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Oral complications in cancer patients

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Oral complications in cancer patients

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Editorial: Oral complications in cancer patients

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Editorial on the Research Topic
Oral complications in cancer patients

Cancer is the second leading cause of death worldwide and future projections place it as the leading cause by 2040 (1, 2, Salazar-Gamarra et al.). Current strategies of treatment include surgery, chemotherapy, radiotherapy, cellular therapies—e.g., stem cell transplantation, chimeric antigen receptor (CAR)-T therapy, bone-modifying agents, immune checkpoint inhibitors (ICIs), and others. These therapies, especially in advanced cancers, produce direct and indirect toxicities involving the oral cavity and neighboring regions. For this reason, it is essential to recognize the role that trained dentists provide in the multidisciplinary teams that treat cancer patients (Harris et al.). Roles include comprehensive dental evaluation and treatment to decrease infection risk prior to initiation of cancer therapy (Yong et al.), intra-therapy assessment to mitigate acute oral toxicities, and long-term follow-up posttreatment therapy to diagnose and manage late complications including, in some cases, prosthodontic rehabilitation (Salazar-Gamarra et al.). The inclusion of dentistry in this multidisciplinary approach is highly beneficial to the patient, but is not yet universal (3).

Oral complications associated with cancer therapy are frequent and can be classified as early or late onset. Early, or acute complications, are those that begin during therapy and resolve within 1 month of completion. Acute complications include oral mucositis, dysgeusia, hyposalivation, candidiasis, radiodermatitis, and dysphagia. Late, or chronic complications, develop after completion of therapy and in some cases may be permanent. Chronic complications include hyposalivation, trismus, radiation caries, osteonecrosis, and dysphagia, among others. In addition, head and neck cancers often require surgery to treat the primary tumor and regional metastases (neck dissection), resulting in permanent physical sequela requiring multidisciplinary therapy to address

functional and social impacts. This topic was chosen to provide new insights into the epidemiology, pathobiology, impact, and management of oral toxicities in cancer patients with the goal of improving patient quality of life.

Mucositis is the principal dose-dependent oral complication of cancer therapy and may lead to interruption of the treatment. Oral mucositis (OM) may trigger febrile neutropenia and blood stream infection and is also commonly associated with feeding problems and the introduction of enteral nutrition (Zecha et al.). Oral mucositis is associated with increased use of hospital resources, physician and multidisciplinary consultations, and prolonged hospitalization (including treatment in intensive care units), increasing cost of care, and the economic burden to patients, in both private and public health systems across various cancer treatment modalities (4). Photobiomodulation, delivered intraorally and extraorally, has shown promising results in OM, including different management approaches, both preventive and curative (Adnan et al). It has also been reported to prevent severe hyposalivation related to radiation therapy (Gobbo et al).

The etiology of oral mucositis has been linked to the direct effects of chemotherapy and radiation in addition to the effects of microbiological co-infection, including the oral-gut axis microbiome. This suggests that control and treatment of microorganisms could be a novel and successful approach to reduce mucositis severity (Al-Qadami et al.). Changes in the microbiome of the oral cavity are related to alteration in saliva, and probiotics have been proposed as an alternative to reduce circulating bacteria and candida in the oral environment (Pispero et al.).

Chronic graft-versus-host disease (GVHD) can broadly impact the oral cavity and oral function in patients undergoing allogeneic hematopoietic cell transplantation. Manifestations include lichenoid mucosal inflammation, lymphocyte-mediated salivary gland dysfunction and associated dental caries, taste and smell disturbances, and trismus. Patients with chronic GVHD are also at increased risk for oral cavity second primary tumors, particularly oral squamous cell carcinoma (Dean and Sroussi and Boor et al.). Immune checkpoint inhibitors have been associated with similar immune-mediated oral toxicities which are still being characterized (Klein et al.).

Salivary gland dysfunction is a potentially permanent side effect of multiple cancer therapies, including head and neck radiation therapy, chronic GVHD, and ICIs. Hyposalivation contributes to the development of caries, candidiasis, and psychological complications related to difficulties in nutrition and social interaction (Vistoso Monreal et al.). Additionally, candidiasis is a common opportunistic infection in cancer patients, secondary to hyposalivation and changes in the quality of saliva.

Radiation caries is a frequent complication of head and neck cancer therapy, characterized rapid onset and destruction of dentition when not promptly diagnosed and treated. Radiation caries can lead to pain, infection, and compromised function. Resulting dental extractions are associated with increased risk of osteoradionecrosis (ORN), which may require extensive surgical resection (Vistoso Monreal et al.). Dental restorations in cancer patients have been shown to have reduced longevity, however, this has yet to yield technological advancement in dental adhesives, resins, and other materials specially designed for patients treated with head and neck radiotherapy (Pedroso et al.). A similar pattern of rampant caries can be observed in GVHD patients. Limited opening secondary to trismus can impede oral hygiene and dental follow-up. Currently, physiotherapy is the first option, but the results are vague and uncertain, giving space to the introduction of surgical alternatives (Smeets et al.).

Osteonecrosis of the jaw can be one of the most impactful late complications, particularly in more extensive cases. Medication-related osteonecrosis of the jaw (MRONJ), like ORN, can be very challenging to manage and may require aggressive surgical resection (Singh et al.). MRONJ is characterized by the exposed necrotic bone and may be related to drug therapy, including antiresorptive and antiangiogenic targeted therapies (Migliorati). Conservative therapy is favored as the first-line intervention and may include irrigation with chlorhexidine, sequestrectomy, and pharmacological coverage with systemic antibiotics and pentoxifylline and tocopherol (Migliorati and Singh et al.). This condition is clinically like ORN, but the differences in etiology and risk factors may affect its treatment and prognosis.

Strategies for risk prediction of oral toxicities related to cancer therapies are needed for a personalized prevention protocol (Sonis) and they have been primarily used in OM. Artificial intelligence and machine learning approaches have been proposed for risk prediction of toxicity for cancer therapy in patients with head and neck cancer (Fanizzi et al.). These strategies have great benefits for the patients and oncologic services because the use of resources is most efficient and effective, reducing the high costs of prevention and treatment of collateral effects.

The rapid evolution of oncologic therapies requires specialists to constantly update themselves to respond to the requirements of patients and their services. It is important to draw attention to the fact that many clinical trials report oral complications in a superficial and protocol-directed manner. We believe that these toxicities need to be considered during the study design stage, including oral medicine expertise within the research team, in order to best characterize these conditions.

This Research Topic provides a glimpse into this complex and ever-evolving oncologic realm of clinical oral medicine.

Author contributions

WG-A wrote the first draft of the manuscript. GO (2nd author), DD, GO (4th author) and AS-S guided and revised the manuscript. NT conceptualized and guided the editorial. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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REVIEW
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The Path to an Evidence-Based Treatment Protocol for Extraoral Photobiomodulation Therapy for the Prevention of Oral Mucositis

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Oral mucositis is a painful complication of hematopoietic stem cell transplantation for which photobiomodulation therapy (PBMT) is a safe and effective intervention. Extraoral delivery of PBMT has clinical advantages over intraoral delivery but requires additional dosimetric considerations due to the external tissue layers through which the light must propagate before reaching the oral mucosa. Additionally, to date there has been no dose modeling study, a task essential to developing a justified treatment protocol. We review here some of the complexities surrounding extraoral photobiomodulation therapy and offer that may help guide researchers toward an evidence-based treatment protocol for the prevention of oral mucositis.

Keywords: photobiomodulation therapy, oral mucositis, low level light therapy, hematopoietic stem cell transplant, monte carlo

INTRODUCTION

Oral mucositis (OM) is a painful complication of hematopoietic stem cell transplantation (HSCT) characterized by inflammation and ulceration of the oral mucosa [1]. Photobiomodulation therapy (PBMT) is a safe and effective light-based intervention that has been shown to prevent and treat OM in HSCT patients [2, 3]. Current recommended PBMT protocols utilize intraoral delivery that involves multiple sequential dose administrations in a spot-by-spot manner, an approach that is technically complex and time consuming, and that requires a high level of patient cooperation (**Figure 1A**) [4].

Extraoral PBMT is likely to be clinically advantageous as its application is simpler and its treatment fields are more likely to include distal mucosae that are not reached by intraoral delivery. However, extraoral delivery requires transport of photons through the external orofacial tissue layers such as skin, fat, and muscle before reaching the inner mucosal lining, attenuating the dose delivered and requiring complex dosimetric considerations (**Figure 1B**). Additionally, no

dosimetric study or justified protocol has been reported. The purpose of this review is to carefully consider the complexities of extraorally delivered PBMT and work toward development of an evidence-based treatment protocol for OM prevention.

CHALLENGES SURROUNDING EXTRAORAL PBMT FOR OM

Intraoral PBMT is delivered directly to the mucosal surface, targeting the underlying connective tissue at an approximate depth of 100–700 μm [5]. The challenges introduced with an extraoral delivery of PBMT result from the additional layers of tissue through which the light must propagate in order to reach the oral mucosa. These layers are optically thick and attenuate the dose delivered. We review here the basic anatomy of the orofacial tissues and discuss some of the salient consequences from a photobiological standpoint.

