, most of the articles included were retrospective studies. Second, except for two articles from Western countries (America and Switzerland), the rest were from Eastern countries, which might have caused our research to be slightly biased towards the Eastern perspective.

5 Conclusion

Our studies proved that female sex, age <60 years, pretherapeutic CEA level >5 ng/ml, cT4, cM1, distance of the tumour from the AV <50 mm, tumour centre located Rb, SA of

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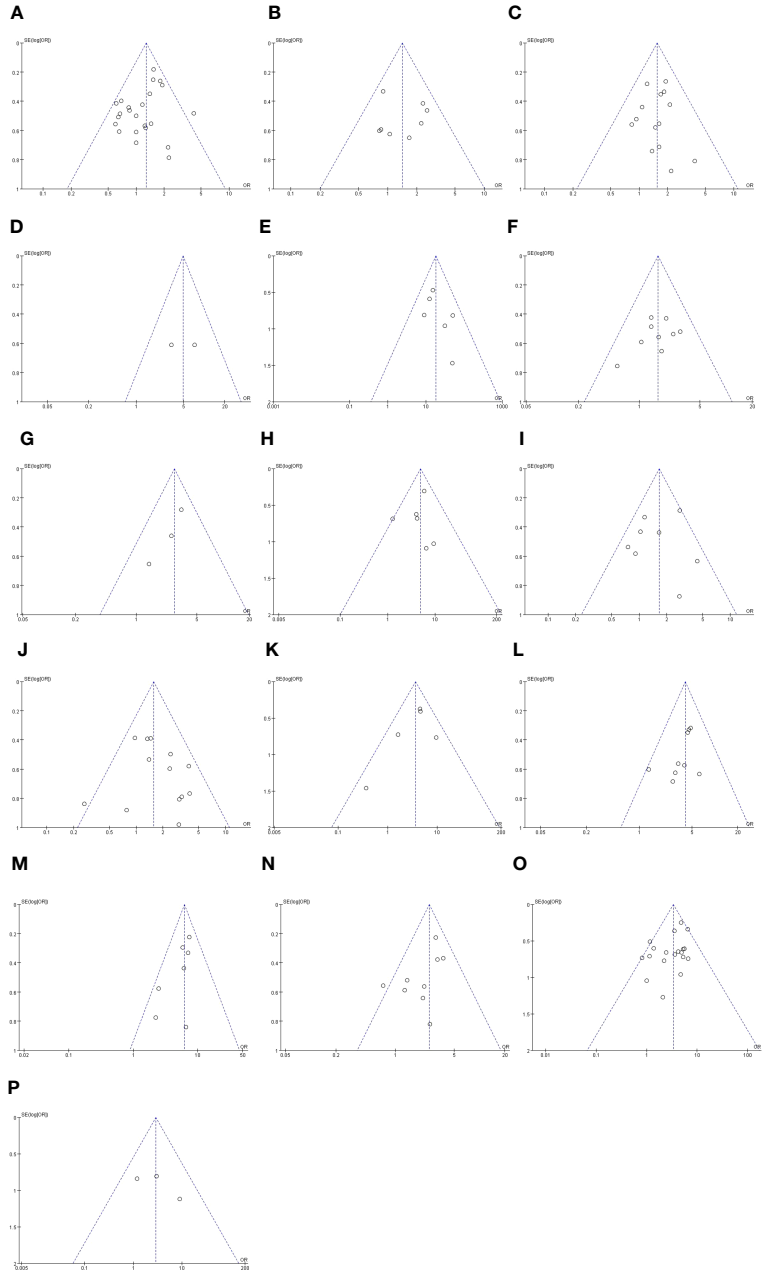

FIGURE 8
Funnel plot of publication bias in the meta-analysis. **(A)** Gender. **(B)** Age **(C)** Pre-therapy CEA level. **(D)** Border irregularity of LPLN. **(E)** SA of LPLN ≥5mm after nCRT. **(F)** The distance of the tumor from the AV <50mm. **(G)** The distance of the tumor from the AV ≤40mm. **(H)** Tumor center located Rb. **(I)** Tumor size ≥50 mm. **(J)** cT. **(K)** cM. **(L)** LI. **(M)** MLNM. **(N)** VI. **(O)** Differentiation. **(P)** CRM.

LPLN ≥8 mm before nCRT, SA of LPLN ≥5 mm after nCRT, border irregularity of LPLN, tumour size ≥50 mm, pT3-4, pN2, MLNM, LI, VI, CRM (+) and poor differentiation were risk factors for LPLN metastasis. In conclusion, although lateral lymph node dissection can reduce the local recurrence rate, increase the number of lymph nodes harvested, and achieve more accurate assessment of rectal cancer, it also has the risk of increasing surgery-related complications. Whether to perform lateral lymph node dissection in clinical practice can be judged in combination with the above risk factors so that patients with rectal cancer who need lateral lymph node dissection can be accurately screened out to reduce the risk of unnecessary surgical trauma. According to the risk factors of lateral lymph node metastasis, we can adopt different comprehensive treatment strategies. High-risk patients can perform lateral lymph node dissection to effectively reduce local recurrence; In low-risk patients, we can avoid overtreatment,

reduce complications and trauma caused by lateral lymph node dissection, and maximize patient survival and quality of life.

Data availability statement

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

Author contributions

D-xZ, ZY, and LT acquisition of data, analysis and interpretation of data, and drafting the article; M-nR and Z-lL collect and organize data, and revising the article; J-wX conception and design of the study, and critical revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1219608/full#supplementary-material

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Treatment for T1 colorectal cancers substratified by site and size: "horses for courses"

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Background: Owing to advances in diagnostic technology, the diagnosis of T1 colorectal cancers (CRCs) continues to increase. However, the optimal management of T1 CRCs in the Western Hemisphere remains unclear due to limited population-based data directly comparing the efficacy of endoscopic therapy (ET) and surgical resection (SR). The purpose of this study was to report outcome data from a large Western cohort of patients who underwent ET or SR for early CRCs.

Methods: The SEER-18 database was used to identify patients with T1 CRCs diagnosed from 2004 to 2018 treated with ET or SR. Multivariable logistic regression models were employed to identify variables related to lymph node metastasis (LNM). Rates of ET and 1-year relative survival were calculated for each year. Effect of ET or SR on overall survival and cancer-specific survival was compared using Kaplan–Meier method stratified by tumor size and site.

Results: A total of 28,430 T1 CRCs patients were identified from 2004 to 2018 in US, with 22.7% undergoing ET and 77.3% undergoing SR. The incidence of T1 CRCs was 6.15 per 100,000 person-years, with male patients having a higher incidence. Left-sided colon was the most frequent location of tumors. The utilization of ET increased significantly from 2004 to 2018, with no significant change in 1-year relative survival rate. Predictors of LNM were age at diagnosis, sex, race, tumor size, histology, grade, and location. The 5-year relative survival rates were 91.4 and 95.4% for ET and SR, respectively. Subgroup analysis showed that OS and CSS were similar between ET and SR in T1N0M0 left-sided colon cancers with tumors 2 cm or less and in rectal cancers with tumors 1 cm or less.

Conclusion: Our study showed that ET was feasible and safe for patients with left-sided T1N0M0 colon cancers and tumors of 2 cm or less, as well as T1N0M0 rectal cancers and tumors of 1 cm or less. Therefore, the over- and under-use of ET should be avoided by carefully selecting patients based on tumor size and site.

KEYWORDS

T1 colorectal cancers, characteristics, lymph node metastasis, survival, endoscopic therapy, surgical resection

1. Introduction

Colorectal cancers (CRCs) rank as the fourth most frequently diagnosed cancer and second leading cause of cancer-related death overall. An estimated 153,020 people in the United States will be diagnosed with CRCs and it will result in the death of 52,550 individuals as of 2023 (1). Although the incidence of CRCs has remained stable or decreased in highly developed countries over the last several decades, recent advances in screening and diagnostic technologies have led to an increase in the detection of early-stage CRCs, including tumors classified as T1 (2). The current treatment options for T1 CRCs include surgical resection (SR) and endoscopic therapy (ET). SR has traditionally been the mainstay of curative intent treatment, but ET is being increasingly adopted for patients with superficial CRCs due to its advantages in reducing treatment-related adverse events, compared to colorectal surgery in clinical practice, especially in the elderly pupulation (3, 4). Several studies have demonstrated that endoscopic removal of tumors is both feasible and suitable for many T1 cancers (5–8). However, ET is technically and clinically challenging due to the varied risks of lymph node metastasis (LNM) among T1 CRCs. Approximately 10% of T1 diseases are found to have LNM at the time of diagnosis, and these patients are candidates for radical surgery. For the remaining patients, endoscopic removal is considered sufficient owing to the low risk of LNM. Moreover, the characteristics of colorectal lesions, such as tumor size, location, and histology, may affect the optimal removal method. Therefore, comparing the long-term survival outcomes of ET and SR is crucial for determining the optimal treatment for T1 CRCs. However, there is a lack of population-based studies that have examined the outcomes of ET versus SR among patients with T1 CRCs in the United States.

Early-stage CRCs present several unresolved clinical questions, including the optimal treatment for T1N0M0 CRCs, which is currently unclear due to the limited population-based data comparing the efficacy of ET and SR in Western hemisphere. Therefore, our study aims to evaluate the relative prevalence, demographics, tumor characteristics, treatment, and survival of patients with T1 CRCs in the United States. In addition, we will analyze the effectiveness of ET versus SR in treating T1 CRCs stratified by tumor size and location.

Methods

Data source and patient population

The Surveillance, Epidemiology, and End Results (SEER)-18 registries were used to identify patients with T1 CRCs diagnosed between 2004 and 2018, based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The institutional review board of Qingdao municipal hospital deemed this cohort study exempt from review and informed consent requirement as the data was deidentified and publicly available. And the work has been reported in line with the STROCSS criteria (9).

Patients were then divided into two groups according to their surgical approach used: ET group and SR group. Other studied variables included patient demographic and clinical characteristics. Patient race was coded as white, black, and other. Age at diagnosis was categorized into two groups of <50 years and ≥ 50 years. This age threshold allows us to better capture the disparities in disease characteristics and outcomes between early-onset and late-onset CRCs in our analysis. Tumor characteristics included tumor grade (well-differentiated and poorly-differentiated), size (≤1 cm, ≤2 cm, ≤3 cm, and > 3 cm), histology (adenocarcinoma, mucous, and other), lymph node status (positive and negative), and tumor location (right-sided colon, left-sided colon, and rectum). The primary endpoints were OS and CSS. Patients were excluded if showed a distant metastasis at baseline. And those lacking data on tumor size, surgery, or survival were also not include in our study.

Statistical analysis

Using the SEER*Stat statistical software, we calculated age-adjusted incidence rates for patients with T1 CRCs overall and specific to sex (male and female) and age groups (0–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥ 85) from 2004 to 2018. All incidence rates were standardized to the 2000 US standard population and reported per 100,000 person-years. Categorical variables were reported as frequency and percentage, and the distribution of variables between groups were analyzed using χ^2 or Fisher exact tests. Univariate and multivariate logistic regression models were utilized to identify factors associated with lymph node metastasis in T1 CRCs patients. The rates of ET utilization in patients were calculated for each year during the study period of 2004 to 2018. Differences in survival outcomes between ET and SR groups were examined using Kaplan–Meier method with log-rank test. To investigate the effect of surgical approaches on patient survival based on tumor characteristics, we conducted a subgroup analysis stratified by tumor size and site (right-sided colon, left-sided colon, and rectum). Two-sided p values and 95% CIs were reported, and $p < 0.05$ was considered as having statistical significance. All statistical analyses were performed by SPSS, version 22.0 and R, version 4.1.1.

2. Results

2.1. Patient characteristics and incidence

After rigorous screening of patients based on inclusion and exclusion criteria, we identified 28,430 eligible patients with T1 CRCs from 2004 to 2018 in the US. Among them, 51.9% were male and the mean age was 64.1 years (SD: 12.6). The majority of patients were White individuals (76.3%) and non-Hispanic (89.7%). LNM was present in only 9.6% of cases. Among these patients, 22.5% underwent ET and 77.5% underwent SR for the tumor. Table 1 shows the detailed demographic and clinical characteristics of all enrolled patients. The overall age-adjusted incidence of T1 CRCs from 2004 to 2018 was 6.15 per 100,000 person-years (Figure 1). Male patients had a higher incidence of T1 CRCs than female patients (7.22 vs. 5.26 per 100,000 person-years). The incidence increased with age, with the highest incidence occurring between 80–84 years old for both male and female patients.

Tumor characteristics and treatment

The number of T1 CRCs patients increased with year synchronously in males and females, with the most pronounced

TABLE 1 Characteristics and survival of patients with T1 CRC between 2004 and 2018.

Variables	No. of patients (%)
Age (years)	
<50	2841 (10.0)
≥50	25589 (90.0)
Mean, y (SD)	64.1 (12.6)
Sex	
Male	14763 (51.9)
Female	13667 (48.1)
Race	
White	21699 (76.3)
Black	3426 (12.1)
Other	3305 (11.6)
Ethnicity	
Non-Hispanic	25504 (89.7)
Hispanic	2926 (10.3)
Marital status	
Married	16539 (58.2)
Other	11891 (41.8)
Year of diagnosis	
2004–2008	7431 (26.1)
2009–2013	9043 (31.8)
2014–2018	11956 (42.1)
Tumor size	
≤ 1 cm	11848 (41.7)
≤ 2 cm	8197 (28.8)
≤ 3 cm	4356 (15.3)
> 3 cm	4029 (13.2)
Histology	
Adenocarcinoma	27616 (97.1)
Mucous	653 (2.3)
Other	161 (0.6)
Grade	
Well differentiated	26382 (92.8)
Poorly differentiated	2048 (7.2)
Location	
Right-sided colon	9771 (34.4)
Left-sided colon	10732 (37.7)
Rectum	7927 (27.9)
Lymph node metastasis	
No	25696 (90.4)
Yes	2734 (9.6)
Surgery	
ET	6403 (22.5)
SR	22027 (77.5)
Chemotherapy	
No	25501 (89.7)
Yes	2929 (10.3)
Radiation	
No	26950 (94.8)
Yes	1480 (5.2)
Overall survival	
Mean (95% CI)	137.8 (136.9–138.7)

CRC, colorectal cancer; CI, confidence interval.

increase appearing in tumors that were 1 cm or smaller (Figure 2A). Most tumors diagnosed were well-differentiated (92.8%), while the remaining 7.2% were poorly differentiated (Table 1). The left-sided colon was the most common location of tumors (37.7%), followed by the right-sided colon (34.4%) and rectum (27.9%). Figure 2 illustrates the trends in tumor size, differentiation, location, and LNM over the study period from 2004 to 2018. The proportion of patients with LNM remained relatively constant throughout the study period. However, there was a significant increase in the percentage of patients receiving ET during the follow-up period, from 14.7% in 2004 to 35.3% in 2018. Despite this, there was no significant change in the 1-year relative survival rate of T1 CRCs patients between 2004 and 2018 (Figure 3). These findings suggest that ET is increasingly being used as a treatment option for T1 CRCs patients.

Predictors of LNM

There were 2734 out of 28487 patients (9.6%) with T1 CRCs who were found to have LNM. The odds of LNM in patients with T1 CRCs were analyzed by a logistic regression model. Factors associated with LNM in multivariate analysis were age at diagnosis [≥50 (OR: 0.68, 95%CI: 0.60–0.77, $p < 0.001$)], sex [male (OR: 0.86, 95%CI: 0.80–0.94, $p < 0.001$)], race [Black (OR: 1.19, 95%CI: 1.05–1.34, $p = 0.005$)], tumor size [size≤2 cm (OR: 1.64, 95%CI: 1.48–1.82, $p < 0.001$), size≤3 cm (OR: 1.73, 95%CI: 1.53–1.95, $p < 0.001$), size>3 cm (OR: 2.25, 95%CI: 2.01–2.53, $p < 0.001$)], histology [mucous (OR: 1.86, 95%CI: 1.52–2.29, $p < 0.001$)], tumor grade (OR: 2.46, 95%CI: 2.18–2.77, $p < 0.001$), and location [left-sided colon (OR: 1.39, 95%CI: 1.27–1.53, $p < 0.001$)] (Table 2).

2.2. Survival

The 5-year relative survival (RS) rates for T1 CRCs were 91.4 and 95.4% for patients who underwent ET and SR, respectively, while the 5-year cause-specific survival (CSS) rates were 94.6% for both groups (Figure 4).