Layers of the Orofacial Tissues

The tissues of the scalp and face are frequently simplified into five layers, from superficial to deep: (1) the skin, (2) the subcutaneous layer, (3) the musculoaponeurotic layer, (4) the spaces and retaining ligament, and (5) the deep fascia (**Figure 2**) [6]. Bone and periosteum are not relevant as they are avoidable during the delivery of extraoral PBMT and would otherwise cause additional dose attenuation. From a photobiological perspective, the orofacial tissue layers can be simplified into skin, fat, and muscle. Each of these layers exhibit different optical properties. Out of the three tissues, skin is the most attenuating layer and responsible for most of the absorption and scattering of light due to the chromophore melanin (more specifically eumelanin, but for simplicity will be referred to more generally as melanin) [7, 8]. Darker skin has a higher concentration of melanin and thus is more attenuating.

Degree of Attenuation

The degree of attenuation by skin, and to a lesser extent the subdermal tissues, is significant. To illustrate, even in skin types of low melanin concentration, light at a wavelength of 600 nm is attenuated to 37% of its incident power at a depth of only 550 μm from the skin surface; increasing the wavelength to 800 nm increases the depth to 1,200 μm [9]. A study of optical properties of human tissues reported a scattering coefficient of 2.73 mm^{-1} at a wavelength of 633 nm in dermis of low melanin concentration, decreasing to 1.63 mm^{-1} at a wavelength of 900 nm. Absorption and scattering coefficients of the subdermal tissues (fat and muscle) were found to be lower though still significant [7]. The average thickness of the human cheek is on the order of 6–7 millimeters [10]. While only a proportion of this is skin, the implication is that a large percentage of the incident power is lost while passing through the various tissues before reaching the oral mucosa. This has important consequences on treatment duration. For example, a 90% reduction in dose transmission would require a 10-fold increase in treatment duration to deliver the same dose to the oral mucosa. Maximizing penetration is therefore advantageous from a protocol feasibility standpoint and, as demonstrated, increasing wavelength decreases the magnitude of scattering and absorption by tissues and is a method to achieve this.

Variability of Attenuation

Variability among patients related to anatomical differences and skin type contributes to differences in the dose transmitted to the oral mucosa. This variability is unpredictable and does not reliably correlate with sex or age. For example, a study of ultrasonographic measurements of the cheek in 30 adults aged 24–61 years revealed an average cheek dermis thickness of 1,639.27 μm with a relatively large standard deviation of 531.53 μm [11]. There were no apparent differences by sex or age, suggesting that splitting patients into groups would not help address this variance.

Skin types of higher Fitzpatrick score, a numerical classification of the color and tanning ability of skin, contain higher concentrations of melanin and thus are more attenuating [7]. In effect, patients with a skin type of higher melanin concentration would receive a lower transmitted dose to the oral mucosa despite receiving the same applied dose. Of note, the difference in attenuation is lessened at longer wavelengths. One study of *ex vivo* dermal samples obtained from subjects with skin types of lower vs. higher melanin concentration reported reduced scattering coefficients of $2.73 \pm 0.54\ mm^{-1}$ vs. $3.21 \pm 2.04\ mm^{-1}$ at 633 nm compared to $1.63 \pm 0.25\ mm^{-1}$ vs. $1.81 \pm 0.040\ mm^{-1}$ at 900 nm [7]. Two additional studies of the optical properties of skin *in vivo* that included patients of Fitzpatrick skin types I–VI similarly found higher absorption coefficients in higher Fitzpatrick skin types. This difference decreased in magnitude across the wavelength range of 600–800 nm, and at 850 nm there was no significant difference in absorption coefficients [12, 13]. Furthermore, skin pigmentation was found to have a greater influence on reflection at wavelengths of 460–700 nm compared to 800–850 nm [14, 15]. These findings suggest that a longer wavelength would help minimize differences in dose delivery based on skin type, as well as increase penetration overall.

Safety and Feasibility

There has been no reported toxicity in any of the studies of PBMT for the prevention and/or management of OM [16]. In the limited number of studies evaluating extraoral PBMT, there has similarly been no reported cutaneous or oral toxicity. In theory, PBMT could lead to heating of tissues and, when applied extraorally, heating of the skin; however, the American National Standards Institute (ANSI) publishes safety standards which establish the maximal permissible exposure (MPE) for skin exposure (applies to all skin types) to a laser beam [17], which can serve as a reference guideline. A study that included patients with skin of and device parameters within ANSI standards investigated the effects of melanin on skin surface temperature when exposed to PBMT. The authors reported no significant skin temperature differences with doses ranging from 0 J to 50 J via concurrent use of super-pulsed lasers and pulsed red and infrared LEDs at wavelengths of 810–904 nm [18].

There have been two studies investigating the feasibility of extraoral PBMT treatments in an inpatient pediatric hematology-oncology unit. Both met goal endpoints in feasibility, tolerance,

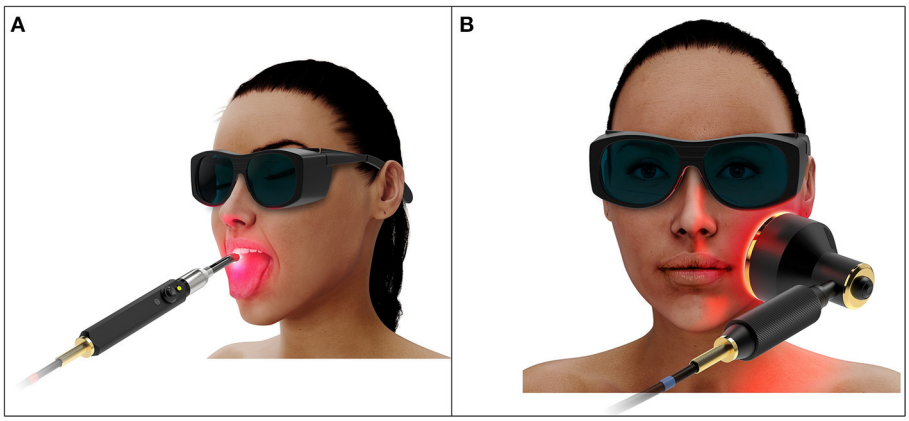

FIGURE 1 | Artistic representation of **(A)** intraoral and **(B)** extraoral photobiomodulation therapy.

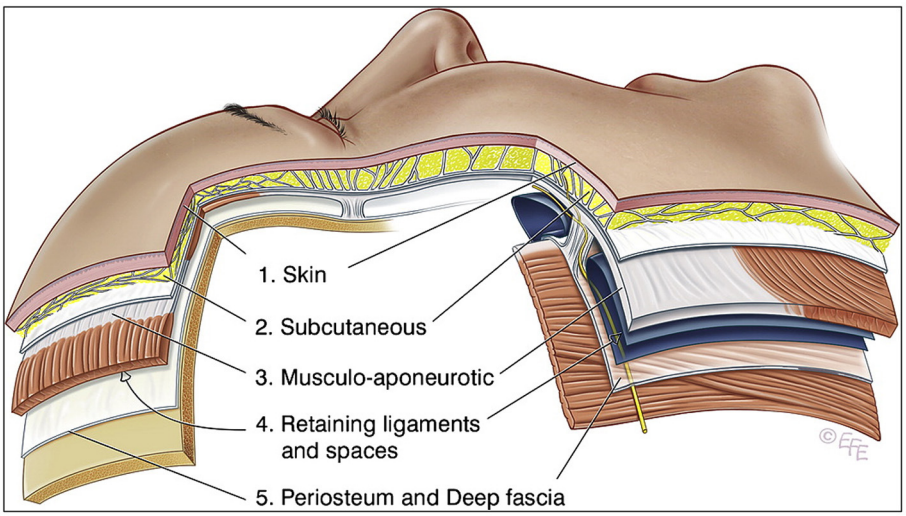

FIGURE 2 | Layer model diagram of facial tissues. Adapted with permission from Mendelson et al.

and safety of the intervention. The first study enrolled 10 patients aged 4 to 21 years and reported successful administration of prophylactic daily extraoral PBMT in 347/355 (97.7%) sessions by 10 trained nurses with no pain or other reason to discontinue therapy [19]. The second study employed a curative (not prophylactic) mixed intraoral/extraoral PBMT protocol that enrolled 22 patients aged 3 to 18 years with WHO Grade $\geq$2 OM, and reported procedural success (administration of PBMT to entire surface of oral mucosa at least 3 times every 2 days in first 7 days of OM) in 77% of episodes. Treatments were well-tolerated and there were no treatment-related adverse events [20].

Summary

These findings taken together guide our approach to developing a treatment protocol for extraoral delivery of PBMT. First, because of the significant degree of attenuation caused by the orofacial skin and tissues, the treatment protocol should aim to maximize penetration lest the treatment time required to achieve an efficacious dose would be infeasible. Second, the same regimen administered to two patients will likely result in two slightly different doses transmitted to the oral mucosa, necessitating a standardized protocol that aims to treat the "median" patient, akin to pharmacological agents with standard dosing despite variable pharmacokinetics and pharmacodynamics.