2.3. Subgroup analysis according to tumor size

The study included 25696 patients with T1N0M0 CRCs, classified into four groups based on tumor size: T ≤ 1 cm ($n = 11056$), 1 cm < T ≤ 2 cm ($n = 7304$), 2 cm < T ≤ 3 cm ($n = 3865$), and > 3 cm ($n = 3471$). The baseline characteristics of all patients, stratified by treatment group, are presented in Table 3. Significant differences were observed in all clinical features between these two cohorts. As expected, patients with small (≤1 cm) and rectal cancer were more likely to receive ET. During the follow-up period, there were 1005 deaths among the 6403 patients in the ET group and 3996 deaths among the 19293 patients in the SR group. To determine the effect of ET on OS and CSS, we analyzed the survival outcomes using the Kaplan–Meier method (Figure 5). Our analysis revealed that OS was comparable between patients who received ET and SR for tumors 2 cm or less (1 cm < T ≤ 2 cm: HR, 0.90, 95%CI, 0.79–1.03, $p = 0.120$; ≤1 cm: HR, 0.97, 95%CI, 0.87–1.08, $p = 0.540$), but SR was associated with

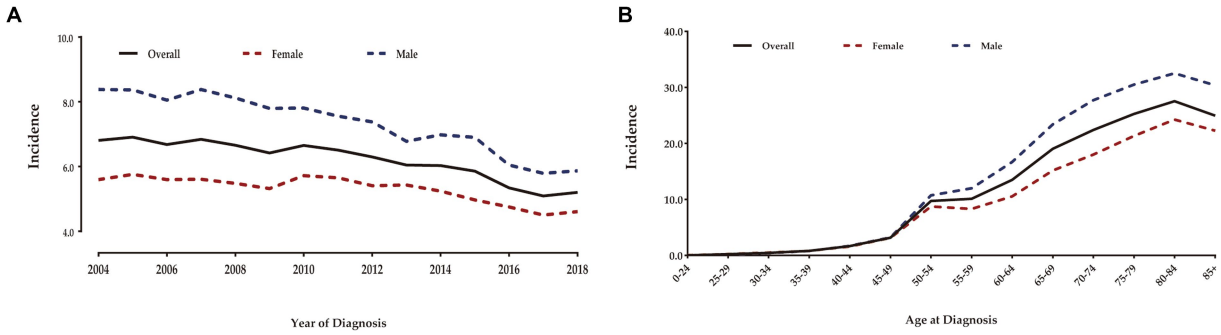

FIGURE 1
Annual age-adjusted incidence of patients with T1 CRCs in US (Per 100,000 person-years) **(A)**. Age-wise incidence of patients with T1 CRCs in US **(B)**.

significantly better OS in tumors larger than 2 cm (>3 cm: HR, 0.69, 95%CI, 0.57–0.83, $p < 0.001$; 2 cm < T ≤ 3 cm: HR, 0.75, 95%CI, 0.63–0.89, $p = 0.001$). Meanwhile, for CSS, there was no significant difference between ET and SR in tumors 1 cm or less (HR, 0.94, 95%CI, 0.75–1.18, $p = 0.610$), but SR was associated with better CSS in patients with tumors larger than 1 cm (>3 cm: HR, 0.65, 95%CI, 0.47–0.90, $p = 0.008$; 2 cm < T ≤ 3 cm: HR, 0.52, 95%CI, 0.38–0.71, $p < 0.001$; 1 cm < T ≤ 2 cm: HR, 0.70, 95%CI, 0.55–0.91, $p = 0.006$).

Subgroup analysis according to tumor site

Table 4 presents the 3-year OS and CSS rates of patients with T1N0M0 CRCs categorized by tumor location. The results of the site-specific analysis indicate that for patients with left-sided colon cancer and tumors 2 cm or less, as well as for patients with rectal cancer and tumors 1 cm or less, the survival outcomes including OS and CSS were similar between ET and SR treatment options.

Discussion

Our study provides a comprehensive analysis on the topic of T1 CRCs, including examining the epidemiology, clinicopathologic characteristics, treatment, and survival from 2004 to 2018 in the United States. To the best of our knowledge, this study is the first to explore two key aspects of T1 CRCs using the SEER-18 database: (1) the epidemiology of T1 CRCs and (2) the subclassifications of treatment modalities for T1N0M0 CRCs based on tumor size and site. We found that the incidence of T1 CRCs was 6.15 per 100,000 person-years, with higher rates observed in males than females (7.22 vs. 5.26 per 100,000 person-years). Incidence increased with age and peaked between ages 80–84 for both genders. Additionally, 9.6% of the patients were found to have LNM. Factors associated with LNM in multivariate analysis were age at diagnosis, sex, race, tumor size, histology, tumor grade, and location. Our findings also suggest an increasing trend in the use of ET as a treatment option for T1 CRCs patients. However, subgroup analysis according to tumor size and site demonstrates that ET was associated with similar survival outcomes to SR only in T1N0M0 patients with left-sided colon cancer and tumors 2 cm or less or in patients with rectal cancer and tumors 1 cm or less.

With the advancement of colonoscopic techniques, endoscopic removal of neoplasms has become one of the preferred treatments for T1 disease. However, the presence of LNM is a crucial factor in determining the feasibility and suitability of ET, as it is only safe for patients in the absence of nodal metastasis. Our study found that LNM occurred in 9.6% of T1 CRCs patients, consistent with previous studies, indicating that nearly 90% of this population can benefit from ET (10–12). Identifying those at low risk of LNM could help balance the potential risks and benefits of ET for treating early-stage CRCs. Multivariable analyses in our study revealed that age, sex, race, tumor size, histology, tumor differentiation, and location were significantly associated with LNM in patients with submucosal invasive CRCs. This information can be used to make evidence-based decisions regarding active surveillance or additional radical resection following endoscopic resection. While previous studies have identified several pathological high-risk features, such as deep submucosal invasion, lymphovascular invasion, positive resection margin, and tumor budding, as predictors of presence of LNM in early CRCs, our study could not investigate these factors due to limitations of the SEER database (13–15). Accurately evaluating the risk of LNM is critical in determining whether further radical resection is necessary for patients who have undergone ET. Kudo et al. developed an algorithm using artificial intelligence that includes patients' age, tumor size, grade, location, lymphatic invasion, and vascular invasion to identify those with T1 CRCs who are at higher risk for LNM (16). This model could help in providing appropriate care without excess or deficient treatment for patients. Future studies should investigate the associations between patient characteristics and LNM to provide more comprehensive guidance for clinical decision-making.

Our study also found a significant increase in the use of ET for T1 CRCs in US from 2004 to 2018, with utilization rates rising from 14.7 to 35.3%. This trend may reflect the growing acceptance of ET as a feasible alternative to SR for treating early-stage invasive CRCs, likely driven by improving endoscopic techniques as well as the higher incidence of T1 disease as a result of population-based screening programs. Similar trends have been observed in the treatment of early-stage esophageal and gastric cancers (17, 18). Considering the increasing detection of CRCs at early stages, we are not surprised to find that the utilization of endoscopic removal for tumors will continue to rise in the future.

Most published studies on the outcomes of ET versus SR for early gastrointestinal cancers have been conducted in Asian countries

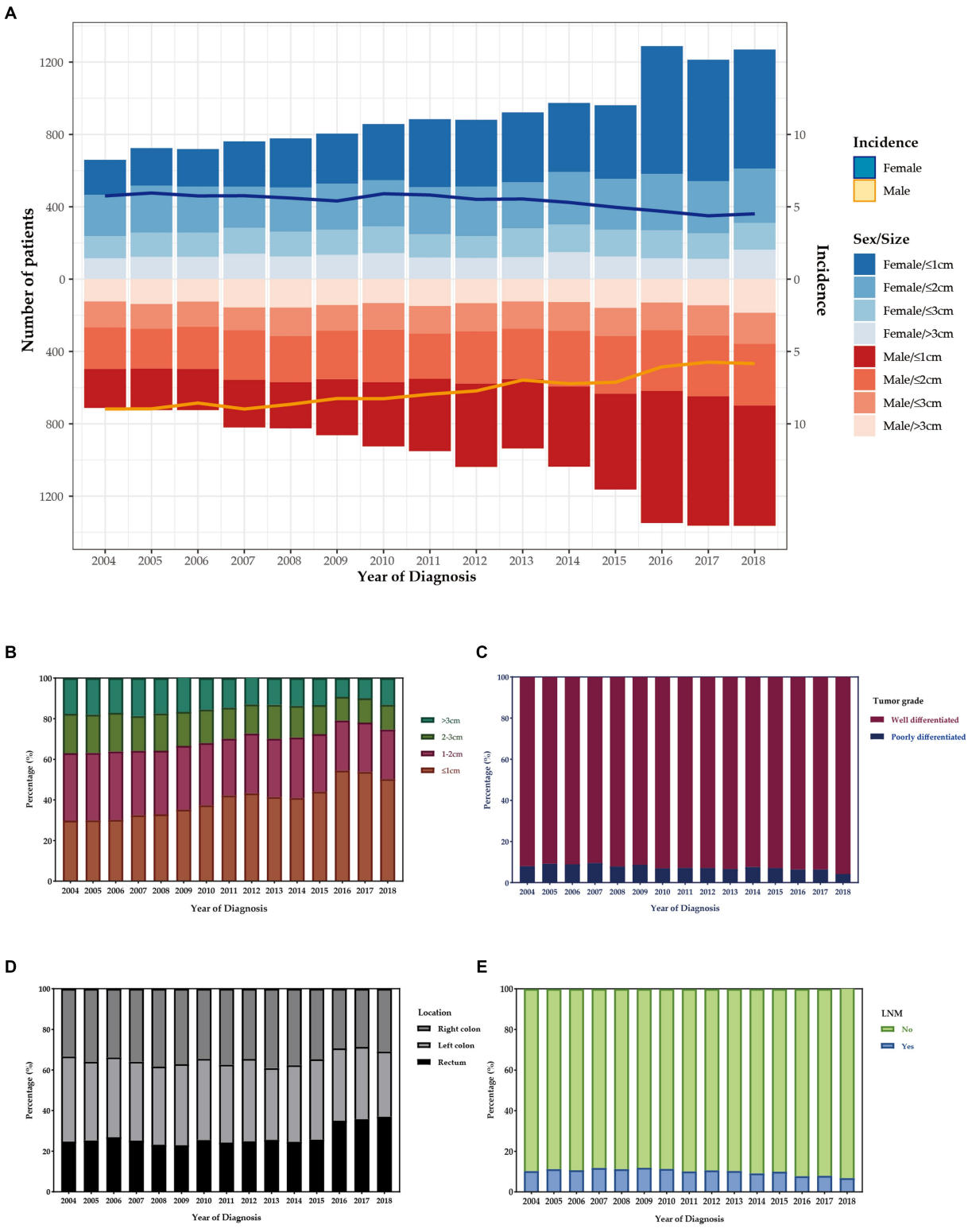

FIGURE 2
(A) The age distribution of cases with T1 CRCs from 2004 to 2018 in US. The bar was the number of cases in females and males, and the line with 95% CI represents age-adjusted incidence. Trends of distribution in tumor size **(B)**, differentiation **(C)**, location **(D)**, and LNM **(E)** over the study period.

(19–22). Therefore, it is essential to validate these findings in the Western population. Our study, based on a population-based registry from US, suggests that ET may be a promising treatment option for T1N0M0 left-sided colon cancers of 2 cm or less and T1N0M0 rectal cancers of 1 cm or less. A systematic review and meta-analysis by Yeh et al. involving 17 studies and 19,979 patients with colorectal cancers

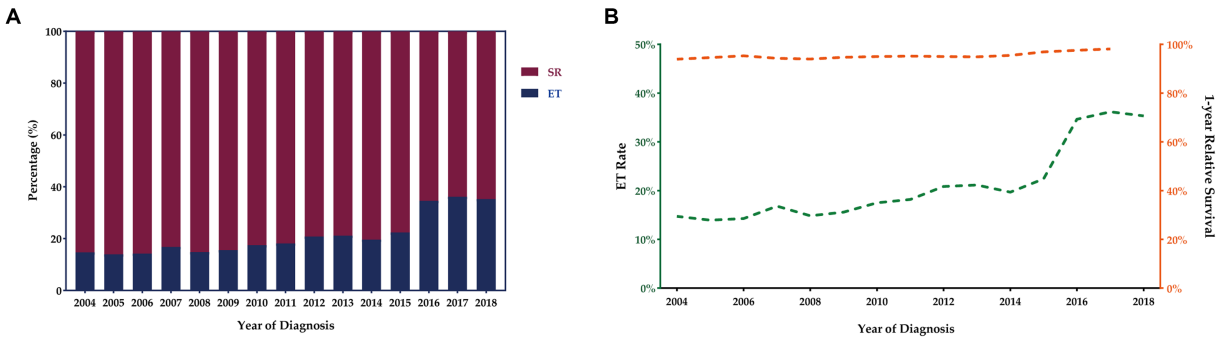

FIGURE 3
Trends in treatment modalities for T1 CRCs in US from 2004 to 2018 **(A)**. ET rates and 1-year relative survival rate for patients with T1 CRCs from 2004 to 2018 **(B)**.

TABLE 2 Factors associated with LNM among patients with T1 CRCs.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
< 50	Ref		Ref	
≥ 50	0.67 (0.59, 0.75)	**<0.001**	0.68 (0.60, 0.77)	**<0.001**
Sex				
Female	Ref		Ref	
Male	0.86 (0.80, 0.93)	**<0.001**	0.86 (0.80, 0.94)	**<0.001**
Race				
White	Ref		Ref	
Black	1.15 (1.03, 1.30)	**0.017**	1.19 (1.05, 1.34)	**0.005**
Other	1.04 (0.92, 1.17)	0.560	1.08 (0.95, 1.22)	0.256
Ethnicity				
Non-Hispanic	Ref			
Hispanic	1.00 (0.88, 1.14)	0.967		
Tumor size				
≤ 1 cm	Ref		Ref	
≤ 2 cm	1.71 (1.54, 1.89)	**<0.001**	1.64 (1.48, 1.82)	**<0.001**
≤ 3 cm	1.77 (1.58, 2.00)	**<0.001**	1.73(1.53, 1.95)	**<0.001**
> 3 cm	2.24 (2.00, 2.52)	**<0.001**	2.25 (2.01, 2.53)	**<0.001**
Histology				
Adenocarcinoma	Ref		Ref	
Mucous	2.17 (1.77, 2.66)	**<0.001**	1.86 (1.52, 2.29)	**<0.001**
Other	1.14 (0.69, 1.88)	0.617	0.76 (0.45, 1.27)	0.297
Tumor grade				
Well differentiated	Ref		Ref	
Poorly differentiated	2.58 (2.30, 2.90)	**<0.001**	2.46 (2.18, 2.77)	**<0.001**
Location				
Right-sided colon	Ref		Ref	
Left-sided colon	1.31 (1.20, 1.43)	**<0.001**	1.39 (1.27, 1.53)	**<0.001**
Rectum	0.88 (0.79, 0.97)	**0.015**	0.91 (0.82, 1.02)	0.104

LNM, lymph node metastasis, CRCs, colorectal cancers, OR, odds ratio, CI, confidence interval, Ref: reference. Bold indicates significance.

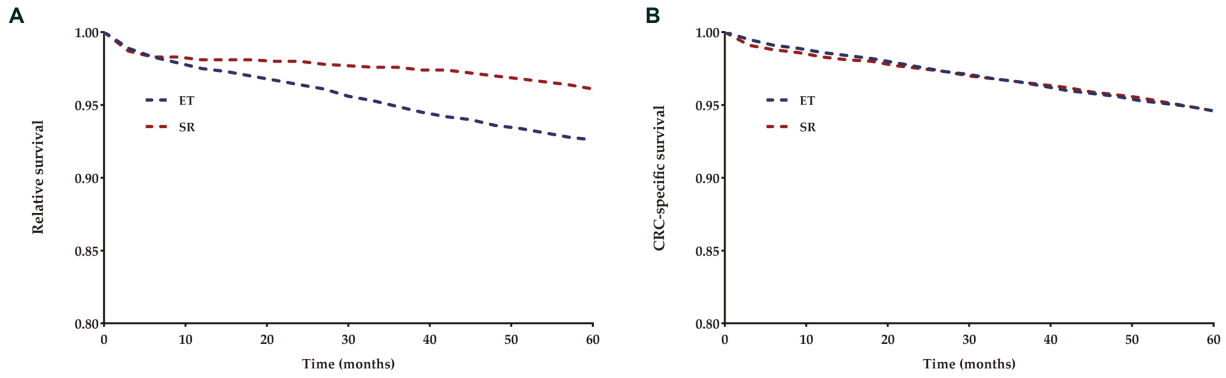

FIGURE 4
Relative **(A)** and cancer-specific **(B)** survival for each treatment group compared to US population.

TABLE 3 Comparison of baseline characteristics of T1N0M0 CRCs by treatment group.

Variables	ET (*n* = 6403)	SR (*n* = 19293)	*p* value
Mean age, y (SD)	61.7 (13.1)	65.2 (12.4)	**<0.001**
Age, y			**<0.001**
< 60	3030 (47.3%)	6377 (33.1%)	
≥ 60	3373 (52.7%)	12916 (66.9%)	
Sex			**<0.001**
Male	3480 (54.3%)	9955 (51.6%)	
Female	2923 (45.7%)	9338 (48.4%)	
Race			**<0.001**
White	4497 (70.2%)	15157 (78.6%)	
Black	881 (13.8%)	2178 (11.3%)	
Other	1025 (16.0%)	1958 (10.1%)	
Ethnicity			**<0.001**
Non-Hispanic	5670 (88.6%)	17382 (90.1%)	
Hispanic	733 (11.4%)	1911 (9.9%)	
Marital status			**<0.001**
Married	3473 (54.2%)	11375 (59.0%)	
Other	2930 (45.8%)	7918 (41.0%)	
Year of diagnosis			**<0.001**
2004–2008	1099 (17.2%)	5522 (28.6%)	
2009–2013	1681 (26.3%)	6398 (33.2%)	
2014–2018	3623 (56.5%)	7373 (38.2%)	
Tumor size			**<0.001**
≤ 1 cm	4137 (64.6%)	6919 (35.9%)	
≤ 2 cm	1328 (20.7%)	5976 (31.0%)	
≤ 3 cm	542 (8.5%)	3323 (17.2%)	
> 3 cm	396 (6.2%)	3075 (15.9%)	
Histology			**<0.001**
Adenocarcinoma	6253 (97.7%)	18766 (97.3%)	
Mucous	66 (1.0%)	467 (2.4%)	
Other	84 (1.3%)	60 (0.3%)	
Grade			**<0.001**
Well differentiated	6111 (95.4%)	17946 (93.0%)	
Poorly differentiated	292 (4.6%)	1347 (8.0%)	
Location			**<0.001**
Right-sided colon	371 (5.8%)	8523 (44.2%)	
Left-sided colon	1990 (31.1%)	7515 (39.0%)	
Rectum	4042 (63.1%)	3255 (16.8%)	
Chemotherapy			0.339
No	6141 (95.9%)	18555 (96.2%)	
Yes	262 (4.1%)	738 (3.8%)	
Radiation			**<0.001**
No	6063 (94.7%)	18610 (96.5%)	
Yes	340 (5.3%)	683 (3.5%)	

ET, endoscopic therapy; SR, surgical resection. Bold indicates significance.

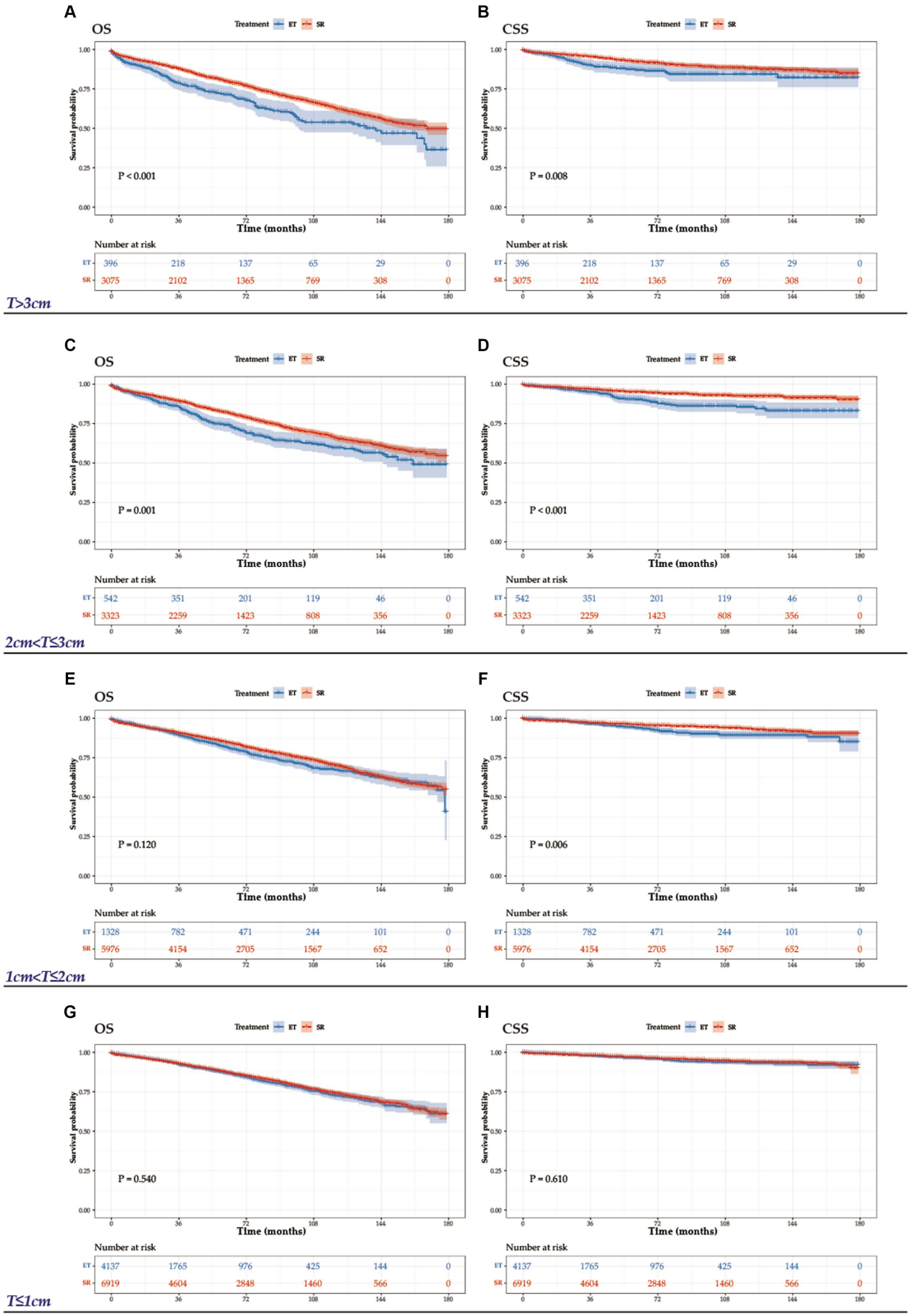

FIGURE 5
OS and CSS graphs by treatment for tumors >3 cm **(A, B)**, 2 cm < T ≤ 3 cm **(C, D)**, 1 < T ≤ 2 cm **(E, F)**, and T ≤ 1 cm **(G, H)**.

TABLE 4 Subgroup survival analysis between ET and SR.

Tumor location	Size	3-Year OS		*p* value	3-Year CSS		*p* value
		ET	SR		ET	SR	
Right-sided colon	T > 3 cm	49.4%	86.5%	<0.001	65.7%	95.1%	<0.001
	2 cm < T ≤ 3 cm	78.1%	87.7%	0.001	89.1%	97.0%	0.005
	1 cm < T ≤ 2 cm	73.0%	88.8%	0.007	92.1%	96.7%	0.027
	T ≤ 1 cm	79.7%	91.5%	<0.001	97.2%	97.9%	0.423
Left-sided colon	T > 3 cm	83.4%	88.5%	0.035	94.6%	96.3%	0.598
	2 cm < T ≤ 3 cm	84.4%	89.4%	0.018	96.0%	96.8%	0.312
	1 cm < T ≤ 2 cm	91.6%	91.5%	0.311	98.0%	97.4%	0.345
	T ≤ 1 cm	92.4%	93.0%	0.271	98.0%	98.3%	0.451
Rectum	T > 3 cm	80.2%	89.3%	<0.001	91.5%	94.6%	0.633
	2 cm < T ≤ 3 cm	86.3%	92.5%	<0.001	95.3%	96.7%	0.045
	1 cm < T ≤ 2 cm	89.6%	93.8%	<0.001	96.0%	97.8%	0.009
	T ≤ 1 cm	93.4%	93.5%	0.933	97.8%	96.6%	0.063

OS, overall survival; CSS, cancer-specific survival; ET, endoscopic therapy; SR, surgical resection.

demonstrated comparable long-term survival outcomes between ET and SR for T1 CRCs (23). Additionally, Jang et al. utilized a Markov model to assess the cost-effectiveness of various treatment strategies in T1 CRCs based on biomarker profiles and concluded that ET was more suitable for patients with less aggressive biomarkers (24). Refinements in the endoscopic technology have significantly improved the management of colorectal lesions. However, one of the main challenges in treating early-stage CRCs is choosing the most suitable method of ET that ensures complete resection, reduces recurrence risk, and mitigates complications. A large meta-analysis, comprising 50 studies and involving 6,442 patients, was carried out to assess the effectiveness and safety of ET, and the results revealed that ET emerged as an exceedingly effective and safe intervention (25). It achieved an initial success rate of 92%, with only 8% of patients ultimately undergoing surgery due to the inadequacy of endoscopic resection for cure. It's worth noting that the incidence of perforation and delayed bleeding stood at 1.5 and 6.5%, respectively. These results collectively underscore the remarkable effectiveness and safety profile of ET in clinical practice. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are two main minimally invasive techniques used to remove superficially invasive CRCs, with ESD facilitating a higher en-bloc resection rate regardless of tumor size (26). However, ESD is associated with certain drawbacks. It is a technically demanding and time-consuming procedure, necessitating specialized training and dedicated equipment. Moreover, ESD entails elevated costs and poses higher risks of bleeding and perforation, especially when applied to colonic cases. Consequently, its execution should be entrusted to experienced gastroenterologists and surgeons operating in well-equipped centers with rigorous quality control protocols. Regrettably, ESD adoption remains relatively scarce in Western countries. A recent meta-analysis, encompassing 238 publications published between 1990 and 2016, investigated the efficacy of ESD on a global scale. Of note, 90% of the included studies originated from Eastern countries, while only 10% were conducted in Western countries (27). The findings revealed that ESD outcomes were significantly superior in Eastern countries compared to Western countries, prompting the authors to emphasize the importance of considering local ESD expertise and regional outcomes when treating gastrointestinal lesions with ESD. Similarly, another meta-analysis involving 97 studies, with 71 conducted in Asia, indicated that the standard ESD technique in non-Asian countries is still falling short in achieving satisfactory performance levels (28). In a retrospective analysis of ESD procedures performed in a high-volume US referral center, Zhang et al. observed that Western practitioners commonly faced a longer learning curve in comparison to their Asian counterparts. This disparity may be attributed in part to the limited availability of experienced trainers and training programs, as well as scarcity of easier lesions (29, 30). Prior studies showed that ESD for CRCs in the western countries achieves en-bloc lesion resection removal in 50–84% and curative resection rate in 74–92%, with a perforation and bleeding rate of 1.3–20% and 7.9–12%, respectively, which is not as favorable as in Eastern hemisphere studies (31–33). Given these limitations, there is a pressing need for developing an endoscopic technique superior to conventional EMR in terms of en bloc resection and local recurrence prevention, while minimizing the occurrence of adverse events. In this context, Underwater endoscopic mucosal resection (UEMR) has emerged as a compelling and oncologically safe alternative to EMR for the treatment of colorectal cancers (34–40). The findings reported by Nagl et al. are valuable additions to the literature, as they suggest that UEMR could serve as an intermediate approach, bridging the gap between smaller lesions suitable for conventional EMR and larger lesions where ESD might be the preferred procedure (36). Further research is warranted to compare the long-term outcomes and cost-effectiveness of various ET methods and to identify the optimal management approach for T1 CRCs.

In the context of our primary focus on comparing the efficacy of ET and SR, it's worth noting that studies conducted by Marcellinaro and colleagues shed light on potential avenues for improving postoperative care and reducing complications in surgical interventions for CRCs. Marcellinaro et al. reported encouraging results with the Microbiota Implementation to Reduce Anastomotic Colorectal Leaks (MIRACLe) protocol in patients undergoing colorectal surgery for cancer (41). The MIRACLe protocol significantly reduced anastomotic leaks (AL), with an incidence as low as 1.7% in the post-matched MIRACLe group compared to 6.5% in the post-matched Control group. Similarly, a pilot

study by the same group observed positive trends with the MIRACLe protocol, with a 1.7% AL incidence in the MIRACLe group compared to 6.4% in the control group (42). These findings suggest the potential benefits of microbiota manipulation as a complementary strategy to enhance surgical outcomes in CRCs patients.

It is important to acknowledge the limitations of our study, which include the reliance on data from the SEER database, limited availability of detailed clinical information, and the absence of prospective clinical trials for validation. The SEER database did not provide information regarding medical comorbidities, complications, lymphovascular invasion, margin status, or disease recurrence. Additionally, the lack of data on ulceration prevented us from determining the effect of this factor on long-term survival outcomes in patients after ET or SR. Patients who were ill or older were more likely to undergo ET due to its less invasive nature. As this was a retrospective study, inherent selection biases could not be fully avoided.

Our study revealed an increasing utilization of ET and promising survival outcomes for patients with T1 CRCs in US, which corresponds with the evolution of endoscopic techniques. Further analysis showed that ET was feasible and safe for patients with left-sided T1 colon cancers and tumors of 2 cm or less, as well as T1 rectal cancers and tumors of 1 cm or less. Therefore, the over- and under-use of ET should be avoided by carefully selecting patients based on tumor size and site. Future studies are required to examine the effectiveness of EMR and ESD at a population level in the Western hemisphere.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Author contributions

KL: conception. KS: data analysis. ZY: writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

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Case report: Rupture of an ileus tube in a patient with recurrent rectal cancer

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The insertion of an ileus tube is an important treatment for intestinal obstruction. According to previous reports, jejunal intussusception has been reported as a complication associated with ileus tube placement. However, rupture of the weighted tip of an ileus tube has not been reported before. Herein, we report a 55-year-old Chinese woman who underwent radical proctectomy (DIXON) for rectal cancer and developed pelvic recurrence and lung metastasis 65 months after surgery, accompanied by symptoms of acute intestinal obstruction. An ileus tube was inserted before the operation (extensive total hysterectomy, bilateral adnexal resection, rectal Hartman operation, partial enterectomy, and intestinal adhesion lysis). Rupture of the ileus tube occurred after the operation and was treated with paraffin oil and enteral nutrition, and the metal beads and spring were eliminated through the colostomy. During the follow-up, the patient received targeted therapy plus immunotherapy, which was successful: the quality of life of the patient was excellent, and no obvious abnormal symptoms were found. Endoscopy-assisted ileus tube insertion should be performed under intravenous anesthesia, and a knot should be tied at the tip of the ileus tube before insertion so that the ileus tube can be inserted easily by grasping the thread with biopsy forceps(the "thread-knotting" method). With the above methods, the procedure of ileus tube insertion could be improved to reduce the incidence of tube-related rupture.

KEYWORDS

rectal cancer, recurrence or metastasis, intestinal obstruction, ileus tube, complication

Background

The insertion of an ileus tube is an important treatment for patients with intestinal obstruction. It reduces the rate of surgery, provides effective preoperative preparation for surgery, and decreases the incidence of surgical complications (1–3). In addition, for patients with advanced intestinal tumors, the ileus tube plays an important role in

bowel rest and effective decompression,which is a therapeutic method with high efficacy and low invasiveness (4). Compared to a gastric tube, a transnasal ileus tube is more effective at decompression for patients with intestinal obstruction (5). According to previous reports, jejunal intussusception has been reported as a complication associated with ileus tube placement (6–8). However, rupture of the weighted tip of an ileus tube has not been reported before.This study reports a rare rupture of the ileus tube in a patient with recurrent rectal cancer, and discusses the diagnosis and prevention associated with this case.

Case presentation

A 55-year-old Chinese woman who underwent radical proctectomy because of rectal cancer 65 months prior.On September 20, 2016, the patient underwent radical proctectomy (DIXON) for rectal cancer under general anesthesia. Postoperative pathologic examination showed stage IIIB, moderately differentiated adenocarcinoma with lymph node involvement (5/17) and two tumor deposits in the rectal mesentery. The circumferential resection margin (CRM) was negative (2 mm). The immunohistochemical marker results were as follows: CK (+), HER-2 (-), p53 (+), Ki-67 (approximately 70%), MSH2 (+), MSH6 (+), MLH1 (+), and PMS2 (+). The patient continued adjuvant chemotherapy after surgery, completing eight cycles of oxaliplatin and capecitabine (CAPEOX regimen).

Four years post surgery, CT showed multiple metastatic nodules located in both lungs, and there were malignant soft masses in the uterus and adnexa. On October 8, 2020, MRI showed multiple metastatic soft masses located in the uterus and adnexa, and there were multiple encapsulated effusions in the pelvis. Transcervical biopsy showed metastatic adenocarcinoma of rectal origin. Genetic testing revealed no mutations in the Braf or Ras gene. The patient was treated with FOLFOX6 plus cetuximab for 6 cycles, and the lesion did not progress. However, the patient's regimen was changed to FOLFIRI plus cetuximab because of numbness in the hands and feet, and 3 cycles of the regimen were completed. Due to the progression of the pelvic and pulmonary lesions, the treatment regimen was changed to XELOX + bevacizumab. Seven cycles of this regimen were completed.

In March, 2022, the woman was admitted to the hospital because of sudden pain in the lower right abdomen. She had no chills, fever, vomiting or blood in the stool at the time of admission. The patient had diabetes and hypertension, her blood glucose level was 7.76 mmol/ml, and her CRP level was 33.32 mg/L. Other parameters were normal. CT showed that the lung and pelvic lesions had progressed significantly (Figures 1A, B). After a week of oral fruquintinib therapy, the patient had worsening abdominal pain and stopped having farts and defecation. Her abdomen was distended, and a hard mass was palpated in the right lower abdomen with clear borders and fair mobility, and she had tenderness pain, and intestinal sounds in her abdominal cavity.

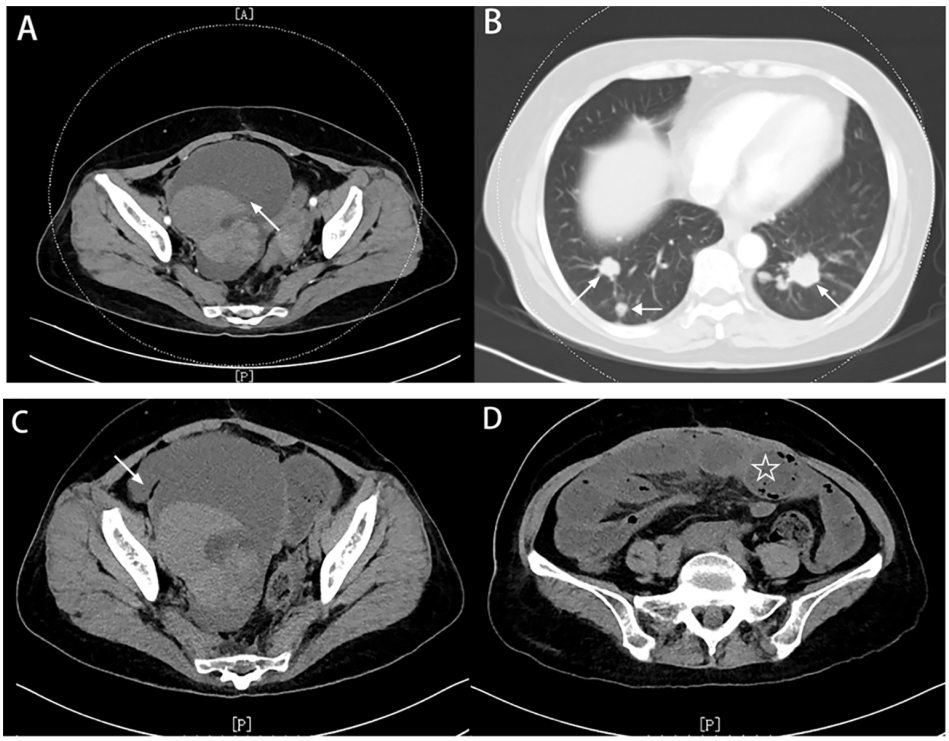

FIGURE 1
Imaging before the insertion of an ileus tube **(A)** CT showed that the pelvic lesions (white arrow) had progressed significantly. **(B)** CT showed that multiple metastatic nodules (white arrow) were located in both lungs. **(C)** CT showed that the obstruction was located in the terminal ileum that had been invaded by the large pelvic tumor (white arrow). **(D)** The small bowel became significantly dilated due to the obstruction (white asterisk).