TREATMENT PROTOCOL FOR EXTRAORAL PBMT

Currently, there is no established treatment protocol for extraoral PBMT for prevention of OM. To our knowledge, no rigorous dosimetric study of extraorally delivered PBMT estimating the dose transmitted to the mucosal surface has been performed. To date, five clinical studies have been reported that investigate the efficacy of extraoral PBMT for OM [21–25]. None provide an

estimated dose transmitted to the oral mucosa by the treatment protocol used. In the first four studies, wavelengths (660–680 nm) and irradiance (50–100 mW), with the exception of two studies which additionally had an 830 nm study arm, were similar to those utilized for intraoral delivery [21–24]; however, as described earlier, this does not result in the same dose delivered to oral mucosa due to attenuation from external tissue layers. The fifth study, which compared intraoral and extraoral PBMT, utilized a higher irradiance of 407 mW/cm^2 in the extraoral arm, delivering 4 J/cm^2 over 10 s at six different locations. A dual wavelength 810/980 nm device was used [25]. While this protocol likely delivered a dose closer to the therapeutic range (1–6 J/cm^2) than the preceding studies, the exact dose is still unknown; to transmit a dose of at least 1 J/cm^2 with this protocol would require a percent transmission of 25%, which is likely higher than the true penetration of infrared/near-infrared light through the average human cheek. The two aforementioned feasibility studies utilized devices with two wavelengths, one red (635–660 nm) and one near infrared (815–830 nm) [19, 20]. One study applied 50 mW/cm^2 to 6 sites for 1 min each [19]. The other employed a scanning approach, applying 4 W/cm^2 with a laser fiber across the external cheek, for 1 second per cm^2, as well as some intraoral application at a lower irradiance [20]. The first protocol likely did not reach the target dose delivered to the mucosa and the second exceeded ANSI safety recommendations. One study of extraoral PBMT for OM in rats has been reported [26]. The study used a dual wavelength 810/980 nm device and applied 407 mW/cm^2 for 15 or 30 s. However, rat orofacial anatomy is different from human anatomy and the percent dose transmitted during extraoral PBMT delivery in rats is not the same as in humans. In nearly all cases, justification for the selection of device parameters has been attributed to prior intraoral or limited extraoral studies rather than an approach based on orofacial anatomy and photobiological principles. The following is our approach to a rational and scientifically based treatment protocol in the context of the previously considered challenges surrounding extraoral PBMT delivery to the oral mucosa.

Target Dose

Intraoral PBMT OM prevention protocols recommend a target dose on the order of 1.0–6.2 J/cm^2, although the true therapeutic range may be broader [4]. Given that extraoral PBMT acts by the same mechanism, the target dose should be the same. However, there are a few considerations to be made. First, as explained previously there is unavoidable variability in the dose delivered to the oral mucosa due to variation in orofacial anatomy. Thus, with a standardized protocol that treats the "median" patient, there will be some degree of under- and overdosing. Given the relatively broad range of effective dose, the transmitted dose should still have a therapeutic effect, particularly if a middling target dose is selected [27]. Second, a potential limiting factor of extraoral PBMT is the long treatment duration required to deliver the total target dose. Consequently, a very high target dose should be avoided, in order to afford a more feasible treatment duration, and the rate of dose delivery should be optimized by maximizing penetration (i.e., wavelength) and power output. Third, in regards to safety, no surface skin temperature changes were observed in volunteers of varying skin type exposed to PBMT at wavelengths of 640, 875, and 904 nm and energy of up to 50 J, an order of magnitude above the usual dose indicated for PBMT for OM [18]. Thus, the degree of under- or overdosing caused by anatomical or skin type variation is likely insufficient to warrant safety concerns.

TABLE 1 | Proposed protocol of treatment locations and trajectories and their target mucosal surface for use in extraoral delivery of photobiomodulation therapy for prevention of oral mucositis.

Treatment location and trajectory	Mucosal surface treated
Left cheek, transversely	Left buccal mucosa and lateral tongue
Right cheek, transversely	Right buccal mucosa and lateral tongue
Philtrum, anteroposteriorly	Upper lip and lower lip
Midline neck, vertically	Midline floor of mouth, ventral tongue, oropharyngeal mucosa, and esophageal mucosa
Left neck, transversely	Left floor of mouth, ventral tongue, oropharyngeal mucosa, and esophageal mucosa
Right neck, transversely	Right floor of mouth, ventral tongue, oropharyngeal mucosa, and esophageal mucosa

Wavelength

Intraoral protocols utilize wavelengths in the red light range: 632.8 nm for He-Ne lasers and 660 nm for diode lasers [4]. While this range is appropriate for superficial treatment, as in the case of direct application to the oral mucosa, there are many reasons to utilize the longest wavelength with evidence of efficacy as mentioned earlier: (1) there is decreased absorption and scattering of light by melanin, fat, and muscle at longer wavelengths allowing for increased dose delivery and thus a more feasible treatment duration, and (2) variation in dose attenuation due to the effects of melanin is lessened at longer wavelengths [7]. There is both preclinical and clinical evidence of efficacy for longer wavelength PBMT for OM. Cytochrome oxidase C, an important chromophore thought to mediate the therapeutic effects of PBMT, holds activity "peaks" or "hotspots" suggesting bioequivalency throughout these peaks rather than at any one wavelength [28]. The highest peak is in the near infrared window at 812.0–846 nm. Additionally, PBMT in the near infrared window has shown efficacy for several other inflammatory/painful indications, such as osteoarthritis, colitis, and temporomandibular disorders [29–36]. Longer wavelengths beyond the near-infrared range lack evidence of efficacy [37].

Irradiance

Irradiance seems to be less significant than fluence with regard to efficacy and can be manipulated to afford a feasible treatment duration. Indeed, intraoral protocols utilize a broad range of irradiances, 24–31.25 mW/cm^2 for He-Ne lasers and 417–1,000 mW/cm^2 for diode lasers [4]. In keeping with the goal of maximizing dose delivery rate, the irradiance should be

maximized while in accordance with ANSI standards. This helps attain a feasible treatment duration while minimizing any safety concerns.

Treatment Sites and Duration

The mucosal surfaces of the oral cavity to consider include the buccal mucosa, upper and lower lip, ventral tongue, lateral tongue, floor of mouth, and soft palate. Mucosae distal to this potentially reachable by an extraoral approach include the oropharyngeal and esophageal mucosa, a concept further supported by studies indicating locoregional or even systemic therapeutic effects [38, 39]. An extraoral protocol should aim to treat all these sites with minimal overlap and avoidance of teeth, bone, and cartilage to decrease dose attenuation (**Table 1**). This approach assumes the oral mucosa itself is very thin and inconsequential in terms of dose attenuation, and that the small amount of air contained within the oral cavity is similarly optically negligible. As a result, the trajectories treating the buccal mucosa should also reach and treat the lateral tongue and soft palate, and those treating the floor of mouth should also reach and treat the ventral tongue.

The treatment duration should aim to deliver the target therapeutic dose and is dependent on the rate of dose delivery (energy fluence rate, $J/cm^2/s$) to the oral mucosa and varies by treatment site. This parameter can only be determined after a rigorous dosimetric study investigating the degree of attenuation of PBMT by orofacial structures along each treatment site trajectory. Due to dose attenuation, it is likely that the treatment duration required for extraoral PBMT will be considerably longer than that required by intraoral PBMT; however, device design can allow for simple and comfortable handsfree delivery. Important practical aspects of the delivery of extraoral PBMT, including device design and handling, will be essential to optimizing efficiency of delivery, for example by allowing delivery to multiple treatment sites concurrently.

Future Directions

There are a few important barriers to implementation of extraoral PBMT for OM. First, to date there has been no reported dose modeling of extraoral PBMT, information which would be essential to inform the creation of a justified, validated treatment protocol. Critical aspects of this dosimetric study include the determination of the "median" patient in terms of orofacial morphology, the modeling of dose transmission to the oral mucosa along several treatment trajectories given a set of treatment parameters, and an *in vivo* validation of these findings. Second, the treatment protocol would need to be evaluated for efficacy in a randomized, placebo-controlled clinical trial evaluating outcomes such as incidence and duration of severe OM.

CONCLUSIONS

Intraoral PBMT is a safe and effective treatment for OM among patients receiving cytotoxic conditioning regimens prior to HSCT. Extraoral PBMT has advantages over intraoral PBMT but lacks evidence of efficacy and requires additional dosimetric considerations due to the anatomical structures the light must pass through before reaching the oral mucosa. Thus, the device parameters used in intraoral PBMT are not appropriate for extraoral PBMT. While it is evident that treatment duration needs to be longer for extraoral PBMT than intraoral PBMT, measures can be applied to minimize treatment time and optimize ease and comfort of delivery. We have outlined the necessary steps to establish and validate a justified treatment protocol that can be evaluated for efficacy in a randomized clinical trial and ultimately used in clinical practice.

AUTHOR CONTRIBUTIONS

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

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Figure 1 courtesy of THOR Photomedicine.

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SYSTEMATIC REVIEW
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The Effectiveness of Surgical Methods for Trismus Release at Least 6 Months After Head and Neck Cancer Treatment: Systematic Review

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Background: The objective of this systematic review was to identify the different surgical treatment modalities of severe trismus after head and neck squamous cell cancer treatment.

Methods: An electronic literature database search was conducted in Medline, Embase, Cochrane, Web of Science, and OpenGrey to determine articles published up to September 2021. Two observers independently assessed the identified papers for eligibility according to PRISMA guidelines. The inclusion criteria were trismus after head and neck squamous cell cancer with consecutive treatment, detailed description of the surgical procedure for trismus release, description of the initial treatment, at least 6 months between initial cancer treatment and trismus release surgery, a minimal follow-up (FU) of 6 months, and availability of full text. The quality was evaluated using the Newcastle-Ottawa scale. A subanalysis of the maximal mouth opening (MMO) was performed using a mixed-effect model.

Results: A total of 8,607 unique articles were screened for eligibility, 69 full texts were reviewed, and 3 studies, with a total of 46 cases, were selected based on the predetermined inclusion and exclusion criteria. Three treatment strategies were identified for trismus release (1) free flap reconstruction (FFR), (2) coronoidectomy (CN), and (3) myotomy (MT). There was a clear improvement for all treatment modalities. A quantitative analysis showed a beneficial effect of CN (mean 24.02 $\pm$ 15.02 mm) in comparison with FFR (mean 19.88 $\pm$ 13.97 mm) and MT (mean 18.38 $\pm$ 13.22 mm) ($P < 0.01$*). An increased gain in MMO after trismus release was found if no primary resection was performed ($P = 0.014$*). Two studies included in the analysis had an intermediate risk of bias and one had a low risk of bias.

Conclusion: Currently available reports suggest a low threshold for performing a CN compared with FFR and MT. There is a need for high-quality randomized controlled trials with carefully selected and standardized outcome measures.

Keywords: trismus, coronoidectomy, myotomy, free flap, oral cancer, trismus release

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INTRODUCTION

Trismus is one of the most evident complications secondary to head and neck squamous cell cancer (HNSCC) treatment, with severe impact on the quality of life [1–3]. The prevalence of trismus after HNSCC treatment varies widely with ranges from 5 to 41.5% [4–12]. The degree of limitation of the maximal mouth opening (MMO) is typically most evident 6 months after treatment [6]. Predictive factors for trismus in HNSCC are still arguable, but despite newer radiation modalities, radiotherapy appears to remain a major contributor to limited MMO [13, 14].

Most patients are treated with conservative tools and instructions to prevent severe trismus. In this context, the early start of exercise therapy is crucial [15–17]. Scherpenhuizen et al. [16] already stated the absolute benefit of exercise therapy over no exercise at all. Multiple tools are currently available for stretching, but a systematic review by Kamstra et al. [15] could not define a preferred exercise therapy. Besides conservative therapy, the role of pentoxifylline is unclear as only one pilot study has covered the effect of pentoxifylline on the mouth opening [18].

In some cases, conservative therapies remain inadequate to reach a sufficient MMO for most essential daily life activities. In cases of intraoral soft-tissue scar tissue caused by reconstructions or radiotherapy, surgical release may be considered. Surgical interventions are based on just one or a combination of different release strategies, namely a myotomy (MT) of the masticatory muscles, a coronoidectomy (CN) and resection of fibrous scar tissue followed with a free flap reconstruction (FFR). No clear therapeutic flowchart for surgical release of trismus is available despite the high prevalence and impact on the quality of life of trismus secondary to the different treatment modalities of HNSCC.

The aim of this systematic review is to identify the surgical methods to improve mouth opening minimally 6 months after HNSCC treatment and to compare their effectiveness on the increase in MMO after surgery.

MATERIALS AND METHODS

Eligibility Criteria

The inclusion criteria were trismus after HNSCC with consecutive treatment, detailed description of the surgical procedure for trismus release, description of the initial treatment, at least 6 months between initial cancer treatment and trismus release surgery, a minimal follow-up (FU) of 6 months, and availability of full text in Dutch, French, English or German. Literature reviews, systemic reviews, histological and animal studies, case reports, and case series with < 6 patients were not included in the study selection due to wrong study design but were used as potential sources to find relevant missing articles in the search. This was performed by careful analysis of all referred references in these manuscripts. The study selection was done in two stages, first by screening titles and abstracts, and then by reading the full text article meeting the inclusion criteria. At the end of each stage, a consensus was sought for disagreements.

Information Sources and Search Strategy

A search strategy was developed for Medline, Embase, Cochrane, Web of Science, and OpenGrey for studies published up to September 2021 (**Supplementary Material**). Consequently, a thorough manual search was conducted.

Selection Process

Two reviewers (MS and TMC) independently assessed titles, abstracts, and full text articles following specific eligibility criteria. All references were collected, and duplicates were removed in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The references of the studies that were included for eligibility screening were all carefully analyzed for any additional manuscripts that were not yet detected via the primary search strategy.

Data Collection Process

Two authors (MS and TMC) independently extracted data from the selected articles.

Data Items

The following parameters were extracted from each included study: name of first author, year of publication, study design, number of participants, gender, mean age, age range, mean FU time, FU range, surgical intervention, MMO at least 6 months after surgical release. In case of combined or missing parameters, the corresponding authors of the manuscript were contacted by email to request the raw data.

Study Risk and Reporting of Bias Assessment

Assessment of the quality was achieved with the Newcastle-Ottawa quality assessment scale [19]. This scoring system requires a grading on several domains: possible biases of selection, comparability, and exposure. Scores ranged from 0 (a very biased article) to 9 (bias very unlikely) (**Table 1**). Studies have a low risk of bias if the score is 7–9, intermediate risk if 4–6, and high risk when the score is below 4. The scores were given by three authors (MS, JVD and TMC) and the mean score was used.

Synthesis Methods

Data was collected from the articles that met the selection criteria. The effect of the primary therapy on the reversibility of the MMO after trismus release was evaluated via a logistic regression. More specific the use of osteocutaneous and fasciocutaneous flaps, the administration of radiotherapy (yes/no), and the performance of a primary resection (yes/no). Differences were evaluated among 3 possible interventions (1) CN; (2) MT; (3) FFR. The mean MMO was evaluated pre-, peri- and postoperative at the end of FU.

Protocol and Registration

This systematic review were performed in accordance with a predefined protocol registered in PROSPERO (CRD42020158770). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed [23].

TABLE 1 | Quality assessment according to the Newcastle-Ottawa quality assessment scale.

		References		
		Bhrany et al. [20]	de Pablo et al. [21]	Mardini et al. [22]
Item				
Selection	Representativeness of the exposed cohort.	⊘	⊘	⊘
	Selection of nonexposed cohort.	⊘	✓	⊘
	Ascertainment of exposure.	✓	✓	✓
	Demonstration that outcome of interest was not present at start of the study.	✓	✓	✓
Comparability	Study controls for other variables.	⊘ ✓	✓ ✓	⊘ ✓
Outcome	Assessment of outcome.	✓	✓	✓
	Degree of FU was long enough for outcomes to occur.	✓	✓	✓
	Adequacy of FU of cohorts.	✓	✓	✓
SCORE (/9)		6	8	6

⊘, *no agreement;* ✓, *agreement.*

PICO Question

The review was designed based on the following PICOS criteria (population, intervention, comparison, outcome, studies): (P) limited MMO secondary to HNSCC treatment (radiotherapy, surgery, chemotherapy, and/or check-point inhibition therapy), (I) surgical release, (C) different surgical techniques, (O) mean MMO pre-, peri- and postoperative at the end of FU, and (S) all studies except literature reviews, systemic reviews, histological and animal studies, case reports, and case series with < 6 patients.

Selection Process of Studies

Two reviewers (MS and TMC) independently assessed titles, abstracts, and full text articles following specific eligibility criteria. The inclusion criteria were trismus after HNSCC with consecutive treatment, detailed description of the surgical procedure for trismus release, description of the initial treatment, at least 6 months between initial cancer treatment and trismus release surgery, a minimal follow-up (FU) of 6 months, and availability of full text in Dutch, French, English or German. Literature reviews, systemic reviews, histological and animal studies, case reports, and case series with < 6 patients were not included in the study selection due to wrong study design but were used as potential sources to find relevant missing articles in the search. This was performed by careful analysis of all referred references in these manuscripts. The study selection was done in two stages, first by screening titles and abstracts, and then by reading the full text article meeting the inclusion criteria. At the end of each stage, a consensus was sought for disagreements.

Synthesis Methods and Statistical Analysis

A general linear mixed-effects model was applied to examine the influence of the different treatment protocols and time points on the MMO. Bonferroni-corrected *post-hoc t*-tests were used to examine significant main and interaction effects.

The statistical analysis was conducted in IBM SPSS statistical software (Version 22.0, IBM, New York, USA). The significance level α was set for all statistical tests at 0.05.

RESULTS

Study Selection

A total of 13,616 articles were identified, and after screening for duplicates, 8,607 unique titles remained. Title and abstract selection resulted in 69 relevant articles for eligibility assessment.

After assessment of the full text, 3 papers remained for qualitative synthesis.

Of the 69 articles that were assessed for eligibility, 37 were excluded as the population did not consist out of former HNSCC cases. Thirteen articles were assessed as a wrong study design such as: literature reviews [24, 25], studies without surgical trismus release [11, 26–29], cohorts with simultaneous release of the mouth opening during the primary tumorectomy [30–32], a different cause for the limited MMO [33, 34], and an inadequate FU [35]. Furthermore, 14 articles were not available, 2 articles were excluded as they were written in a language apart from English, German, French, Spanish or Dutch. An overview of the selection and screening process is shown in **Figure 1**.

Study Characteristics and Individual Results of the Included Papers

Bhrany et al. [20] described a mean gain in MMO of 21.8 mm in this population of 11 cases, who all underwent a CN, without MT or FFR. A mean gain at the end of FU of 8.9 ± 7.0 mm was the outcome of De Pablo et al. [21] analyzing the role of a FFR with ($n = 17$) or without ($n = 11$) a CN. Lastly, Mardini et al. [22] reached a gain in MMO between 1 and 20 mm using a technique combining CN, FFR and MT. Two studies included in the analysis had an intermediate risk of bias [20, 22] and one had a low risk of bias [21].