The site of obstruction was located in the terminal ileum invaded by the large pelvic tumor (Figures 1C, D).

As the symptoms of intestinal obstruction significantly worsened, the ileus tube (CLINY Ileus tube suite, Create Medic, Tokyo, Japan; 300 cm in length, 16 Fr) was inserted under endoscopic guidance on March 23, 2022. The decompression tube was first placed into the stomach through the nasal cavity, and then the gastroscope was placed into the gastric cavity. After endoscopic suction of the stomach contents, the tube was moved into the descending duodenum by forceps, where it was kept fixed. Then the anterior balloon was inflated with 20 mL distilled water. The gastroscope was withdrawn after the long tube was fixed to the cheek. The tube was propelled by bowel peristalsis and its weighted tip, and the outside terminal of the tube was connected to a spontaneous negative-pressure bag.

The patient was ventilated and defecated via decompression. On March 31, 2022, CT showed that the intestinal obstruction had improved, and the head of the tube was now in the left lower abdomen (Figure 2A). Since the obstruction was only temporarily relieved and the patient was otherwise still unable to eat and continue treatment, surgery needed to be performed eventually.

Bilateral ureteral catheterization was performed before surgery (to avoid a ureteral injury), and on April 4, 2022, extensive total hysterectomy + bilateral adnexal resection + rectal Hartmann operation + partial small bowel resection + intestinal adhesion release was performed.

According to the intraoperative exploration, an 18*15 cm cystic mass was seen in the right ovary (Figure 3A), and a 5*3 cm cystic mass was seen in the left ovary. At a distance of 20 cm from the ileocecum, the terminal ileum was infiltrated by and adhered to the right mass, the proximal small intestine was significantly dilated, and the left mass had infiltrated and adhered to the sigmoid colon. The uterus and cervix were not clearly distinguishable from the rectum. The tip of the ileus tube was located in the left lower abdomen.

The patient recovered well after the operation. The postoperative pathologic examination showed moderately differentiated adenocarcinoma with lymph node involvement (1/13) invading beyond the rectal wall; the patient was positive for intravascular tumor thrombus and nerve involvement; and the resection edge was negative. Adenocarcinoma tissue was found in the uterus and bilateral appendages. The immunohistochemical marker results were as follows: CK20 (+), SATB-2 (+), and PAX-8 (-) (suggesting that the tumor had originated from the rectum).

On April 9, 2022, CT did not show intestinal obstruction or intestinal leakage but showed separation between the metal beads at the head of the ileus tube (Figure 2C). When we removed the ileus tube, the metal beads and spring were not observed.

Considered that the patient had no signs of intestinal obstruction or perforation, she was given conservative treatment, including paraffin oil and a liquid diet. Paraffin oil was chosen to

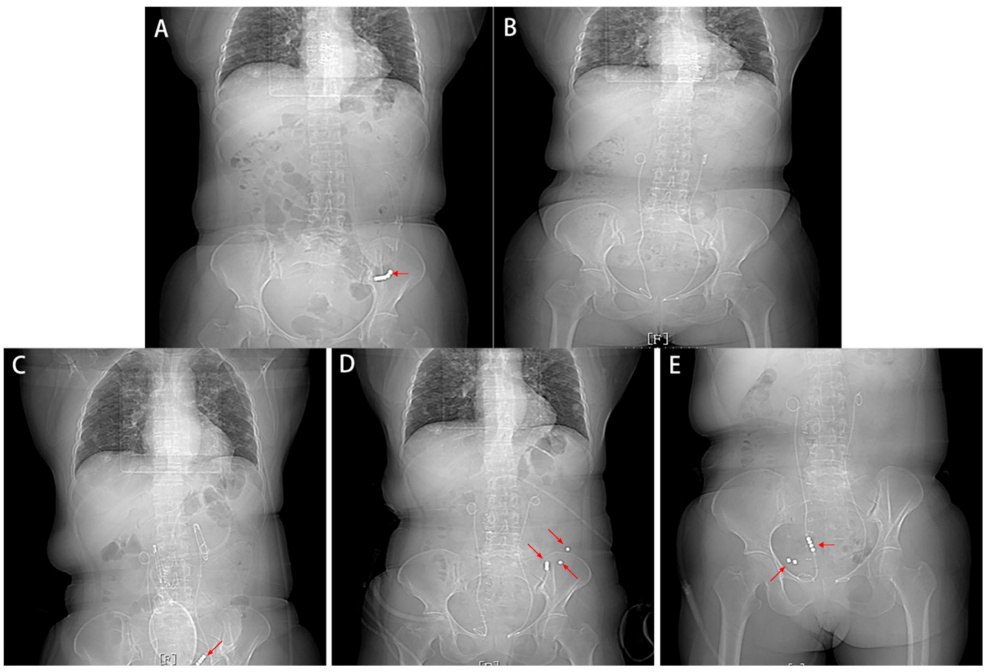

FIGURE 2
Imaging after the insertion of an ileus tube **(A)** CT showed that the intestinal obstruction was improved, and the head of the tube was now in the left lower abdomen. **(B)** CT showed no metallic shadow, and the rest of the CT findings were normal. **(C)** CT did not show intestinal obstruction or intestinal leakage but showed separation between the metal beads at the head of the ileus tube. **(D, E)** Follow-up CT showed that six scattered metal beads had moved toward the distal small intestine with no signs of intestinal obstruction or perforation.

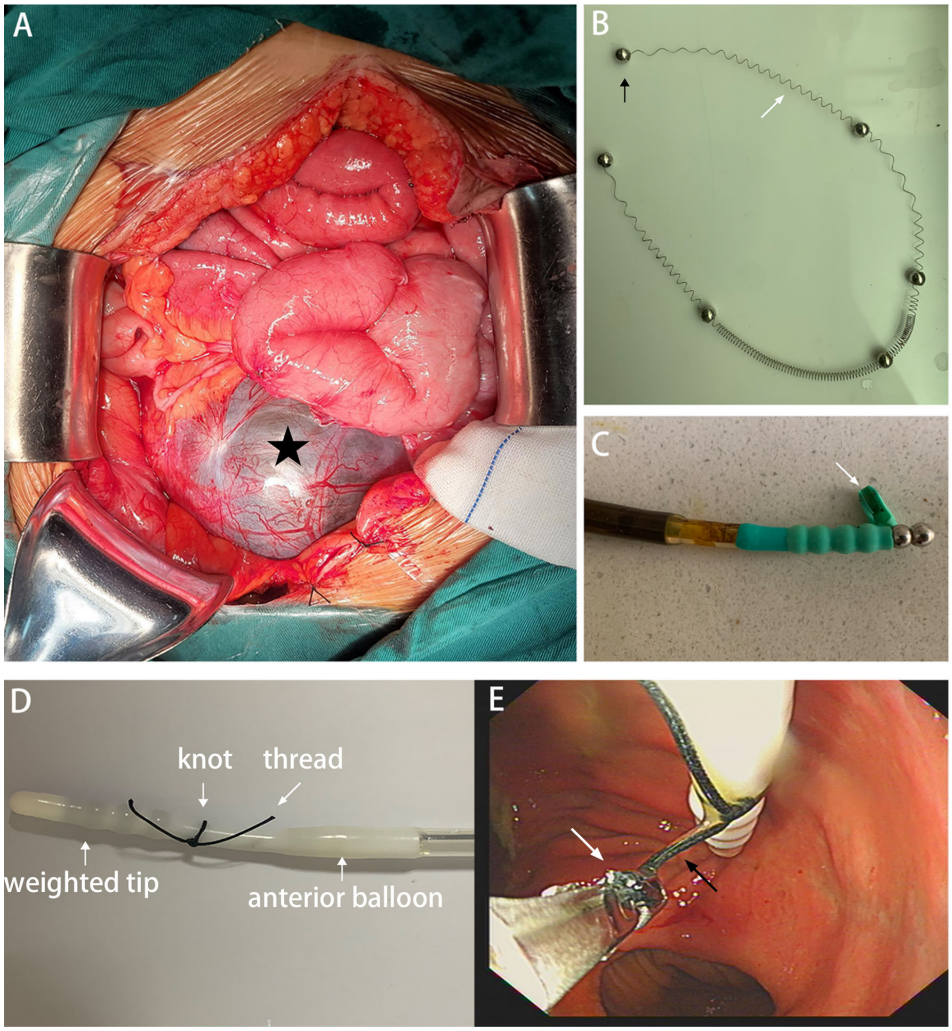

FIGURE 3
(A) Intraoperative exploration showed that an 18*15 cm cystic mass(black asterisk) was seen in the right ovary. **(B)** The metal beads(black arrow) and spring(white arrow) were eliminated through the colostomy. **(C)** The wall of the weighted tip(white arrow) was damaged caused by the biopsy forceps. **(D)** A knot was tied at the tip of the ileus tube before insertion ("thread-knotting" method). **(E)** The ileus tube could be inserted easily by grasping the thread (black arrow) with biopsy forceps (white arrow).

promote bowel motility, and the liquid diet was a diet that reduced stool formation and did not interfere with fecal observation, plus it did not affect the timing of emergency surgery in case of failure of conservative treatment.

Follow-up CT showed that six scattered metal balls had moved toward the distal small intestine, with no signs of intestinal obstruction or perforation (Figures 2D, E). On April 19, 2022, the metal beads and spring were eliminated through the colostomy (Figure 3B), CT showed no metallic shadow, and the other organs were not abnormal (Figure 2B). The patient received treatment with sindilizumab in combination with fruquintinib on May 6, 2022 and completed 18 cycles of the regimen. The patient was in good general condition. The metastatic nodules of both lungs were stable, and no pelvic metastatic lesions were found in the last follow-up. The timeline is shown in Table 1.

Discussion

An ileus tube can approach or reach the proximal segment of the obstruction, has a large drainage volume and high drainage efficiency, and can play an active role in decompression (9). The guidelines point out that in the nonoperative treatment of adhesive intestinal obstruction, a long three-lumen nasointestinal tube is more effective than a nasogastric tube (it needs to be placed under endoscopy) (10, 11).

The reasons why the current patient underwent surgery are as follows: 1. Since the recurrent tumor nearly completely compressed the small bowel, decompression therapy failed to fundamentally improve the patient's symptoms, and the patient's nutritional status was too poor for the patient to tolerate the comprehensive treatment. 2. Based on physical examination and imaging, this patient had a high chance of having her pelvic tumor removed. 3.

TABLE 1 The medical history of the patient.

Time series	Diagnosis and treatment details
September 20, 2016	The patient underwent radical proctectomy (DIXON) for rectal cancer, and received adjuvant therapy after surgery.
October 8, 2020	Imaging showed multiple metastatic soft masses located in the pelvic and pulmonary areas.
Between October 2020 and March 2022	The patient was treated with the chemotherapy plus targeted therapy.
In March, 2022	The patient presented with right lower abdominal pain because of tumor progression.
March 28,2022	An ileus tube was inserted because of symptoms of acute intestinal obstruction.
April 4, 2022	Bilateral ureteral catheterization was performed before surgery (to avoid a ureteral injury), extensive total hysterectomy + bilateral adnexal resection + rectal Hartmann operation + partial small bowel resection + intestinal adhesion release was performed.
April 9, 2022	When the ileus tube was removed, the metal beads and spring were not seen.
April 19, 2022	The metal beads and spring were eliminated through colostomy after conservative treatment.
From May 2022 to present	Targeted therapy and immunotherapy were continued, and the metastatic nodules of both lungs were stable, and no pelvic metastatic lesions were found in the last follow-up.

The patient was intolerant to decompression tubes and had a strong desire for surgery. Eventually, the patient resumed a normal diet after the operation, improved her physical fitness, and was able to successfully complete the follow-up treatment.

There were several reasons for the rupture of the weighted tip. First, we were used to guiding the insertion of the tube by directly clamping the weighted tip with forceps and ignoring the damage to the wall caused by the clamp (Figure 3C). Second, because the retention time was too long(15d), the original damaged rubber of the weighted tip could be further damaged by the corrosion of digestive juice.

At present, there is no uniform standard for the retention time of ileus tube. In our country, only one scholar has ever reported rupture of a nasogastric tube in China, and the nasogastric tube was retained for more than two weeks in his case. Wang found that the average retention time of ileus tubes in the successful treatment group for small bowel obstruction(SBO) was 15 days using propensity score matching (PSM) analysis (12). Therefore, since the patients could fail to benefit from an ileus tube after 15 days, we recommended that the retention time was not more than two weeks.

This case is enlightening due to the following: 1. Endoscopic-assisted insertion should be performed under intravenous anesthesia to minimize any patient discomfort and distress that may interfere with the insertion of ileus tubes. 2. Previously, we were used to guiding the insertion of the tube by directly clamping the weighted tip with biopsy forceps and ignoring the damage to the wall caused by the clamp (Figure 3C). Now, we can tie a knot at the tip of the tube and then complete the insertion by tugging on the thread (the "thread-knotting" method) (Figures 3D, E). Ten patients with intestinal obstruction in our institution treated by ileus tube from March 2022 to October 2023 were successfully inserted with "thread-knotting" method. Informed consent for the procedures was obtained from all patients. In addition,our "thread-knotting" method not only prevents rupture of the weighted tip but also avoids damage to the anterior balloon. Because of the close distance between the anterior balloon and the weighted tip, it is easy to accidentally break the balloon during tube insertion (Figure 3D). 3. Since this patient had undergone a terminal ileal resection, the reason for the longer retention time of the ileus tube was to reduce anastomotic leakage through effective decompression.

In addition to our "thread-knotting" method, Yamaguchi et al. reported that the transnasal endoscope was moved into the descending duodenum for insertion of the guidewire, and after the endoscope removal, the ileus tube was inserted into the duodenum through the guidewire (13). Guo et al. reported that the guidewire was placed 2 cm above the tip of the long tube so that it could be grasped easily by the biopsy forceps, and the scope and tube were passed through the pylorus and advanced as far as possible (14).

The main shortcoming of this report was the lack of information on the fractured tip excreted out of the body. Nevertheless, this case report has complete imaging data detailing the entire process relating to the tube, from its rupture in the small intestine to its complete expulsion.

Although this woman is very lucky and has a good prognosis, her success does not rule out that other patients may need a secondary surgery due to obstruction or perforation caused by broken tips or metal beads. The purpose of this case report is to encourage physicians to be more vigilant to reduce the incidence of such adverse events.

Conclusion

The procedure of endoscopy-assisted ileus tube insertion could be improved to reduce the incidence of tube-related rupture with our "thread-knotting" method and intravenous anesthesia.

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

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

JM: Investigation, Project administration, Software, Supervision, Writing – original draft. YJ: Data curation, Writing – review & editing. CPZ: Formal analysis, Writing – review & editing. DW: Writing – review & editing. CXZ: Writing – review & editing. YZ: Writing – review & editing.

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Conflict of interest

The 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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Case Report: Recurrent colonic metastasis from lung cancer—diagnostic pitfalls and therapeutic challenge of a peculiar case

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Lung cancer (LC) mortality exceeds 20%, and detecting metastases from LC is becoming a challenging step in understanding the real prognostic role of specific localization. We report a case of a patient with lung metastasis to the colon with local recurrence at the anastomosis after radical resection for metastasis. In both cases, the diagnosis was on oncological follow-up, and surgery was offered in consideration of reasonable life expectancy, good control of LC, and high risk of intestinal occlusion. A 67-year-old male, with a history of LC 18 months ago, was referred to our surgical unit after a positron emission tomography CT total body, where an area of intense glucose metabolism (SUV max: 35.6) at the hepatic colic flexure was reported. A colonoscopy revealed an ulcerated, bleeding large neoplasm distally to hepatic flexure, almost causing resulting total occlusion. Histologic examination revealed a tumor with complete wall thickness infiltration, which appears extensively ulcerated, from poorly differentiated squamous carcinoma (G3), not keratinizing, with growth in large solid nests, often centered by central necrosis. Two of the 30 isolated lymph nodes were metastatic. The omental flap and resection margins were free from infiltration. The malignant cells exhibited strong positive immunoreactivity only for p40. The features supported metastatic squamous carcinoma of lung origin rather than primary colorectal adenocarcinoma. After 8 months from surgery, intense Fluorodeoxyglucose (FDG) uptake of tissue was confirmed in the transverse colon. Colonoscopy evidenced an ulcerated substenotic area that involved ileocolic anastomosis on both sides. Reoperation consisted of radical resection of ileocolic anastomosis with local lymphadenectomy and ileotransverse anastomosis. The second histologic examination also revealed poorly differentiated squamous carcinoma (G3), not keratinizing, with positive immunoreactivity only for p40, suggesting the origin of LC. This case report confirmed that the possibility of colonic secondary disease should be part of the differential diagnosis in asymptomatic patients and those with a history of LC diagnosis. In addition, relapse of colonic metastasis is infrequent but should be considered during follow-up of LC. More studies on colonic metastasis of LC are required to better understand the clinical features and outcomes.