The demographic factors were described in **Table 2**. All three articles used a different subdivision for the tumor localization, so a detailed analysis of the localization was assumed too heterogeneous. Although, the buccal mucosa can be considered as the most common localization based on the finding that 25 out of a total of 46 cases were described as located in the buccal mucosa [20–22].

Results of Synthesis and Statistical Analysis

A significant increased gain in MMO was found if no primary surgery was executed (Nagelkerke $R2 = 0.350$; $P = 0.014^*$). No significant advantage was detected regarding the type of free flap during primary treatment ($R2 = 0.083$; $P = 0.226$) or the administration of radiotherapy ($R2 = 0.089$; $P = 0.327$).

Table 3 illustrates the mean increase in MMO at the different time points for each of the three methods.

A main effect of surgical procedure group was found overall significant between the described release methods ($F = 11.16$; $P < 0.01^*$). The MMO in the CN group (mean 24.02 ± 15.02 mm) was significantly ($P < 0.01^*$) improved compared with the MT group (mean 18.38 ± 13.22 mm), and the FFR group (mean 19.88 ± 13.97 mm). No significant difference was observed between MT and FFR groups ($P = 1.00$) (**Figure 2**).

A significant effect of time was also noted between the three time points ($F = 195.01$; $P < 0.01^*$). The perioperative MMO (mean 37.60 ± 5.78 mm) was the largest ($P < 0.01^*$) compared with preoperative (mean 7.34 ± 5.98 mm) and postoperative MMO (mean 19.94 ± 9.98 mm). A significant improvement of the postoperative compared with the preoperative MMO was also noted ($P < 0.01^*$) (**Figure 2**).

There was no interaction between time points and release method groups, indicating that the three surgical interventions exposed a similar evolution of the MMO over time ($F = 1.492$; $P = 0.206$).

DISCUSSION

Despite advances in the surgical techniques of head and neck cancer treatment, adequate long-term functional results are not always achieved. Limitation of mouth opening is one of the major factors leading to functional impairment. Secondary trismus release can be achieved by a variety of techniques. This systematic review identified three possible surgical techniques: FFR, CN and MT. A subsequent statistical analysis in a total of 46 patients identified the largest gain in CN.

A systematic review by Bouman et al. [36] described different therapeutic options for trismus release, although a majority of the included studies covered patients with OSF. Since the pathogenesis is different in OSF compared to HNSCC, we decided to exclude these patients from this analysis [37]. First of all, OSF is most frequently caused by betel nut chewing and is associated with superficial buccal scar tissue. On the other hand, deeper scar tissue is expected after extensive surgical reconstructions and radiotherapy for HNSCC. Furthermore, both of these treatments not only create scar tissue but also affect the availability of blood vessels and even perfusion in the head and neck area.

The main result of this statistical analysis is the significant gain in MMO in the group where a CN was effectuated compared with other methods of trismus release. Kumar et al. have published the beneficial effect of CN in Sawhney's type I-III temporomandibular joint ankyloses. A gain of 76% at least 1 year after surgery was shown in their population of 23 cases [38]. Similar benefit could hence be expected in trismus resulting from HNSCC treatment. It would be interesting to investigate specific variables affecting the MMO after HNSCC such as the role of coronoid size and hyperplasia.

Based on this analysis, scar tissue release with FFR was significantly less effective for MMO increase compared with the CN group. Comparison between these groups is however biased as preoperative MMO was lower in the population were a FFR was performed. These findings might suggest the difficulty of gaining an important quantity of MMO if the initial MMO is limited until just a few millimeters. Despite these noteworthy findings, no important conclusion can be made based on this small sample size regarding a FFR in trismus release.

No significant advantage of a myotomy was perceived in the analysis, nor in the individual studies. A myotomy is seen as one of the most accessible methods of trismus release, but none of the original research teams conducted a MT without a FFR or a CN. The overall consensus is that solely a MT is insufficient in releasing the MMO. One of the reasons for the latter is that the installed fibrous tissue after HNSCC is the major factor contributing to chronic trismus, especially for more severe trismus cases [39]. This was supported by the fact that all but one of the included articles described the simultaneous

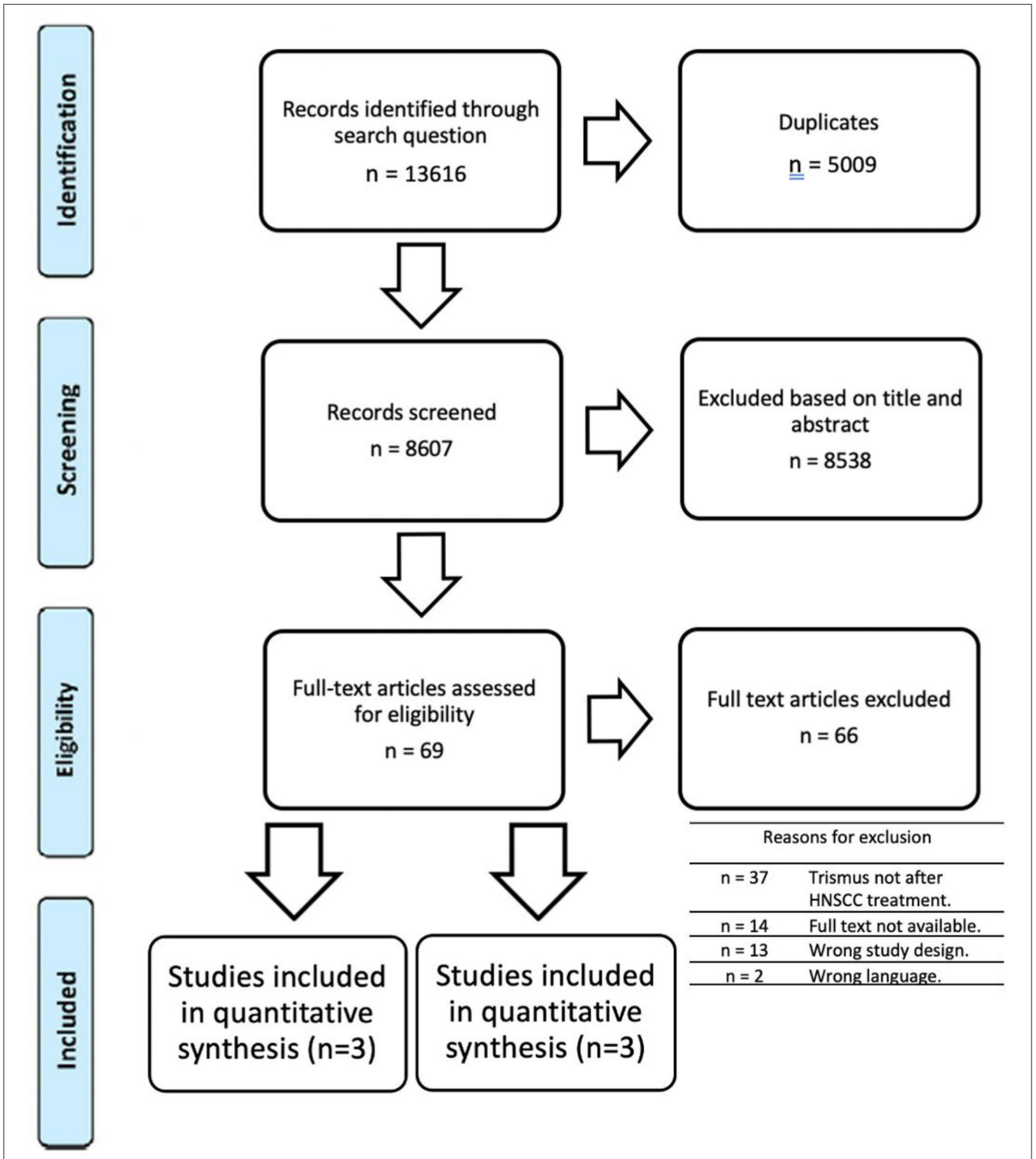

FIGURE 1 | Prisma flow chart.

resection of the surrounding fibrous tissue. Furthermore, the reformation of fibrosis after a MT is to be expected with consequent recurrent trismus. Silberstein et al. identified the possible additional role of Botulinum toxin A in the MT procedure. According to this study, administration of Botulinum toxin A into a muscle immediately after MT might interfere with

TABLE 2 | Demographics of the included cases.

	Bhrany et al. [20]	de Pablo et al. [21]	Mardini et al. [22]
n	11	28	7
Male/female ratio	NS	26/2	6/1
Tumor localization	5 tonsil 6 palate	19 buccal mucosa 3 alveolar ridge 2 retromolar trigonum 2 lip 2 soft palate 1 tongue	4 buccal mucosa 2 buccal mucosa and maxillary bone 1 maxillary bone
Primary resection	5	28	7
Maxillectomy	3	15[a]	3[a]
Mandibulectomy	-	19[a]	-
Buccal mucosa resection	-	26[a]	6[a]
Tonsillectomy	2	-	-
Cheek through and through defect	-	2[a]	-
Free flaps harvested	2	28	7
Osteocutaneous	-	3	1
Fasciocutaneous	2	25	6
Radiotherapy (yes/no)	11	28	5
Chemotherapy (yes/no)	NS	18	NS
Time after primary treatment (m)	7–15	6–91	7–37
Mean FU after release (m)	12	38	31
Minimal FU (m)	12	12	7

[a]*combination of multiple defects described. n, number of cases; NS, not specified; m, months; FU, follow-up.*

TABLE 3 | The mean maximal mouth opening and standard deviation (SD) for three surgical techniques and time points: preoperative, perioperative and at the end of follow-up.

Surgical technique	*n*	Time (m)		
		Preoperative	Perioperative	End of follow-up
Myotomy	7	4.14 ± 5.18	32.43 ± 3.36	18.57 ± 8.79
Coronoidectomy	35	8.94 ± 6.75	39.43 ± 5.82	23.69 ± 11.51
Free flap release	35	6.37 ± 4.91	36.80 ± 5.41	16.46 ± 7.01

m, months.

muscle healing, thus contributing to a more successful long-term result [40].

Subgroup analysis of the primary treatment revealed that a higher gain in MMO is to be expected after trismus release if no primary resection was performed, which can be attributed to fibrous scar tissue formation after primary surgery. Despite extensive reports on the role of radiotherapy as one of the main predictive factors for trismus, only little is known on the impact of the surgical resection [13, 14]. This is due to the impaired differentiation regarding the cause of the limited MMO between radiotherapy, surgery and an increased tumor staging [6, 13, 14]. No evidence was found for the lower reversibility of the MMO after trismus release due to radiotherapy or the type of FFR during primary treatment, which is most likely because of the low number of cases, respectively, with composite free flaps and without radiotherapy in this sample. Current scientific evidence suggests a lower trismus incidence is to be expected since the introduction of the intensity-modulated radiotherapy (IMRT) [14].

The loss of MMO between perioperative and the end of FU was noticed in all 46 cases, indicating the degree of trismus refractoriness that is to be expected. Immediate beginning of physical therapy and a mouth-exercising device [e.g., Therabite (Atos Medical, Malmö, Sweden) or Jaw Dynasplint (Dynasplint Systems, Severna Park, Maryland, USA)] might support the preservation of gained MMO. Nevertheless, it remains a matter of debate whether the perioperative measurement is significantly affected by induction and perioperative absence of pain limiting MMO.

A first limitation in this study is the limited number of eligible articles. The increasing disease-free survival due to new HNSCC treatment modalities explains the current shift toward a raising interest in the posttreatment quality of life and, thus, trismus. Therefore, the available number of articles regarding trismus after HNSCC treatment was considered disappointingly

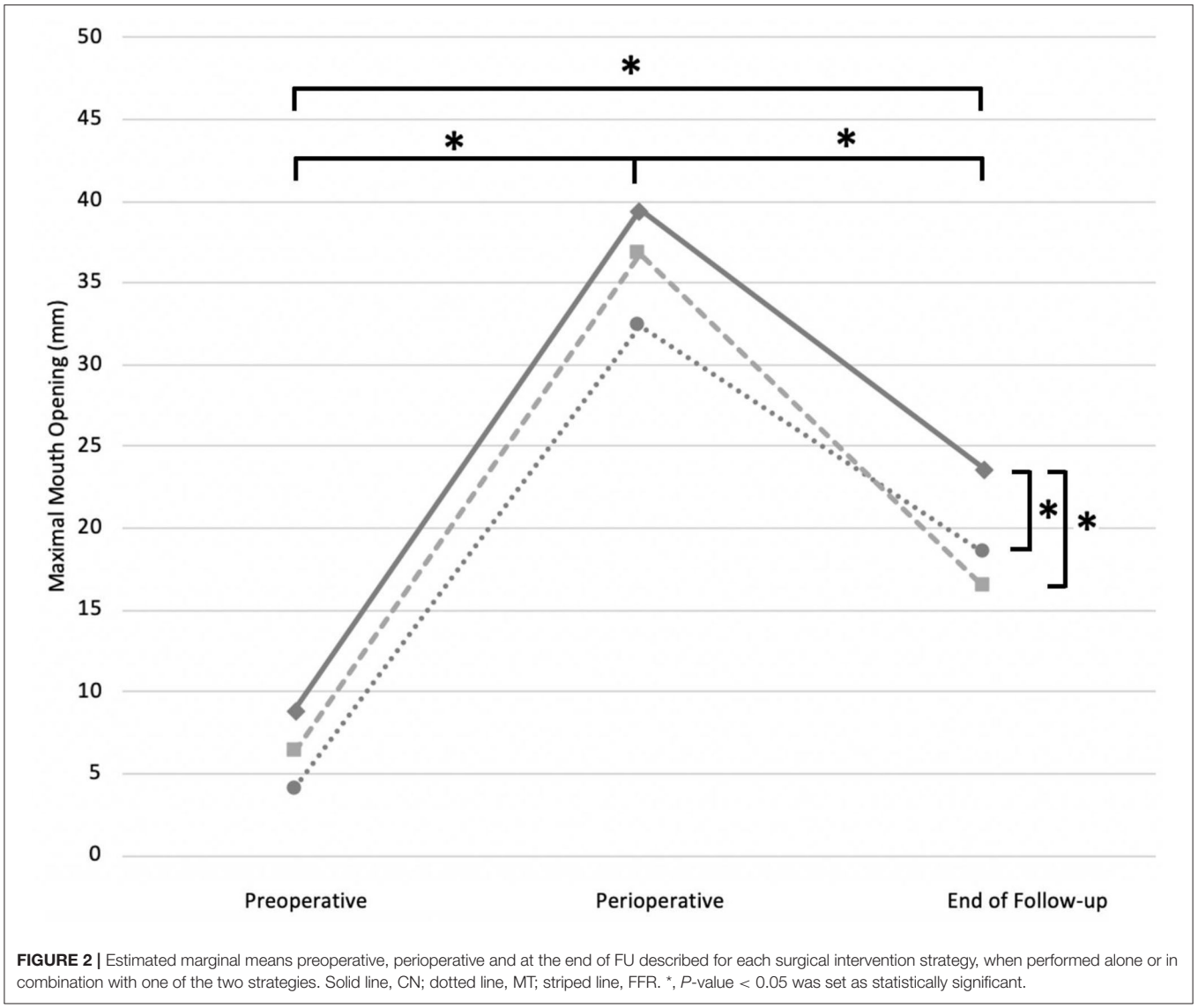

FIGURE 2 | Estimated marginal means preoperative, perioperative and at the end of FU described for each surgical intervention strategy, when performed alone or in combination with one of the two strategies. Solid line, CN; dotted line, MT; striped line, FFR. *, *P*-value < 0.05 was set as statistically significant.

little. Secondly, the three described release methods were often combined, which hinders the differentiation between the used methods and their separate effect on the MMO. The third limitation is the multifactorial nature of this complication, despite addressing this with narrowing of the inclusion criteria to only HNSCC cases at least 6 months after oncologic treatment. Therefore, a higher sample size is needed for subgroup and multivariate analysis.

CONCLUSION

Three methods were discovered for trismus release after HNSCC treatment: CN, MT and FFR. The currently available results support the low threshold for performing a CN in less severe limitation of the MMO. There is, despite the given results, a clear role for a FFR after scar tissue release for primary closure of the created defects, but the impact of a MT after scar tissue resection is still unclear. Further research is indispensable to reproduce the given studies on a larger homogeneous population to allow understanding of the surgical options in cases with a more severe objective and subjective limitation of the MMO.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: doi: 10.1097/MLG.0b013e31812eee13; doi: 10.1002/jso.24806; doi: 10.1097/01.prs.0000221118.31863.c4.

AUTHOR CONTRIBUTIONS

All authors contributed in a different way regarding the conception and design of this review, acquisition of data *via* literature search, analysis and interpretation of data collected, drafting of the critical revision, and final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/froh.2021.810288/full#supplementary-material

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MINI REVIEW
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Oral-Gut Microbiome Axis in the Pathogenesis of Cancer Treatment-Induced Oral Mucositis

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Oral mucositis (OM) is one of the most common and debilitating oral complications of cancer treatments including chemotherapy, radiotherapy, and hematopoietic stem cell transplantation. It is associated with severe pain and difficulties in chewing, swallowing, and speech. This leads to impairment of basic oral functions and could result in unplanned treatment interruption or modification. As such, OM negatively impacts both patients' quality of life as well as tumor prognostic outcomes. Understanding pathways underlying OM pathogenesis help identify new targets for intervention or prevention. The pathophysiology of OM has been widely studied over past decades with several pathways related to oxidative stress, inflammation, and molecular and cellular signaling being implicated. In this mini-review, we will discuss the emerging role of the oral-gut microbiome axis in the development of OM. Particularly, we will elaborate on how the alterations in the oral and gut microbiota as well as intestinal dysfunction caused by cancer treatments could contribute to the pathogenesis of OM. Further, we will briefly discuss the potential methods for targeting the oral-gut microbiome axis to improve OM outcomes.

Keywords: oral mucositis, chemotherapy, radiotherapy, HSCT, oral microbiota, gut microbiota, oral-gut microbiome axis

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INTRODUCTION

The oral/oropharyngeal mucosa is highly sensitive to cytotoxic anti-cancer agents causing profound inflammation and breakdown of the mucosal barrier [1]. The resulting ulcerative lesions, termed oral mucositis (OM), is one of the most frequent oral complications affecting 80–100% of patients with head and neck cancer (HNC) treated with radiotherapy [2, 3], up to 40% of patients receiving chemotherapy [4], and 70–87% of patients undergoing hematopoietic stem cell transplantation (HSCT) [5, 6]. OM has been identified as one of the most debilitating toxicities that significantly impact patients' quality of life due to its associated pain, difficulty chewing and swallowing, weight loss, and infection [2, 7–9]. In cases where these cannot be optimally managed, treatment is often withheld or the dose reduced, which therefore negatively impacts patient prognosis [10, 11]. In addition to clinical consequences, OM is also associated with a significant economic cost as patients often require intensive medical interventions for symptoms management [2, 7, 12].