KEYWORDS

colonic metastasis, lung cancer, relapse, colon, lung

Introduction

Nowadays, lung cancer (LC) mortality exceeds 20% (1), and detecting metastases from LC is becoming a challenging step in understanding the real prognostic role of specific localization (2). A new concept of overall survival (OS) in pulmonary metastatic disease was recently discussed (3). Non-small cell lung carcinoma (NSCLC) accounts for the majority of all LC cases (1). A metastatic disease often occurs at the time of diagnosis, regardless of the primary LC type. The most common sites of metastasis are the brain (47%), bone (36%), liver (22%), adrenal glands (15%), thoracic cavity (11%), and distant lymph nodes, but numerous locations were also described in the literature (2, 4). Colonic metastases are rare. Large bowel metastases have an incidence rate of approximately 12% in autoptic series (4). The report estimated lower incidence, mostly because symptomatic colonic metastasis infrequently occurs. Colonic metastases are significantly rare, with less than 50 cases of colonic metastasis from an LC reported to date (5). Clinicians should have a high index of suspicion and a low threshold for intestinal tract investigation when primary LC patients present with abdominal symptoms (6). We report a case of lung metastasis to the colon with local recurrence at the anastomosis after radical resection for metastasis. In both cases, the diagnosis was on oncological follow-up, and surgery was offered in consideration of reasonable life expectancy, good control of LC, and high risk of intestinal occlusion. No report was described in the literature of double colonic metastasis with relapse at the same location of colonic metastasis, although radical resection was performed and documented by histopathology.

Case description: diagnostic assessment

A 67-year-old male was referred to our surgical unit by his oncologist after a positron emission tomography CT (PET-CT) total body, where an area of intense glucose metabolism (SUV max: 35.6) at the hepatic colic flexure was reported. LC consisted of a squamous type non-small cell cancer (S-NSCLC) and was diagnosed 18 months ago, with a local advanced pattern (T2N3M0). The patient was treated with immunotherapy, according to the international guidelines. He was thought to be in remission following 18 months of pembrolizumab. This pattern of disease was stable until December 2021, when PET-CT documented colonic metastasis. This was confirmed by colonoscopy, which revealed an ulcerated, bleeding large neoplasm distally to the hepatic flexure (transverse colon), almost causing total occlusion. Biopsy reported suspicion of a squamous type of LC origin. Oncological markers, such as carcinoembryonic antigen (CEA), α-fetoprotein (AFP), CA 19-9, and CA-125, were all within the range. Total body examination was negative for other localizations. After a multidisciplinary evaluation, considering good control of primary cancer, optimal physical status, and high risk of occlusion, a laparoscopic enlarged right hemicolectomy was performed. The postoperative course was uneventful. Histologic examination revealed a tumor with complete wall thickness infiltration, which appears extensively ulcerated, from poorly differentiated squamous carcinoma (G3), not keratinizing, with growth in large solid nests, often centered by central necrosis. The lesion was located over 5 cm from the colonic margin, while proximally ileal transection was over 30 cm distally from the lesion. Two of the 30 isolated lymph nodes were metastatic. The omental flap and resection margins were free from infiltration.

To evaluate these high-grade and poorly differentiated malignant changes further, we performed properly controlled routine immunohistochemical (IHC) stains for cytokeratin 7 (CK7), caudal type homeobox 2 (CDX2), and cytokeratin 20 (CK20) based not only on the age, gender, and past medical history of the patient but also on her recent clinical, radiologic, and operative findings. The malignant cells exhibited a strong positive immunoreactivity only for p40, while the tumor was negative for CDX2, CK20, and CK7. The features supported metastatic squamous carcinoma of lung origin (S-NSCLC), rather than primary colorectal adenocarcinoma. This hypothesis was supported by numerous colonic and regional lymph node samples lacking malignant carcinoma cells and properly controlled IHC stains of the right colon and ileum biopsy cells exhibiting negative immunoreactivity for CK7 and TTF-1. In addition, PD-L1 was determined on this specimen, with an expression of <1%, while EGFR resulted without mutations (wild type).

After surgery, radiotherapy was associated with pembrolizumab to reinforce the effectiveness of treatment on primary cancer. After 8 months from surgery (26 months from diagnosis of S-NSCLC), subsequent PET-CT scans suggested substantial metabolic stability of the known right hilar lung lesion (SUV max: 6.6) and subcarinal lymphadenopathy (SUV max: 5.1) at the first follow-up. In addition, intense FDG uptake of tissue was confirmed in the transverse colon (SUV max: 38.3 vs. 35.6). It was suggestive of local relapse or peritoneal carcinosis. Abdominal magnetic resonance (MR) excluded peritoneal involvement, while colonoscopy evidenced an ulcerated substenotic area that involved ileocolic anastomosis on both sides. The multidisciplinary evaluation confirmed surgical indication, considering stable local primitive cancer, good general condition, and a high risk of complications (**Figure 1**).

Reoperation consisted of radical resection of ileocolic anastomosis with local lymphadenectomy and ileotransverse anastomosis 5 cm proximally and distally from the previous localization. The procedure required splenic flexure preparation. Intraoperative exploration excluded posterior infiltration of the gastric and duodenal walls.

No surgical complications were observed, and the patient was discharged on the sixth postoperative day (POD). On the third POD, asthenia, fever, and general hypomotility occurred. Due to the chronicle therapy with prednisone (25 mg/die), we hypothesized postoperative adrenal insufficiency by the abolition of the hypothalamus–pituitary axis. Starting with an endovenous therapy with hydrocortisone (bolus of 500 mg and subsequent therapy with 200 mg every 12 h), the symptoms were solved in 24 h, confirming the diagnosis. The endocrinological evaluation

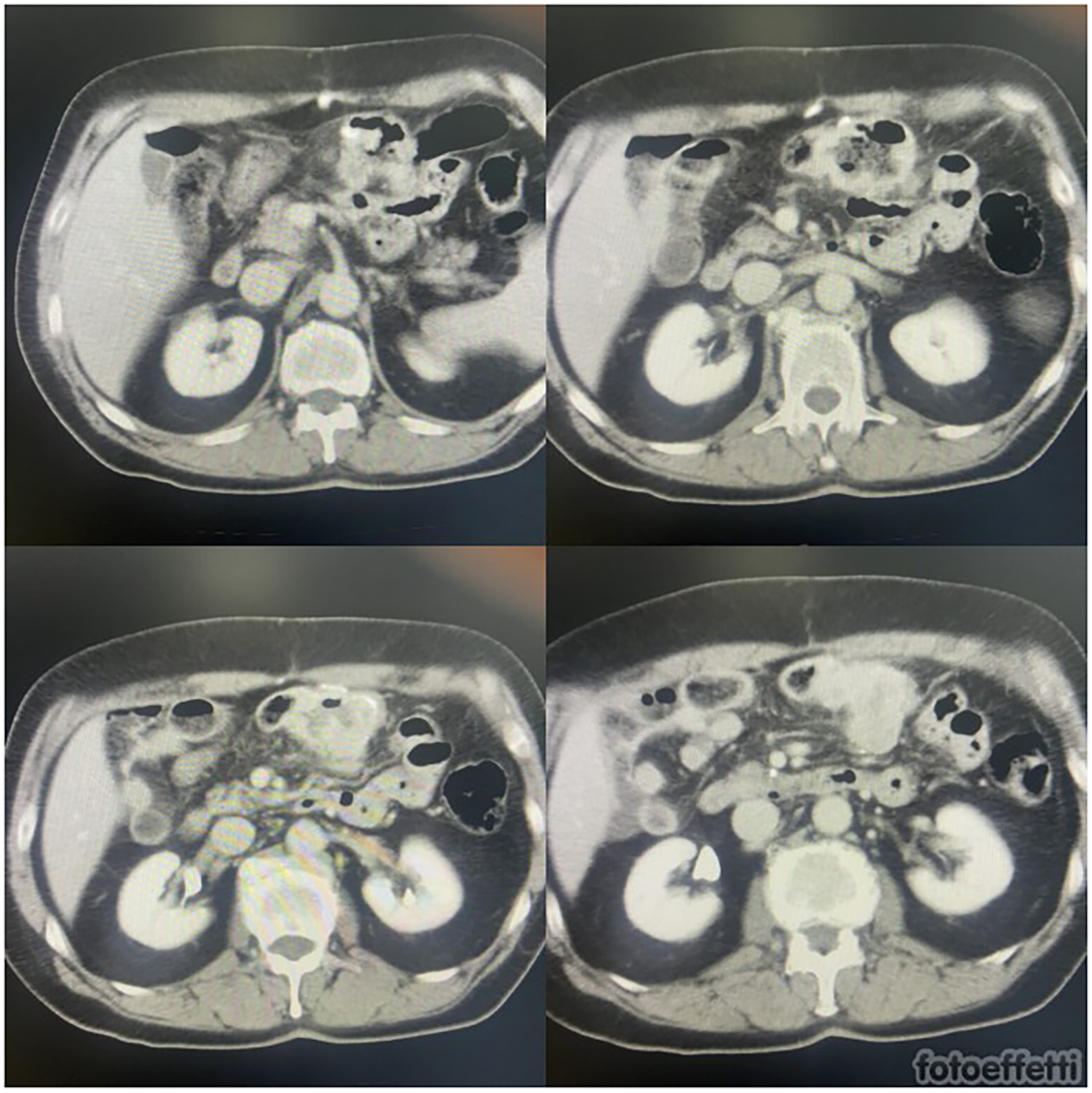

FIGURE 1
CT assessment of colon metastasis detected during follow-up.

indicated chronic treatment with hydrocortisone per os, until recovery of the hypothalamus–pituitary axis.

The second histologic examination also revealed a tumor with full wall thickness infiltration of ileocolic anastomosis, which appears extensively ulcerated, from poorly differentiated squamous carcinoma (G3), not keratinizing, with growth in large solid nests. Neoplastic perineural infiltration and embolus were present. The lesion was located over 4 cm from the colonic margin on both sides. One of the isolated lymph nodes was metastatic. The omental flap and resection margins were free from infiltration. On routine IHC, the malignant cells exhibited strong positive immunoreactivity only for p40, while the tumor was negative for CDX2, CK20, and CK7 (confirming S-NSCLC metastasis). The features supported metastatic squamous carcinoma of lung origin (S-NSCLC). Similar genetic results were found also on this specimen (PD-L1 <1% and EGFR wild type).

After surgery, the patient started chemotherapy platinum-based for advanced LC. At 18-month follow-up, the patient was free from disease at PET-CT evaluation and asymptomatic. He continued immunotherapy with a standardized schedule and finished steroid therapy.

Discussion

We report a peculiar case of colonic metastasis from LC that relapsed after 8 months at the site of anastomosis after colonic resection of metastasis, although radical resection was performed. Its uniqueness is related to the same location of metastasis, related probably to lymphovascular involvement of this gastrointestinal site.

The most common metastatic sites of LC are bone and brain (over 30%), but many other locations were discovered during the evolution of this cancer (2). The incidence rate of gastrointestinal metastasis of primary LC ranges from 0.3% to 1.7% (4).

Interestingly, the incidence ranges between 4.6% and 14% in postmortem studies (5). This discrepancy indicates that most patients have asymptomatic gastrointestinal metastases. LC metastasis can spread to any gastrointestinal location from the oral cavity to the anus through lymphatic and hematogenous pathways being the probable routes of spread (4, 5). Specifically, colonic metastasis is uncommon with an incidence rate of 0.1%: it has been reported by numerous studies, but the incidence in autoptic series is relevant (4, 6). Kim et al. (7) reported 10 (0.19%) out of 5,239 patients with LC metastasis to the colon and rectum. A literature review of 15 cases of metastatic LC to the colon demonstrated that S-NSCLC is the most common subtype, similar to that in our report, while adenocarcinoma had the second highest potential for colonic metastasis (8). Approximately 50 case reports of LC metastasizing to the colon have been published worldwide, with various cellular differentiations.

The majority of cases of this disease are diagnosed in symptomatic patients, and detection during follow-up, similar to that in our case, is uncommon (6). With over 12% of colonic metastasis from LC in autoptic series, detection during follow-up is also uncommon (9). Gastrointestinal complications usually occur after the diagnosis of LC is established (6). Sometimes they can occur early in the course of the disease or even before an LC diagnosis has been made. Metastatic LC to the colon was also associated more with serious complications such as perforation, hemorrhage, and intussusception (6, 9).

Synchronous colonic metastasis is rarely described (10). Initial diagnosis of colonic metastasis of LC is challenging since its incidence has been reported sporadically. This phenomenon has been reported more frequently due to the recent higher rates of long-term survival of LC patients, increased availability and utilization of endoscopic examinations, and advancements in immunotherapy (10). Differently from primary cancer, an asymptomatic diagnosis of colorectal metastasis can be associated with a worse prognosis (10). This is related to the oncological evolution of primary neoplasm. Moreover, early detection and surgical intervention have been postulated to improve survival (11).

Moreover, it is very difficult to distinguish if the colon is the primary cancer site or a metastasis from LC. Despite that, CT scans can miss small asymptomatic gastrointestinal lesions that can be detected with PET-CT scans (12). Specimen histology is useful for suspecting the pulmonary origin of colonic lesions, as evidenced by many case reports. Endoscopic and clinical data are not specific for this differentiation, but a previous endoscopic biopsy is very useful for suspicion of colonic metastasis (6). Histological examination on intestinal resection, in correlation with the clinical findings, remains the gold standard for diagnosis (12). IHC is of utmost importance for the diagnosis and differentiation of metastasis from primary colonic malignancy (13). Colorectal adenocarcinoma is typically CDX-2 positive, cytokeratin (CK) 20 positive, and CK7 negative (13). Most primary lung malignancies are TTF-1 and p40 positive and CK7 and CK20 negative (14).

The average survivability of patients with LC varies widely, from the time of diagnosis of colonic metastasis to death. Moreover, outcome data for small and large bowel metastases are often aggregated. The 5-year survival rate for stage IV metastatic NSCLC is approximately 10% (2, 4). All forms of intestinal metastasis of LC are considered late-stage complications of the disease. However, a new concept of *oligometastatic* disease was introduced just over two decades ago and has been expanded to a multitude of cancer types, such as NSCLC (2, 15). Notably, oligometastatic NSCLC may represent a disease state with limited disease burden amenable to localized therapy (i.e., resection, radiation, and ablation) and improved survival outcomes similar to that of locoregionally advanced NSCLC (16). A recent single-institution retrospective review showed that patients with both synchronous and metachronous oligometastases from NSCLC had excellent overall survival (OS) (median OS = 21.8 months) when the oligometastatic disease was treated radically either with surgery or stereotactic radiation (17). Lengthy OS has been shown in patients with oligometastatic LC to a variety of organ sites (16). This approach reinforced the surgical indication of our case, either in the first recurrence or the second colonic recurrence. This new concept also includes new oncological targeted drugs. The combination of chemotherapy and platinum-based pemetrexed and carboplatin is the first-line treatment for advanced NSCLC. Our patient initially received pembrolizumab before the discovery of colonic metastasis. This is a novel and well-researched cancer immunotherapy most commonly used for tumors that are unresectable, recurrent, or metastatic (18). Until recently, pembrolizumab has been recommended as a second-line agent (19). Trends are now focusing on tumor genotype-specific characteristics and in favor of earlier use of immunotherapeutic agents (20). These are generally associated with fewer adverse events compared to platinum-based chemotherapy.

Regarding the therapeutic approach to colonic metastasis, the goal is the choice of surgery. In the case of synchronous metastasis, the most important decision is which lesion needs to be treated first. It depends on the extent of colonic metastasis and the nature of the presentation. For patients with complicated colonic metastasis, proper surgical treatment provides better outcomes in terms of complication rate, quality of life, and palliation (5). In the case of metachronous metastasis, the risk of complications (bleeding, obstruction, perforation) and evaluation of life expectancy from LC are two topics in the surgical approach (6, 21). When a primary disease is controlled and other locations are lacking, similar to that in our report, surgery is mandatory and safe (22). This is valid properly also when a second location is detected. As evidenced in the description of the case, the same location of the second metastasis is an unfortunate condition that may be related to local massive lymph node involvement or micrometastasis located at other sites of the transverse colon. Moreover, an omental flap free from disease at the first procedure is another interesting question: relapse was observed, despite clear peritoneal invasion. This infrequent and atypical oncological course will need other reports for assessment. We hypothesized that lymphnodal diffusion and probably combs of cells in microcircle led to early recurrence, similar to primary cancer.

Our case is unusual and peculiar for almost three characteristics: asymptomatic diagnosis in both detections; early

second recurrence at the site of anastomosis, although radical surgery, confirmed by pathological specimen; and no systemic or peritoneal disease on both histological studies. In view of the second point, another similar case was described, reporting a large tumor at the colonic anastomosis with a specimen consistent with primary NSCLC (23). Moreover, in this case, the previous intestinal resection was for primary colonic cancer, while the first resection was for metastatic LC in our report.

Conclusion

Colonic metastasis should be considered when patients have abdominal symptoms and a history of primary LC. In literature, like our report, PET-CT scans and endoscopy are highly sensitive for detection, but histological examination with IHC confirms the diagnosis. This case report confirmed that in asymptomatic patients and those with a history of LC diagnosis, the possibility of colonic secondary disease should be part of the differential diagnosis. In addition, relapse of colonic metastasis is infrequent but should be considered during follow-up of LC. Surgical treatment, associated with medical therapy, is useful, in consideration of reasonable life expectancy, good control of LC, and high risk of complications. More studies on colonic metastasis of LC are required to better understand the clinical features and outcomes.

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

Ethical approval was not required for the studies involving humans because this is a retrospective report on a peculiar case. No experimentation was performed. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

ST: Writing – original draft, Writing – review & editing. GS: Writing – original draft, Writing – review & editing. VP: Writing – original draft, Writing – review & editing. AT: Writing – original draft, Writing – review & editing. AG: Writing – original draft, Writing – review & editing. UB: Writing – original draft, Writing – review & editing.

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Conflict of interest

The 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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Effect of regional block technique on postoperative high-grade complications according to Clavien-Dindo classification in elderly patients with thoracic and abdominal cancer: a retrospective propensity score matching analysis

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Background: Postoperative complications have an influence on postoperative rehabilitation, length of hospital stay and hospitalization expenses in elderly patients, especially those with higher Clavien-Dindo (C-D) classification. Patients with cancers often experience more serious postoperative complications after surgery. Different anesthesia methods can affect the postoperative outcomes of cancer patients. Regional block techniques have been recommended in guidelines for enhanced recovery after surgery. However, the relationship between regional blocks and high-grade postoperative complications remains unclear, thus, the study explored the relationship between regional block techniques and high-grade postoperative complications graded by C-D classification in elderly patients with thoracic and abdominal cancer.

Method: Retrospective enrollment of eligible elderly patients admitted to Peking University People's Hospital between January 2018 and March 2022 was conducted. Propensity score matching (PSM) and univariate and multivariate regression analyses were used to analyze the potential benefits of regional blocks for elderly patients in real world practice.

Results: A total of 2769 patients were enrolled in this study, including 568 who underwent colorectal resection, 2201 who underwent video-assisted thoracoscopic pneumonectomy. Among them, 2033 patients received regional block, while 736 patients did not. Statistical analysis indicated that regional blocks could reduce the incidence of postoperative complications of C-D classification Grade II or higher, with an Odds ratio (OR) of 0.742, 95% Confidence interval (CI) (0.552 to 0.996) (P = 0.047).

Conclusion: Regional block is associated with a reduction in the occurrence of postoperative complications graded by C-D classification in elderly patients with thoracic and abdominal cancer. The application of regional blocks can lower the risk of high-risk complications and mortality.

KEYWORDS

regional block, old age, postoperative complications, pain, Clavien-Dindo classification, cancer

Introduction

The postoperative outcome of cancer patients is often the focus of attention. Different anesthesia methods can affect the postoperative outcome of cancer patients (1).Poorly controlled perioperative pain has been shown to associate with increased morbidity, impaired quality of life, longer hospital stays, more opioid use, and higher healthcare costs (2). Systemic opioid analgesics has been used to provide relief from severe trauma-related pain but their use is hampered by serious risks such as respiratory depression, opioid-use disorder, and potentially fatal overdose (3). The more the patients take and the longer the patient takes opioids for, the higher the risk for becoming emotionally and physically dependent on them. Another common type of regional anesthesia is the peripheral regional block (PNB), which is produced by injections made with great exactness near a cluster of nerves to numb the appropriate area of the body extremity (arm, leg, trunk) that requires surgery. Studies have consistently found that patients receiving PNBs experienced superior pain control and less opioid consumption in a wide range of operational procedures, including colorectal surgery, thoracic surgery (4–6). Obviously, PNBs provide a safe and effective way to improve pain management and reduce opioid consumption (7). It has been recommended by Guidelines for Perioperative Care in Elective Colorectal Surgery to accelerate recovery after surgery (8). Such Clinical recommendations are often based on evidence derived from meta-analysis of randomized controlled trials (RCTS) but their interpretation is often hindered by the fact that they do not always consider current clinical relevance (9). Recently, a few studies have found that the use of regional blocks can reduce the incidence of postoperative complications in patients with real data (10), however, the findings are more limited to orthopedic surgery and do not grade the severity of complications in them (11, 12). The same complications may have different levels of severity with different levels of management. The severity of postoperative complications in patients is often graded during surgery according to the Clavien-Dindo (C-D) classification, which grading complications by postoperative management measures (13). Consistent and comparative regional anesthesia outcome data are still lacking, and no study has systematically examined the effects of PNBs on the occurrence of postoperative complications graded by the C-D classification in elder patients with cancer (14). Another challenge lies in the management of perioperative pain in elderly patients. Not only the number of procedures performed on patients over 65 years of age increases significantly, but also older patients are at increased risk of adverse postoperative outcomes (15, 16). In prospective cohort study conducted in the United States, patients aged 80 and above showed significantly higher 30-day all-cause mortality than younger patients (17). As a part of multimodal analgesia, PNBs are preferred for anesthesia in elderly patients to promote rapid recovery after surgery. To the authors' knowledge, studies evaluating the effect of PNBs on all postoperative complications graded by the C-D classification in elderly patients with cancer have not been performed. The aim of the present study was to investigate the relationship of PNBs with high-grade complications in older patients with thoracic and abdominal cancer using real-world data. Our findings provide expanded insights to guide clinical practice and optimize patient care.

Abbreviations: C-D, classification Clavien-Dindo classification; PSM, Propensity score matching; OR, Odds ratio; CI, Confidence interval; CCI, Comprehensive complication index; LOS, Length of stay; PNB, Peripheral regional block; RCT, Randomized controlled trial; TAPB, Transversus abdominis plane block; BIS, Bispectral index; PACU, Post-anesthesia care unit; BMI, Body mass index; ASA, America Society of Anesthesiologists; SD, Standard deviation; ICU, Intensive care unit; RB Regional block; GA, General anesthesia; ARDS, Acute respiratory distress syndrome.

Methods

Ethical considerations

This single-center retrospective study was conducted in accordance with the Declaration of Helsinki at Peking University People's Hospital between 1 January 2018 and 31 March 2022. Ethical approval for this study (Approval No. 2022PHB159-001) was provided by the Medical Ethics Committee of Peking University People's Hospital, Beijing, China (Chairperson: Dr. Xueguang Zhu) in 2022.

Inclusion and exclusion criteria

Patients aged 65 years or more were enrolled in this study. Inclusion criteria was scheduled for elective surgery including radical colorectal resection and thoracoscopic pneumonectomy. Patients who were admitted to the intensive care unit (ICU) before the surgery, those who underwent a second or more operation during this admission, or those with missing or incomplete prognostic records were excluded from this study.

Anesthetic procedure

All patients were divided into two groups, the regional block group (RB) was anesthetized with general anesthesia and regional block, and the general anesthesia group (GA) was only anesthetized with general anesthesia. Preoperative regional block was carried out by an experienced anesthesiologist in a dedicated room equipped with professional operating equipment (ultrasound, nerve stimulator, etc.) according to the patient's surgical site. Transversus abdominis plane block (TAPB) was used for colorectal resection, paravertebral block was provided for thoracoscopic pneumonectomy. All regional block procedures were performed under ultrasound guidance. Low concentrations of ropivacaine were used as local anesthetics for all regional blocks.

All patients underwent general anesthesia with intravenous administration of propofol (1.5 to 2.5 mg/Kg), sufentanil (0.3 μg/Kg) and rocuronium (0.6 mg/Kg). Anesthesia was maintained by inhalation of sevoflurane or desflurane and continuous infusion of propofol and remifentanil to keep the bispectral index (BIS) between 40 and 60. After surgery, the patients were extubated in post-anesthesia care unit (PACU) or in operation room or transferred to the ICU with endotracheal intubation. All extubations were followed by consciousness, respiratory and circulatory stability, and recovery of muscle strength, and the patient was subsequently returned to the ward.

Moreover, during all surgeries, vasopressor agents can be empirically used by the anesthesiologist according to the patient's initial and intraoperative blood pressure.

Postoperative complication assessment

The C-D classification and comprehensive complication index (CCI) were used as the primary outcome to evaluate postoperative complications. The C-D classification is a standardized system to report postoperative morbidity by rating any deviation from the normal postoperative course in 7 grades (I, II, IIIa, IIIb, IVa, IVb and V) (13). Grade I complications are usually mild but Grade II and higher complications are more significant. The CCI is a widely-used tool to assess patients' overall morbidity after an intervention. It based on the complication grading by the C-D classification and calculated as the sum of all complications that were weighted for their severity by patients and physicians, with the final formula yielding a score than rages from 0 (no complication) to 100 (death) (18, 19). In this study, postoperative complications were graded according to the official website (https://www.assessurgery.com/clavien-dindo-classification/) (Table 1), and the CCI was calculated using the CCI Calculator (AssesSurgery GmbH c/o GHM Partners AG Poststrasse 24 6300 Zug). To further analyze the association of anesthetic procedure with postoperative complication, additional data were collected and analyzed as the secondary outcome, including postoperative length of stay (LOS) and hospitalization expense (ten thousand RMB).

TABLE 1 The Clavien-Dindo Classification.

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III - IIIa - IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV - Iva - IVb	Life-threatening complication (including CNS complications)* requiring IC/ICU-management single organ dysfunction (including dialysis) multiorgandysfunction
Grade V	Death of a patient

*brain hemorrhage, ischemic stroke, subarrachnoidalbleeding, but excluding transient ischemic attacks (TIA); IC, Intermediate care; ICU, Intensive care unit.
Quoted from https://www.assessurgery.com/ clavien-dindo-classification/.

Data collection

Data collection included patients' characteristics [gender, age, body mass index (BMI), ASA classification], previous medical history (hypertension, diabetes, coronary heart disease or other types of heart diseases, chronic lung disease, liver failure, renal insufficiency, venous thromboembolism, coagulation dysfunction, immune system disorders, hypoproteinemia, anemia, and hyponatremia) and preoperative medications (antiplatelet or anticoagulant therapy, chemotherapy). Preoperative hypoproteinemia, anemia and hyponatremia were determined based on the last laboratory examination before surgery. Anemia was defined as a hemoglobin concentration of less than 13 g/L in men and 12 g/L in women. Hypoproteinemia was defined as albumin of less than 30 g/L or total protein of less than 60 g/L. Hyponatremia was defined as a serum sodium concentration of less than 135 mmol/L. The details about the operation were also recorded such as duration, intraoperative use of vasopressor, application of regional block.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (SPSS Inc, Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation (SD), and categorical data were expressed as frequency and percent. The differences between continuous variables with from Gaussian distribution were compared using Student's t-test. Otherwise, the non-parametric Mann-Whitney U test was used. Categorical data were compared using Pearson's chi-square test or Fisher's exact test. 1:1 propensity score matching was performed with duration, ASA classification, preoperative venous thromboembolism and chemotherapy. Univariable and multivariable logistic regression were used to identify the factors associated with categorical outcome measures, univariable and multivariable linear regression were used to identify the factors associated with continuous outcome measures. A *P* value of less than 0.2 and factors thought to have influenced in the results were admitted to the multivariable logistic regression. A *P* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

As shown in Figure 1, a total of 2769 eligible subjects who underwent elective surgery were enrolled in the study. All eligible subjects were divided into regional block (RB) group (2033 patients, 73.4%) and general anesthesia (GA) group (736 patients, 26.6%). There were statistically significant differences between the two groups in gender(P=0.022), ASA classification(P<0.001), type of surgery(P<0.001), duration(P<0.001), use vasopressor during the surgery(P=0.008), preoperative diabetes(P=0.048), chronic lung disease(P=0.010),venous thromboembolism(P=0.001), hypoproteinemia(P=0.018), anemia(P<0.001), hyponatremia (P=0.023), chemotherapy(P=0.003) (Table 2). After matching, all eligible subjects were divided into RB group (712 patients, 50.0%) and GA group (712 patients, 50.0%). There were no statistically significant differences between the two groups other than type of surgery(P<0.001), preoperative anemia(P=0.003) and antiplatelet or anticoagulant therapy(P=0.025).

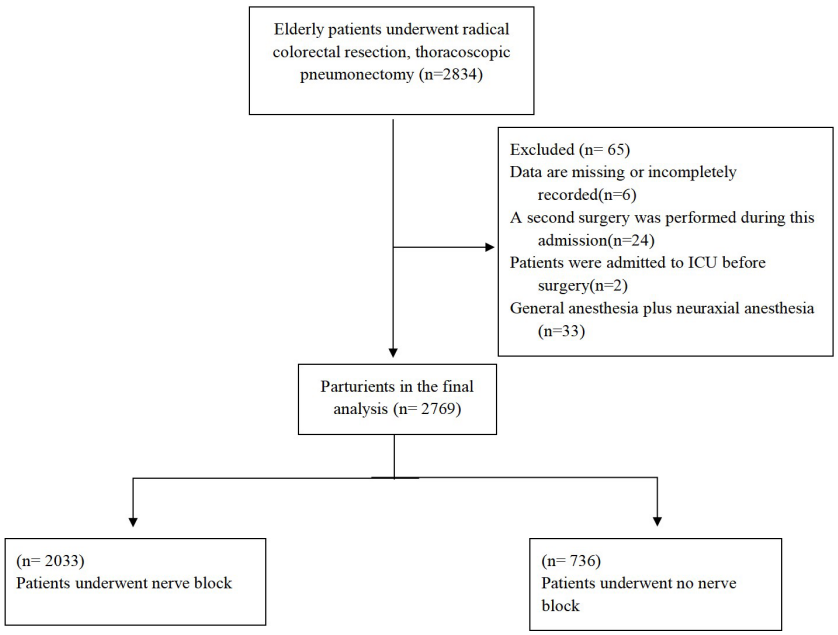

FIGURE 1
Quoted from https://www.assessurgery.com/clavien-dindo-classification/.

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TABLE 2 Comparison of patient demographics, intraoperative findings and preoperative history between groups.

	Unmatched			Matched		
	RB (2033)	GA (736)	*P value**	RB (712)	GA (712)	*P value**
Patient characteristics						
Age, mean (SD)	71 (5)	72 (6)	0.065	71 (5)	72 (6)	0.635
Females, n (%)	1034 (50.9)	398 (54.1)	**0.022**	323 (45.4)	325 (45.6)	0.915
BMI, n (%)			0.063			0.069
> 28 Kg/m^2	242 (11.9)	69 (9.4)		85 (11.9)	64 (9.0)	
≤28 Kg/m^2	1791 (88.1)	667 (90.6)		627 (88.1)	648 (91.0)	
ASA, n (%)			**<0.001**			1.000
≥ Grade III	330 (16.2)	204 (27.7)		191 (26.8)	191 (26.8)	
< Grade III	1703 (83.8)	532 (72.3)		521 (73.2)	521 (73.2)	
Surgery and anesthesia, n (%)						
Type of surgery			**<0.001**			**<0.001**
Radical colorectal resection	200 (9.8)	368 (50.0)		131 (18.4)	344 (48.3)	
Thoracoscopic pneumonectomy	1833 (90.2)	368 (50.0)		581 (81.6)	368 (51.7)	
Duration			**<0.001**			0.955
> 3 h	326 (16.0)	266 (36.1)		241 (33.8)	242 (34.0)	
≤ 3 h	1707 (84.0)	470 (63.9)		471 (66.2)	470 (66.0)	
Use vasopressor during operation, n (%)	1276(62.8)	502 (68.2)	**0.008**	461 (64.7)	483 (67.8)	0.217
Previous history, n (%)						
Hypertension	982 (48.3)	356 (48.4)	0.975	326 (45.8)	345 (48.5)	0.313
Diabetes	405 (19.9)	172 (23.4)	**0.048**	145 (20.4)	163 (22.9)	0.247
Coronary heart disease	299 (14.7)	98 (13.3)	0.356	118 (16.6)	93 (13.1)	0.062
Other heart diseases	188 (9.2)	70 (9.5)	0.833	69 (9.7)	69 (9.7)	1.000
Chronic lung disease	50 (2.5)	32 (4.3)	**0.010**	19 (2.7)	30 (4.2)	0.110
Liver failure	47 (2.3)	16 (2.2)	0.830	16 (2.2)	16 (2.2)	1.000
Renal insufficiency	40 (2.0)	15 (2.0)	0.906	15 (2.1)	14 (2.0)	0.851
Venous thromboembolism	7 (0.34)	11 (1.5)	**0.001**	6 (0.84)	5 (0.70)	0.762
Coagulation dysfunction	9 (0.44)	3 (0.41)	0.901	4 (0.56)	3 (0.42)	0.705
Immune system disorder	17 (0.84)	2 (0.27)	0.112	5 (0.70)	2 (0.28)	0.452
Hypoproteinemia	189 (9.3)	91 (12.4)	**0.018**	82 (11.5)	85 (11.9)	0.805
Anemia	405 (19.9)	238 (32.3)	**<0.001**	176 (24.7)	226 (31.7)	**0.003**
Hyponatremia	27 (1.3)	19 (2.6)	**0.023**	17 (2.4)	18 (2.5)	0.864
Antiplatelet or anticoagulant therapy	327 (16.1)	106 (14.4)	0.282	130 (18.3)	99 (13.9)	**0.025**
Chemotherapy	59(2.9)	39 (5.3)	**0.003**	19 (2.7)	19 (2.7)	1.000

*Fisher's exact test was used for dichotomous and categorical variables; Mann-Whitney (Wilcoxon rank-sum) test was used for continuous variables; Propensity score matching was performed based on ASA classification, duration of surgery, venous thromboembolism, and preoperative chemotherapy.
RB, regional block; GA, general anesthesia; BMI, body mass index; ASA, American Society of Anesthesiologists.
P value of less than 0.05 was considered statistically significant.