OM pathophysiology is a complex multifactorial process involving direct and indirect injury pathways including DNA damage, oxidative stress, inflammatory responses, and bacterial

translocation [13]. OM develops through five phases i.e., initiation, signal upregulation and amplification, ulceration, and healing [14–19]. Briefly, exposure to cytotoxic agents initiates epithelial cell death through direct DNA damage and the production of reactive oxygen species causing tissue damage and activating subsequent molecular pathways including nuclear factor kappa-B (NF-κB). This results in the production of pro-inflammatory mediators such as tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 leading to the ulcerative phase in which painful deep ulcers are formed creating a thriving environment for bacterial colonization which in turn exacerbate inflammatory responses. During the healing phase, signals from the submucosa and extracellular matrix stimulate proliferation and differentiation of epithelial cells allowing the restoration of the normal tissue structure [14–19].

The significant pathological changes in the oral cavity have led to the assumption that alterations in the oral microbes following cancer treatments could contribute to OM development. As such, the role of oral microbiota in the pathogenesis of OM has been an area of interest for several decades, with changes in oral microbiota following radiation therapy documented as early as the 1980s [20]. The significant increase in bacterial load in the ulcerated epithelium, and the correlation between bacterial load and OM peak severity [19], has suggested a causal relationship between oral bacteria and OM [19, 21, 22]. Hence, multiple clinical trials have used antimicrobial agents targeting oral bacteria to reduce OM severity; however, these attempts have failed to achieve positive outcomes [23]. This might be due to non-selective targeting of the oral microbiota and a lack of understanding of which specific microbes are contributing to OM. The recent advances in culture-independent microbial detection technologies (e.g., 16S rRNA sequencing) have allowed for extensive characterization of oral microbiota and subsequent investigation of its association with OM [24].

In addition to oral pathology, cancer treatments are also associated with major pathological changes in the lower gastrointestinal tract including intestinal inflammation, and disruption of intestinal barrier integrity and functions [13, 25]. These are often accompanied by changes in the gut microbiota, which serve to exacerbate gastrointestinal dysfunction [26]. In addition to disrupting local gut homeostasis, these changes are thought to impact organ systems at distant sites and therefore have prompted speculation that disruption of intestinal homeostasis could also contribute to OM pathogenesis. This mini-review focuses on the role of oral-gut microbiome axis pathways including oral and gut microbiota dysbiosis, intestinal dysfunction, and gut microbiota oralization in OM pathogenesis and briefly discusses potential methods to target these pathways to prevent or reduce the severity of OM.

ORAL-GUT MICROBIOME AXIS IN OM

Oral Microbiota Dysbiosis and OM

The oral microbiota, a collection of microorganisms residing in the oral cavity, is composed of more than 700 bacterial species representing the second-largest microbial community in the human body after the gut microbiota [27]. Different bacterial populations are found in different oral cavity sites with a distinctive microbial community found in saliva, oral mucosa, and dental plaque [28, 29]. Oral microbiota plays a key role in maintaining oral homeostasis and preventing the colonization of exogenous pathogenic microorganisms [28, 30]. However, disruption of the oral microbial ecosystem could contribute to local and systemic diseases, with a growing body of evidence implicating the oral microbiota with oral diseases (periodontitis, dental caries, and oral cancer) and systemic conditions (colorectal cancer, diabetes, Alzheimer's disease, and cardiovascular diseases) [31].

Exposure to cytotoxic cancer therapies is widely associated with changes in the oral microbiota, *directly* caused by bactericidal or bacteriostatic anti-cancer agents, and *indirectly* through the breakdown of the mucosal lining and alteration of immunological properties of the oral environment [32–35]. Similarly, changes in saliva production and composition, xerostomia, are also associated with microbial changes in the mouth [36, 37]. Alterations in the oral microbiota have been extensively studied using both culture-dependent and independent methods. While culture-based studies confirmed the alterations in oral microbiota following cancer treatments, they failed to demonstrate an association between the oral microbiota and OM severity as the analysis was limited to cultivated microorganisms [32]. The rapid advances in culture-independent molecular and next-generation sequencing techniques have allowed for more efficient detection of low abundance and non-cultivable taxa and helped overcome the detection limitations of culture-based methods [34, 38]. Hence, multiple studies have used these methods to characterize the oral microbiota in patients undergoing cancer treatments [39–41]. For instance, using 16S rRNA sequencing, Napeñas et al. reported a shift in the oral microbial community, which was dominated by *Streptococcus mitis* and *Gemella haemolysans* in patients with breast cancer treated with chemotherapy [39]. The same method was used by Hu et al. and demonstrated a temporal shift in the relative abundance of core oral microbiota throughout radiotherapy with a negative correlation between radiation doses and the oral microbial richness in patients with HNC undergoing radiotherapy [40]. Studies also attempted to identify a specific oral microbial signature associated with the risk or severity of OM (**Table 1**) [6, 33, 41–50]. Although no clear microbial signature was identified across these studies, one of the consistent observations is the enrichment of oral pathobiont *Fusobacterium* (*F. nucleatum*) in patients with severe OM [6, 41, 44–46, 48]. Interestingly, patients who experienced more severe OM had more profound changes in the oral microbiota while a more resilient oral microbiota, minimal alterations, and faster recovery of the microbial community were observed in those with less severe OM [33, 46, 49, 50]. Collectively, the current evidence suggests that oral microbiota alterations are associated with OM onset and severity; however, a clear microbial pattern is yet to be established. This might be due to the variation in study subjects, samples collection time, sampling sites and methodology, or OM scoring methods. Thus, there is a need for a standardized methodology

TABLE 1 | Studies investigated the association between the oral microbiota and the development of OM (*studies that used culture-independent methods only were included*).

Study	Subjects	Therapy	Sampling/analysis method	Key findings
Laheij et al. [6]	Adult patients with hematological malignancies ($n = 49$)	Myeloablative or reduced intensity-conditioning + HSCT	Oral rinsing samples/real-time PCR	The presence and load of *P. gingivalis* were associated with a higher risk of ulcerative OM in non-keratinized and keratinized oral mucosa Percentage (in relation to total load) of *P. gingivalis, P. micra, F. nucleatum,* and *T. denticola* was associated with ulcerative OM in non-keratinized oral mucosa
Ye et al. [33]	Pediatric patients with hematological and solid malignancies ($n = 37$) Healthy children ($n = 38$)	Chemotherapy	All patients and controls: lip and buccal mucosa samples Patients with mucositis: lesion samples/16S rRNA gene 454 pyrosequencing	Pre-chemotherapy, patients who developed OM had higher microbial diversity and increased abundance of Bacteroidetes (*Capnocytophaga*), Firmicutes (*Peptostreptococcaceae Incertae Sedis, Lactococcus*), *Fusobacteria*, and *Spirochaetes* During chemotherapy, patients who developed OM had more pronounced alterations in bacterial composition and a lower abundance of the Proteobacteria Mucositis lesions: an increased abundance of *Peptostreptococcus*, *Lactobacillus*, and *Mycoplasma*
Osakabe et al. [42]	Patients with hematological malignancies ($n = 19$)	Myeloablative or reduced-intensity conditioning + HSCT	Bilateral buccal mucosa, tongue, and palate samples/mass spectrometer	Post-HSCT, a decrease in *Streptococcus spp.* and an increase in coagulase-negative *staphylococci* were observed OM was significantly associated with an increase in *Candida spp.* and detection of *Enterococcus spp.*
Zhu et al. [43]	Patients with nasopharyngeal carcinoma ($n = 41$) Healthy controls ($n = 49$)	Radiotherapy/ chemoradiotherapy	Retropharyngeal mucosa or lesion swabs/16S rRNA gene sequencing	Radiotherapy caused progressive alterations in the bacterial community structure with an increase in the relative abundance of Gram-negative bacteria Patients who developed severe OM had a significantly lower alpha diversity and higher *Actinobacillus* during the erythema phase
Hou et al. [44]	Patients with nasopharyngeal carcinoma ($n = 19$)	Radiotherapy	Oropharyngeal mucosa swabs/16S rRNA gene sequencing	No change in bacterial alpha diversity during treatment 20 genera were positively associated and 10 negatively associated with radiation dose The abundance of *Prevotella*, *Porphyromonas, Fusobacterium*, and *Treponema* showed dynamic variations during radiotherapy, with peak abundance at severe OM onset
Vesty et al. [45]	Patients with HNC ($n = 19$)	Radiotherapy	Saliva and buccal mucosa swabs/16S rRNA gene sequencing	*Saliva:* *Parviomonas micra*, *Capnocytophaga leadbetteri*, *Olsenella uli*, *Neisseria mucosa*, and *Tannerella forsythia* were enriched in patients with ≥ grade 2 OM The abundance of *Bacteroidales G2*, *Capnocytophaga*, *Eikenella*, *Mycoplasma*, *Sneathia*, *periopathogenic Porphyromonas*, and *Tannerella* genera were positively correlated with ≥ grade 2 OM *Buccal mucosa:* Increased relative abundance of *Fusobacterium*, *Bacteroidales G2*, and *Sneathia* in ≥ grade 2 OM The abundance of *Fusobacterium, Porphyromonas, Haemophilus*, *Eikenella*, and *Tannerella* are associated with OM risk