Postoperative complications graded by C-D classification

Before matching, 140(6.9%) patients had no complication in RB group, and 22(3.0%) patients had no complication in GA group. Among those receiving a regional block, 15 (0.74% of all patients) of the complications were rated as Grade III, including 10 (0.49% of all) as Grade IIIa(P<0.001) and 5 (0.25% of all) as Grade IIIb (P=0.004). Besides, 8 (0.39% of all patients) of the complications were rated as Grade IV, including 2 (0.10% of all) as Grade IVa (P=1.000) and 6 (0.30% of all) as Grade IVb(P=1.000). 3(0.15%) patients experienced C-D classification Grade V complication in those who received a regional block(P=0.570). After matching, 34 (4.8%) patients had no complication in RB group, and 22(3.1%) patients had no complication in GA group (P=0.102). 460(64.6%) patients had C-D classification Grade I with regional block and 347 (48.7) patients had C-D classification Grade I without regional block (P<0.001). 202(28.4%) patients had C-D classification Grade II with regional block and 319(44.8) patients had C-D classification Grade II without regional block (P<0.001). 7 (0.98% of all patients) of the complications were rated as Grade III, including 5 (0.70% of all) as Grade IIIa (P=0.058) and 2 (0.28% of all) as Grade IIIb (P=0.057), 6 (0.84% of all patients) of the complications were rated as Grade IV, including 1 (0.14% of all) as Grade IVa (P=1.000) and 5 (0.70% of all) as Grade IVb (P=0.452) and 3(0.42%) patients had C-D classification Grade V in those who received a regional block. (Get more specific information in Table 3).

In patients who had C-D classification Grade III or higher, 8 cases of anastomotic fistula, 3 cases of ileus, 6 cases of wound dehiscence, 11 cases of postoperative infection, 1 case of acute myocardial infarction, 4 cases of active hemorrhage, 1 case of delayed gastric emptying, 1 case of subcutaneous abscess, 1 case of arrhythmia, and 11 cases of persistent air leaks in the lungs, 2 cases of chest chyle fistula, 1 case of hypoxemia, 1 case of heart failure, 1 case of ARDS, 1 case of dysuresia occurred. A total of three patients experienced postoperative complications of Grade V in C-D classification, postoperative death, and the causes of death were postoperative infection, acute cardiac infarction and ARDS, respectively. (See Table 4 for specific classifications).

Effects of regional blocks on postoperative complications graded by higher C-D classification

As shown in Table 3, among patients with C-D classification Grade II or higher complications, regional blocks were used in 462 (22.7%), (Odds ratio (OR) 0.714, 95% Confidence interval (CI) 0.559 to 0.912 (P=0.007). Among patients with C-D classification Grade III or higher complications, regional blocks were used in 33 (1.6%), with OR 0.736, 95% CI 0.427 to 1.269 (P=0.270). The mean ± SD of CCI in two groups was 14.0 ± 9.7 vs 20.6 ± 11.9, the β value of regional block application was -0.843, 95%CI (-1.629 to -0.056) (P=0.036).After matching, in Table 5, among patients with C-D classification Grade II or higher complications, regional blocks were used in 216(30.3%) patients, with 348(48.9%) in GA group (OR 0.742, 95% CI 0.552 to 0.996 (P =0.047). Among patients with C-D classification Grade III or higher complications, regional blocks

TABLE 3 Comparison of C-D classification, CCI and postoperative length of stay, total cost between two groups.

	Unmatched			Matched		
	RB (2033)	GA (736)	P value*	RB (712)	GA (712)	P value*
Clavien-Dindo classification						
No complication, n (%)	140 (6.9)	22 (3.0)	**<0.001**	34 (4.8)	22 (3.1)	0.102
I, n (%)	1429 (70.3)	348 (47.3)	**<0.001**	460 (64.6)	347 (48.7)	**<0.001**
II, n (%)	439 (21.6)	340 (46.2)	**<0.001**	202 (28.4)	319 (44.8)	**<0.001**
IIIa, n (%)	10 (0.49)	14 (1.9)	**<0.001**	5 (0.70)	13 (1.8)	0.058
IIIb, n (%)	5 (0.25)	9 (1.2)	**0.004**	2 (0.28)	8 (1.1)	0.057
IVa, n (%)	2 (0.10)	1 (0.14)	1.000	1 (0.14)	1 (0.14)	1.000
IVb, n (%)	6 (0.30)	2 (0.10)	1.000	5 (0.70)	2 (0.28)	0.452
V, n (%)	3 (0.15)	0 (0)	0.570	3 (0.42)	0 (0)	0.249
≥Grade II, n (%)	462 (22.7)	371 (50.4)	**0.007**	216 (30.3)	348 (48.9)	**<0.001**
≥Grade III, n (%)	33 (1.6)	40 (5.4)	0.270	19 (2.7)	38 (5.3)	**0.010**
CCI, %, mean(SD)	14.0 (9.7)	20.6 (11.9)	**0.036**	16.2 (11.9)	20.2 (11.7)	**<0.001**
postoperative length of stay, mean(SD)	5 (4)	8 (10)	0.133	6 (4)	8 (9)	**<0.001**
Total cost#, mean(SD)	7.8 (3.8)	10.0 (18.2)	0.397	8.6 (4.7)	9.9 (18.4)	**0.019**

*Fisher's exact test was used for dichotomous and categorical variables; Mann-Whitney (Wilcoxon rank-sum) test was used for continuous variables.
#Ten thousand RMB.
RB, regional block; GA, general anesthesia; CCI, comprehensive complication index.
P value of less than 0.05 was considered statistically significant.

TABLE 4 Cases of C-D classification Grade III or higher.

Complications	Number	IIIa	IIIb	IVa	IVb	V	Proportion of all,%
Anastomotic fistula	8	4	3		1		0.29
Ileus	3	3					0.11
Wound dehiscence	6	2	4				0.22
Postoperative infection	11	2	2	1	5	1	0.40
Acute myocardial infarction	1					1	0.04
Active hemorrhage	4	2	1		1		0.14
Delayed gastric emptying	1	1					0.04
subcutaneous abscess	1	1					0.04
arrhythmia	1	1					0.04
Persistent air leaks in the lungs	11	8	2	1			0.40
Chest chyle fistula	2		2				0.07
Hypoxemia	1			1			0.04
Heart failure	1				1		0.04
ARDS	1					1	0.04
Dysuresia	1	1					0.04

One patient may have a combination of complications.
ARDS, Acute respiratory distress syndrome.

TABLE 5 Sensitivity and adjusted analyses.

Unmatched				
Outcome variables*	OR	*P* value	Lower 95%	Upper 95%
≥Grade II	0.714	**0.007**	0.559	0.912
≥Grade III	0.736	0.270	0.427	1.269
Outcome variable†	Unstandardized Coefficients B	*P* value	Lower 95%	Upper 95%
CCI (%)	-0.843	**0.036**	-1.629	-0.056
postoperative length of stay	-0.371	0.133	-0.856	0.113
Total cost#	-0.399	0.397	-1.322	0.524
Matched				
Outcome variables*	OR	*P* value	Lower 95%	Upper 95%
≥Grade II	0.742	**0.047**	0.552	0.996
≥Grade III	0.818	0.522	0.441	1.514
Outcome variable†	Unstandardized Coefficients B	*P* value	Lower 95%	Upper 95%
CCI (%)	-0.651	0.221	-1.694	0.392
postoperative length of stay	-0.331	0.374	-1.061	0.399
Total cost#	-0.184	0.809	-1.679	1.310

*Multivariable logistic regression was used.
†Multivariable generalized linear modeling was used.
#Ten thousand RMB.
P value of less than 0.05 was considered statistically significant.

were used in 19(2.7%), with OR 0.818, 95% CI 0.441 to 1.514 (P=0.522). The mean ± SD of CCI in two groups was 16.2 ± 11.9 vs 20.2 ± 11.7, the β value of regional block application was -0.651, 95%CI (-1.694 to 0.392) (P=0.221).

LOS and cost

After matching, there were no noteworthy variations between the two groups regarding the postoperative LOS and total cost incurred during hospitalization, with 6 ± 4 vs 8 ± 9(P=0.374) in postoperative LOS and 8.6 ± 4.7 vs 9.9 ± 18.4(P=0.809) in total cost incurred during hospitalization.

Besides, the incidence of C-D classification Grade II/III or higher complications and CCI was strongly associated with postoperative hospitalization days before or after matching(P<0.001).

Discussion

Postoperative outcomes in elderly patients with cancer are often worrisome. The prevention of postoperative complications in elderly patients with cancer is a challenging and critical task because of co-existing diseases and concurrent medications, diminished functional status and physiological reserve and age-related pharmacodynamic and pharmacokinetic changes in elderly patients. Undoubtedly, PNBs improve analgesia efficacy and reduce opioid requirements and their side effects. The present study evaluated the occurrence of postoperative complications in elderly patients with cancer receiving a PNB in the real world and demonstrated that the utilization of PNBs reduced high-grade complications graded by C-D classification.

Population aging, resulting from the decline in fertility rates and increased life expectancy, has significant social and economic impacts on the world. By 2030, 1 in 6 people in the world will be aged 60 years or above (20). At the same time, the number of elderly cancer patients is increasing year by year, often with one or two underlying diseases and a worrisome health condition. Despite great progress in the care of older surgical patients, they remain more likely to have more postoperative complications, extended length of hospital stays, and higher healthcare costs than younger counterparts (21, 22). Numerous studies have shown high operative mortality in older patients who underwent emergency procedures (10, 23). Although we did not have as large a volume of data and were a single-center study, we included all relevant postoperative complications requiring action and graded them according to the C-D classification, demonstrating that regional blocks do reduce postoperative interventions for patients, reduce medical consumption, and decrease length of stay. To systematic measurement of whether regional blocks provide benefit to older patients, we assessed the effects of PNBs on postoperative complications in elderly patients with cancer undergoing radical colorectal resection, thoracoscopic pneumonectomy. By using the C-D classification to rank postoperative complications, we found that the patients receiving a regional block were less likely to experience postoperative complications of Grade II or above. To further verify it, we also calculated CCI to estimate the burden of complications more accurately as only the most serious complication was considered for grading when using the C-D classification system. The CCI has been widely validated for grading the severity of complications and predicting postoperative outcomes in elderly surgical patients (24–26). However, only significant differences of CCI between the two groups before matching were observed.

In addition, we observed postoperative LOS and total cost during the hospitalization. A shorter stay can reduce the cost per discharge and shift care from inpatient to less expensive settings, indicating better efficiency of hospital management (27). In the study, there was not a significant effect of the application of regional block on postoperative LOS or total cost but a marked reduction in RB group, which may be related to the type of surgery and other confounding factors. Elderly patients with cancer have more comorbidities, a poor basic state, and are more easier affected by surgery than normal adults. Among the different types of surgeries, regional blocks can be an effective means of reducing the incidence of postoperative complications and the LOS. Furthermore, individualized care and rapid recovery programs are necessary to reduce mortality rates. Although training in regional anesthetics has increased, the use of PNB in patients requires more experience and modifications in local anesthetic concentrations, adjuvants, and infusions (28). Of course, large-scale real world studies are needed to verify the effects of regional block in elderly patients with cancer.

It is noteworthy that the single-center study may have a certain bias despite we used real data to illustrate the benefits of regional block in elderly patients. First, considering the type of surgery and the application of nerve blocks the type of surgery was restricted to radical colorectal resection and thoracoscopic pneumonectomy. We studied an elderly population, so we chose the two surgeries in which postoperative complications had a greater impact on survival, however, it may increase the incidence of serious postoperative complications and produce bias in the results. Second, the use of regional block was inevitably influenced by the patient, anesthesiologist, timing of surgery, surgeons, and other subjective factors (29). Moreover, long-term outcomes in older patients also awaits further investigations, such as readmission and mortality rates of patients at 3 months, 6 months and even 1 year after surgery.

Conclusion

In summary, the results indicate that the utilization of regional block is a promising approach to enhance postoperative outcomes in elderly patients with thoracic and abdominal cancer, as it effectively reduces the incidence of high-risk complications graded by Clavien-Dindo classification. The center has a standardized algorithm for regional block, which has been shown to benefit older patients undergoing thoracic and abdominal surgery. However, an advantage of regional block in reducing CCI and saving hospital stay were not observed. To achieve optimal results, it is crucial to utilize appropriate regional block techniques and to provide individualized treatment plans based on the patient's specific needs.

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

This study was conducted in accordance with the Declaration of Helsinki at Peking University People's Hospital between 1 January 2018 and 31 March 2022. Ethical approval for this study (Approval No. 2022PHB159-001) was provided by the Medical Ethics Committee of Peking University People's Hospital, Beijing, China (Chairperson: Dr. Xueguang Zhu) in 2022.

Author contributions

WD: Formal Analysis, Methodology, Writing – original draft. YZ: Data curation, Writing – review & editing. HL: Formal Analysis, Writing – review & editing. TZ: Data curation, Writing – review & editing. WZ: Data curation, Writing – review & editing. YF: Methodology, Writing – review & editing. HA: Visualization, Writing – review & editing.

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Conflict of interest

The 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.

Publisher's note

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The role of superior hemorrhoidal vein ectasia in the preoperative staging of rectal cancer

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Objective: The prognosis of colorectal cancer has continuously improved in recent years thanks to continuous progress in both the therapeutic and diagnostic fields. The specific objective of this study is to contribute to the diagnostic field through the evaluation of the correlation between superior hemorrhoidal vein (SHV) ectasia detected on computed tomography (CT) and Tumor (T), Node (N), and distant metastasis (M) examination and mesorectal fascia (MRF) invasion in the preoperative staging of rectal cancer.

Methods: Between January 2018 and April 2022, 46 patients with histopathological diagnosis of rectal cancer were retrospectively enrolled, and the diameter of the SHV was evaluated by CT examination. The cutoff value for SHV diameter used is 3.7 mm. The diameter was measured at the level of S2 during portal venous phase after 4× image zoom to reduce the interobserver variability. The parameters evaluated were tumor location, detection of MRF infiltration (defined as the distance < 1 mm between the tumor margins and the fascia), SHV diameter, detection of mesorectal perilesional lymph nodes, and detection of metastasis.

Results: A total of 67.39% (31/46) of patients had SHV ectasia. All patients with MRF infiltration (4/46, 7.14%) presented SHV ectasia (average diameter of 4.4 mm), and SHV was significantly related with the development of liver metastases at the moment of primary staging and during follow-up.

Conclusion: SHV ectasia may be related to metastasis and MRF involvement; therefore, it could become a tool for preoperative staging of rectal cancer.

KEYWORDS

computed tomography, CT, rectal cancer, superior hemorrhoidal vein, tumor diagnosis, prediction

Abbreviations: EMVI, Extramural vascular invasion; MRF, Mesorectal fascia; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; SHV, Superior hemorrhoidal vein; LVI, Lymph-vascular invasion; SR, structured reporting.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of cancer-related death and, in Western countries, represents about 30% of large bowel cancers (1–5).

The CRC includes a dissimilar group of diseases in terms of mutations and mutagens, representing a challenging field for molecular therapy. Furthermore, the heterogeneity of embryological origins, anatomy, and functions underlines the differences between colon and rectal cancer. More than 30% of patients experience metastasis after primary tumor diagnosis, whereas peritoneal dissemination has long been associated with unfavorable prognosis (6–8).

Rectal cancer has a wide distribution from the seventh decade onward, although diagnoses in patients under 50 are increasing (9).

The median age at diagnosis is 70 years old, with an increase among frailty patients (10). However, many studies demonstrated rapidly increasing incidence rates among adults younger than 50 years (11, 12).

Accurate preoperative staging is mandatory to choose the most precise treatment strategy, taking into account the continuously rising rates of minimally invasive surgery (13–21). It is usually conducted through American Joint Committee on Cancer (AJCC) TNM classification (22, 23). Among the radiological features, the tumor infiltration pattern is strictly related to the patient's prognosis (24). In particular, the invasion through the rectal wall, expressed by the T stage, is defined by imaging features in the pre-operative evaluation. T stage is related with local recurrence and has a role in the choice between up-front surgery and neo-adjuvant therapy (25–27).

In preoperative staging, rectal ultrasound endoscopy (EUS) is essential for early-stage tumors (T1 and T2). MRI is generally unable to distinguish T1 tumors (growing into the submucosa) from T2 tumors (growing into the muscularis propria) and is considered the standard tool for rectal cancer in more advanced stages (T3–T4) where accuracy in evaluating the infiltration of the mesorectal fascia (MRF) is fundamental.

As highly reported in the literature since the 1990s (28–30), in patients affected by locally advanced T3–T4 and/or N1–N3 low or middle rectal cancers or for tumors with circumferential margin < 1 mm regardless of the site and stage at magnetic resonance imaging (MRI) (31), preoperative radiotherapy followed by surgery represents the curative treatment.

According to the European Society of Medical Oncology guidelines, neoadjuvant chemotherapy is deserved to patients with a grade of infiltration > 5 mm at MRI evaluation (32, 33). MRI has a great sensitivity in the evaluation of T and N stages, approximately of 90%, and is the most accurate tool for the loco-regional staging of rectal cancer (34, 35).

Although radiological and surgical efforts to reduce the side effects of radiotherapy as proctitis, anal incontinence, anastomotic leak or stenosis, the optimal dose of radiotherapy is still debated (36–41).

In this clinical scenario, the most challenging stage to characterize with the standard imaging protocols is the T3, which is related to an overall 5-year survival ranging from 25% to 90%, depending on the T3 subgroup (32, 42–44).

A prognostic role has also been attributed to extramural vascular invasion (EMVI) and involvement of MRF representing poor prognostic factors (45–47). The EMVI is defined as the presence of tumor cells beyond the muscularis propria in endothelium-lined vessels (48, 49), and it is defined by the histological report as lymph-vascular invasion (LVI) (50). EMVI is reported as a risk factor for recurrent disease and metastasis and as a stage independent negative prognostic factor, increasing the risk of developing liver metastases (51, 52).

MRF is considered involved when the distance between the tumor and MRF is ≤1 mm. MRI has the highest accuracy concerning T and N stages and EMVI evaluation; however, the evaluation of EMVI and MRF can be challenging in many cases (53).

The reduced territorial availability of MRI, higher costs, longer execution times, and limited patient characteristics (claustrophobia, marked obesity, metal devices implanted in the body, etc.) reduce the possibility of carrying out an MRI in all patients. On the other hand, the possible presence of marked colorectum stenosis makes the use of the EUS impossible. In these cases, computed tomography (CT) examination and subsequent SHV evaluation become the first choice.

CT can be an alternative diagnostic imaging technique that allows to study of the entire abdomen and pelvis; CT is widely diffuse in clinical practice to assess the preoperative staging of abdominal lymphatic stations and distant metastases. CT is mandatory as 25% of patients affected by CRC have synchronous liver metastases (7, 54–56). Concerning the limited visualization of the mesorectal and the rectal wall, CT cannot be considered the gold standard, as it lacks of contrast resolution, especially for early-stage lesions confined to the rectal wall (32, 57, 58).

On the other hand, CT allows a clear visualization of the vascular anatomy. Concerning venous vascular system of rectum, the superior rectal venous plexus drains into superior hemorrhoidal vein (SHV), which has its origin in the hemorrhoidal plexus and, through this plexus, communicates with the middle and inferior hemorrhoidal veins. The superior rectal vein leaves the lesser pelvis and crosses the left common iliac vessels with the superior rectal artery and is continued upward as the inferior mesenteric vein and finally in the portal vein.

Many diseases are associated with focal or diffuse vascular enlargement of pelvic vessels, among which are pelvic tumors (59). In patients with CRC, it seems to be a variation in the splanchnic circulation. In particular, the SHV ectasia seems to be related to the extramural spreading of the tumor, being a new important negative prognostic factor (60).

This study aims to evaluate the correlation between the SHV ectasia, metastasis, and MRF invasion in the preoperative staging of rectal cancer.

Materials and methods

Image acquisition

Between January 2018 and April 2022, all consecutive patients with histopathological diagnosis of rectal cancer were enrolled at the Polyclinic of Bari, Italy, and their data were retrospectively analyzed.

Inclusion criteria:

- diagnosis of rectal cancer;
- informed signed consent to the use of their anonymous data for scientific research; and
- no sign of portal hypertension, cirrhosis, pelvic masses, and splanchnic vein thrombosis (59).

Exclusion criteria:

- any sign of portal hypertension, cirrhosis, pelvic masses, and splanchnic vein thrombosis; and
- lack of consent to participate to the study.

All patients underwent CT examination within 15 days before surgery and histopathological diagnosis as indicated by the standard of care of our institution.

All patients underwent multidisciplinary team discussion before treatment.

CT exams were obtained with a 320-row CT scanner (Multidetector CT Aquillon, Toshiba Medical System, Tokyo, Japan; detector collimation, 0.5 mm; increment, 0.5; 120/87 kVp/mAs).

CT protocol included a non-enhanced scan followed by multiphasic acquisition after the intravenous injection of 1.5 mL/kg of Iopromide (370 mgI/mL) at 2.5 mL/s through the ante-cubital vein using an automatic power injector. The patients were scanned in supine position.

The acquisition was performed from the diaphragm to the pubic symphysis in the non-enhanced and arterial phases; in the portal venous phase, the scan was extended to the thorax. No bowel preparation was performed before CT examination (61).

All CT data were transferred to a workstation equipped with dedicated software for image reconstructions (Vitrea FX 4.1, Vital Images, Minneapolis, Minnesota, USA).

Dataset

Patients underwent surgery following the Italian National Guidelines (Italian Association of Medical Oncology (AIOM)) (62) with curative intent within 3 weeks from CT examination; then, the surgical specimens were submitted to the pathology department for examination. For each patient, we analyzed cancer location (low, middle, and high) and TNM parameters according to the VIII edition of the TNM classification by AJCC (22).

The present retrospective clinical study complied with ethical principles, including the Declaration of Helsinki of the World Medical Association and the additional requirements of Italian law and our Institutional Ethical Committee. In addition, the study was considered free from ethical review as it carries only negligible risk and involves the use of existing data, which contains only non-identifiable human data. The patient signed a written informed consent form approved by the local ethical board.

Preoperative CT scans were examined by two blinded radiologists with 10-year experience in gastrointestinal and oncologic radiology.

According to the literature, the cutoff value for SHV diameter used is 3.7 mm (60); the diameter was measured at the level of S2 vertebral level during portal venous phase after *4× image zoom* to reduce the interobserver variability (61). SHV was detected in all patients.

The parameters evaluated were as follows:

- tumor size and location: location of rectal cancer is classified in a cranio-caudal direction basing on the distance of the tumor from the anal verge as low (up to 5 cm), middle (from >5 cm to 10 cm), or high (from >10 cm up to 15 cm);
- detection of MRF infiltration, defined as the distance < 1 mm between the tumor margins and the fascia (26, 48, 63);
- SHV diameter;
- detection of mesorectal perilesional lymph nodes; and
- detection of metastasis.

Statistical analysis

The baseline characteristics of the patients, the SHV ectasia, the presence of synchronous metastasis at CT examination, and the presence of lymph nodes involvement at pathological examination were evaluated by descriptive statistics. The relationship between SHV ectasia and the disease progression was evaluated through the Chi-square test or the Fisher test. P-value was judged statistically significant when less than 0.05.

The interobserver agreement was evaluated by using Cohen's kappa (K). $k > 0.81$ assessed an almost complete agreement, and $0.61 < k < 0.8$ and $0.41 < k < 0.6$ assessed a substantial and a moderate agreement, respectively.

The statistical analysis was performed by using NCSS2007® software.

Results

Forty-six patients were included in our study: 20 men (43.48%) and 26 (56.52%) women with a median age of 62 years. Descriptive statistics of pre-operative staging show that 16/46 (34.78%) patients had low rectal cancer, 18/46 (39.13%) patients had medium rectal cancer, and 12/46 (26.09%) patients had high rectal cancer.

Twelve of the 46 (26.09%) patients had synchronous metastatic involvement at the time of diagnosis of primary tumor.

Neoplastic infiltration of MRF was found in 4/46 (8.69%) patients: None of these patients presented hepatic metastasis. No lung metastases were detected in any patient.

Thirty-one of the 46 (67.39%) patients were SHV positive.

All patients undergoing surgery did not show any MRF infiltration.

At CT examination, 30/46 (65.21%) patients had a suspicion of perirectal lymph nodes.

Postoperative staging of patients undergoing surgery with neoadjuvant radiotherapy with or without chemotherapy after a minimum of 18 months of follow-up shows that 8 of the 31 patients who were SHV positive and M0 developed liver metastasis.

SHV ectasia

The radiological evidence of SHV ectasia was shown in Figures 1A–E. Cohen's kappa (K) was 0.78, indicating a high grade interrater agreement among the two expert radiologists.

All patients with MRF infiltration (4/46, 7.14%) presented SHV ectasia (average diameter of 4.4 mm).

Table 1 shows that 67.39% (31/46) of patients had SHV ectasia. SHV ectasia was significantly related with the development of liver metastases at the moment of primary staging and during follow-up.

Discussion

In our experience, we evaluated the relationship between SHV diameter and T parameter, lymph node involvement, distant metastasis, and MRF infiltration. SHV ectasia may be related to metastasis development.

We found a significant relationship between SHV and advanced disease and disease progression. Hence, in further studies considering our preliminary data, SHV should be considered in the preoperative staging to better stratify the risk classification of disease progression. Our suggestion is to detect the high-risk patient group to perform a more intensive follow-up integrated with liver MRI that can more accurately detect and characterize also small potential liver lesions.

However, it should be underlined that venous vessel enlargement could be due to three principal mechanisms: increasing of venous drainage associated to neoplastic hypervascularization (64), splanchnic vein arterialization due to arterio-venous shunt, and increasing of venous pressure in neoplastic thrombosis (65). Considering this possible bias in patient selection, we preliminarily excluded from this study patients with cirrhosis, portal hypertension, pelvic masses, and splanchnic vein thrombosis, because SHV ectasia is frequent in these patients due to the presence of collateral circulation (59). Patient's prognosis was affected by tumor invasion of the rectal wall, N stage, and MRF involvement (66, 67).

Following other literature experiences, we chose the cutoff of 3.7 mm to determine SHV ectasia. Some authors established that those patients with SHV diameter equal to or more than 3.7 mm had LVI (26, 60).

The nodal stage is often a challenge for radiologists especially because preoperative staging CT has a limited value in predicting lymph node metastasis in early rectal cancer and it is strongly related to metastatic disease and the treatment (6, 14, 25, 68–74). The study population showed that SHV diameter exceeded the cutoff by 3.7 mm in 79% of patients who had N+ confirmed after surgery and pathological examination. About distant metastasis, 75% of patients with liver metastasis had a SHV enlargement. Thus,

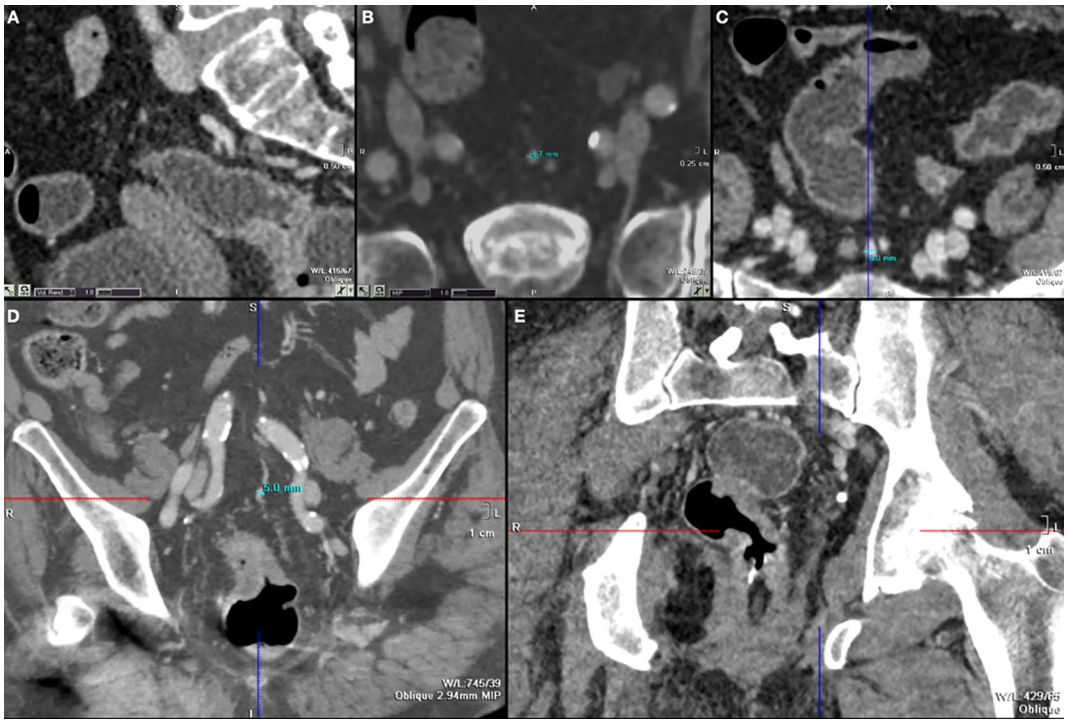

FIGURE 1
(A) S2 plane to evaluate SHV and S2 (sagittal reconstruction); **(B–D)** cases of SHV ectasia seen axial plane **(B, C)** and coronal plane **(D)**; **(E)** tumor of left lateral wall with MRF invasion and SHV ectasia.

TABLE 1 Relationship between N and M status and SHV diameter.

	SHV−	SHV+	P-value
M−	12	14	0.031
M+	3	17	

patients with SHV diameter equal to or more than 3.7 mm tended to have nodal and distant metastasis.

In addition, we observed that, in the 16 patients who underwent neoadjuvant therapy, 3 did not show SHV ectasia although they had advanced cancer disease. Out of these three patients, two had low rectal cancer, and one had middle rectal cancer. We supposed that a lower rectal cancer, next to the anal verge, could have a different cancer venous vascular drainage, as inferior and/or middle hemorrhoidal vein that could justify no enlargement of SHV.

MRF is considered involved when the distance between the tumor and MRF is ≤1 mm. In our study, all patients with MRF involvement had SHV ectasia; this suggests a possible correlation between these two factors, both predictive of major invasion of the tumor.

Our experience confirms that SHV diameter measurement could be a meaningful tool to analyze LVI, as previously demonstrated in other reports (26, 75). Furthermore, the study suggests that SHV diameter could be a potential marker of MRF involvement.

If this were to be confirmed by further studies, then SHV ectasia may be integrated into the standardized parameters of the structured reporting (SR) for rectal cancer staging. The implementation of SR is important to offer referring physicians and patients an optimal quality of service and to provide researchers with data of the best quality (76, 77).

Obviously, we have to underline that MRF involvement and SHV diameter are useful only if integrated to the standard procedures concerning diagnosis and treatment of rectal cancer.

Nowadays, MRI is the most accurate non-invasive imaging modality to assess local staging at the moment of primary diagnosis (78–80).

MRI, through fast spin echo T2-weighted (FSE T2W), diffusion weighted imaging (DWI), and Apparent diffusion coefficient (APC) sequences, allows to recognize locally advanced diseases suitable of neoadjuvant CRT and to identify poor prognostic factors (81–83).

The identification of a locally advanced disease is mandatory to select the most precise treatment strategy, as the 25% of patients develop local recurrence after surgery and to improve the quality of life after surgery (14, 24, 44, 58, 84, 85).

The differentiation between T2 and T3 needs the MRI and the endorectal US in selected patients (86).

However, MRI has a high risk of over-staging disease due to the modification of muscolaris propria related to penetrating vessels or tissue desmoplastic reaction into the mesenteric fat (49, 87–89).

MRI is also useful for studying the locoregional nodal involvement and the extra-mesorectal lateral nodes, which, if pathological, makes the patients suitable for neoadjuvant chemotherapy (74).

MRI sensitivity is approximately 85% in nodal characterization; however, malignant cells might also be present in nodes < 5 mm of short axis, so our diagnosis power is still lower than our desire (83, 90).

All cases are characterized by a locally advanced disease diagnosed at MRI scan, and, in patients with a middle-low rectal tumor, the neoadjuvant treatment is mandatory before surgery, allowing organ-sparing surgical procedures with lower recurrence rates (87, 91, 92).

Therefore, for the local staging, MRI is the most complete diagnostic modality as it allows to accurately evaluate tumor location, Circumferential resection margin (CRM) involvement, nodal involvement, tumor deposits, or EMVI (93, 94).

Obviously, after any local treatment, it is also considered the gold standard for the restaging to assess the response to therapy (95–97).

At the same time, contrast-enhanced CT of the whole body is mandatory to detect distant metastases and complete the M-staging even in the pre-operative time even after neoadjuvant therapy (98, 99).

The diagnostic performance of CT of liver metastases is high, but it decreases for the lesions < 10 mm (56). In these cases, a diagnostic integration with liver MRI should be performed in selected patients (100, 101).

For this reason, several studies are focusing on the identification of the high risk patients (102–104).

Surely, rectal MRI allows to identify some negative features, such as EMVI, which is related to a higher incidence of developing distant metastases, particularly liver metastases (105–107).

Thus, taking into account what discussed above, the presence of SHV ectasia could also be considered a prognostic feature, suggesting the need of an MRI follow-up (60).

However, this tool should be validated in clinical practice in randomized prospective studies. In addition to radiological imaging, several studies are proposing liquid biopsy to detect circulating DNA that can contribute to the risk stratification of patients affected by CRC (108, 109).

In the era of precision medicine, liquid biopsy associated to imaging features could ensure a personalized follow-up or treatment strategy for different patients (110, 111).

Furthermore, radiomics tools have been proposed to analyze both the primary tumor and the most common site of metastatization.

In particular, many studies focused their attention on liver metastases, not only predicting genetic mutations on liver lesions but also predicting the future development of metachronous liver metastases in apparently healthy liver parenchyma (112, 113).

Currently, both liquid biopsy and radiomics have not already been validated in clinical practice due to the lack of prospective studies on multicentric cohorts; therefore, the analysis of the radiological features can be useful to create the first hybrid tools to create more intensive follow-up for high-risk patients. A more intensive follow-up can identify earlier patients affected by liver metastases and treat them with chemotherapy regimens.

This study has some limitations such as the small number of patients and, overall, the impossibility of comparing CT results with MRI data.

Conclusion

SHV ectasia may be related to metastasis and MRF involvement; a cutoff of 3.7 mm in diameter is considered significant in our experience according to the literature. Therefore, SHV diameter could become an interesting tool to complete the preoperative staging and follow-up of rectal cancer.

Data availability statement

The datasets presented in this article are not readily available because the raw data supporting the conclusions of this article will be made available by the authors, with undue reservation. Requests to access the datasets should be directed to dottchiaramorelli@gmail.com.

Ethics statement

The studies involving humans were approved by University of Bari Medical School "Aldo Moro". The studies were conducted in accordance with the local legislation and institutional requirements. The 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

NL: Writing – original draft, Writing – review & editing. AM: Writing – original draft, Writing – review & editing. NM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. CM: Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation. RC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. SB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. PA: Software, Visualization, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. DS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. SG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. AI: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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