(Continued)

TABLE 1 | Continued

Study	Subjects	Therapy	Sampling/analysis method	Key findings
Hong et al. [41]	Adult patients with cancer ($n = 49$) Healthy control ($n = 30$)	Chemotherapy (5-fluorouracil or doxorubicin)	Saliva and mucosal swabs/16S rRNA gene sequencing	Oral bacteria disruption was strongly associated with OM severity OM was associated with depletion of commensal bacteria belonging to *Streptococcus*, *Actinomyces Veillonella*, *Granulicatella*, and *Gemella* genera and enrichment of *Fusobacterium nucleatum* and *Prevotella oris*. OM-enriched *F. nucleatum* displayed pro-inflammatory and pro-apoptotic capacity
Laheij et al. [46]	Patients with multiple myeloma ($n = 51$)	High dose melphalan + autologous HSCT	Oral rinse samples/16S rRNA gene sequencing	Significant alteration in oral microbiota post- autoSCT which recovered within three months More pronounced changes in oral microbial diversity in patients who developed ulcerative OM Distinctive pre-autoSCT taxa discriminate between patients who developed OM and those who did not Pre-autoSCT, patients who developed OM had increased abundance of in *Veillonella, Enterococcus faecalis*, *Streptococcus*, *Staphylococcus spp.*, *Fusobacterium*, *Prevotella oris*, and *Prevotella veroralis*, and reduced abundance of *Actinomyces graevenitzii* and *Streptococcus constellatus* Patients who did not develop ulcerative OM had a more resilient microbial community
Mougeot et al. [47]	Patient with hematological cancers ($n = 22$)	Conditioning regimens + HSCT	Saliva and buccal mucosa, tongue, and supragingival plaque swabs/16S rRNA gene sequencing	Patients with score 2 OM had increased abundance of *Gammaproteobacteria* (*Escherichia-Shigella* genus) and decreased abundance of *Haemophilus parainfluenza* *Veillonella* enriched in patients with score 1-2 OM
Reyes-Gibby et al. [48]	Patients with HNSCC ($n = 66$)	Chemotherapy/ radiotherapy/ chemoradiotherapy	Buccal mucosa swabs/16S rRNA gene sequencing	At baseline: a higher abundance of *Cardiobacterium* and *Granulicatella* was associated with early onset of severe OM (grade 3) Immediately before OM development: an increased abundance of *Prevotella* and *Fusobacterium*, and decreased abundance of *Streptococcus* were associated with the early onset of severe OM Immediately before severe OM development: an increased abundance of *Megasphaera* and *Cardiobacterium* was associated with the early onset of severe OM
Shouval et al. [49]	Patients with hematological conditions ($n = 184$) Healthy controls ($n = 19$)	High intensity/ myeloablative conditioning + allogeneic HSCT	Saliva/16S rRNA gene sequencing	HSCT was associated with a decrease in oral alpha diversity Pre-HSCT: an increased abundance of *Kingella* and *Atopobium* correlated to a higher risk of developing severe OM (grade 3-4) Post-HSCT: *Methylobacterium spp*. were enriched in patients with severe OM, while *Treponema* and *TG5* were increased in grade 0-1 OM A more pronounced change in the salivary microbial diversity and metabolites post-HSCT in those developed grade 3-4 OM
Takahashi et al. [50]	Patients with hematological malignancies ($n = 19$) Healthy controls ($n = 3$)	Cyclophosphamide + total body irradiation OR fludarabine and melphalan + HSCT	Tongue, buccal mucosa, and teeth swabs/16S rRNA gene-based terminal restriction fragment length polymorphism (T-RFLP)	Patients with severe OM had larger changes in the oral bacterial community post-HSCT than patients with mild OM Faster recovery of the microbial diversity and abundance in patients with mild/moderate OM compared to patients with severe OM

for oral microbiota sampling and analysis to obtain more consistent results.

Most of the present research has focused on the association between oral microbiota and OM; however, the causal relationship remains poorly understood. Only one study has been conducted and demonstrated that germ-free mice treated with chemotherapy had less oral epithelial tissue injury and lower levels of pro-inflammatory cytokines and matrix metalloproteinases in the tongue tissues compared to specific pathogen-free mice [51]. Although the authors suggested that these outcomes are mediated by the oral microbiota, this does not exclude the impact of the gut microbiota as germ-free mice are completely free of all microbes. Overall, despite limited research, current evidence suggests that oral microbiota may contribute to OM through the regulation of oral innate immune pathways including NF-κB and toll-like receptors (TLRs) [22]. Microbiota-derived molecules like lipopolysaccharides can interact with TLRs in infiltrating immune cells leading to the further activation of NF-κB and, therefore, exacerbating inflammatory signals [21]. Further, the oral microbiota could influence OM healing phase by regulating the rate of mucosal recovery and restoration. It has been demonstrated that co-culturing the oral microbiota biofilms and epithelial cell layer alters its wound healing capacity [52]. Moreover, oral pathobiont associated with OM e.g., *Porphyromonas gingivalis* (*P. gingivalis)* has been found to inhibit cell migration in an *in vitro* assay of human buccal epithelial cells, suggesting the oral microbiota could contribute to the epithelial wound healing process [53, 54].

OM-Associated Intestinal Dysfunction

It is well-documented that systemic chemotherapy and HSCT myeloablative regimes cause significant gastrointestinal toxicities characterized by gastrointestinal mucositis, diarrhea, nausea, vomiting, and abdominal pain [55]. These toxicities are often associated with major gastrointestinal pathological changes including gut microbial dysbiosis, disruption of barrier functions, and intestinal inflammation [13, 25]. While these are expected consequences in patients receiving systemic therapies, local radiotherapy to the head and neck could also cause intestinal inflammation and disrupt intestinal barriers. For instance, Fernández-Gil et al. demonstrated that irradiation of the rat oral cavity was associated with intestinal damage, oxidative stress, and reduction in intestinal tight junction protein, Zonula occludens-1 [56]. Gastrointestinal toxicity characterized by disruption of intestinal barriers can lead to increased translocation of bacterial endotoxins into the circulation, activation of systemic inflammation, and eventually aggravating tissue injury in other parts of the body such as the brain [57, 58], liver [59], and heart [60]. Similarly, these pathological changes could enhance the severity of OM by enhancing systemic inflammatory responses; however, this is yet to be investigated. Nevertheless, reduced intestinal inflammation and increased expression of tight junction proteins were associated with lower severity of radiation-induced OM in a rat model suggesting that intestinal homeostasis is a potential target for alleviating OM [56]. Together, intestinal pathologies during cancer therapies may contribute to OM development and severity through activating systemic inflammation (**Figure 1**), and hence further research is warranted.

Bottom-Up: Gut Microbiota Dysbiosis and Its Impact on OM

The gut microbiota refers to trillions of microorganisms found along the gastrointestinal tract [61]. Our understanding of these microbes has evolved enormously, and it is now well established that the gut microbiota controls the development and modulation of several host physiological processes including intestinal homeostasis, immune responses, and host metabolism [62]. As such, perturbations in the gut microbiota have been implicated in several intestinal and extraintestinal conditions at distant sites [63]. It has been widely demonstrated that the gut microbiota is disrupted in patients at high risk of OM, including those undergoing systemic chemotherapy or HSCT [64, 65]. While HNC local radiotherapy is not expected to cause a significant change in the gut microbiota, chemoradiotherapy regimens may lead to gut microbial dysbiosis in patients with HNC. Currently, only one study has investigated the impact of chemoradiotherapy on the gut microbiota of patients with oropharyngeal cancer and reported no changes in the gut microbiota post chemoradiotherapy [66]. However, this was only evaluated in a small sample size ($N = 22$) with limited resolution; hence further research is required.

Since the gut microbiota plays a critical role in modulating systemic immune and inflammatory responses, it may influence the development and/or severity of OM [34, 67]. However, the current evidence supporting this is limited. As discussed earlier, germ-free mice (lacking both oral and gut microbiota) are less susceptible to oral injury and inflammation following chemotherapy [51]. Similarly, we have shown that treating rats with broad-spectrum antibiotics in drinking water, to deplete the gut microbiota, decreased radiation-induced OM severity by reducing the inflammatory cytokines in tongue tissues [68]. Although it is difficult to dissect whether these findings are due to changes in the oral or gut microbiota, the immunomodulatory capacity of the gut microbiota is undoubtedly larger than that of the oral microbiota. As such, it is likely that the gut microbiota plays an important role in OM pathobiology. In fact, this concept is supported by more recent evidence which used a more targeted approach to deplete the gut microbiota using intragastric antibiotics. Mice exposed to antibiotics had reduced epithelial damage and immune cell infiltration in the tongue after irradiation, indicating that gut microbiota is implicated in OM development [69]. Minimal effects of intragastric antibiotics on the oral microbiota were reported suggesting that the protective effect is mainly mediated by the gut microbiota depletion independent of the oral microbiota [69].

Mechanistically, it is well-known that gut microbiota plays a pivotal role in maintaining intestinal homeostasis and enhancing intestinal barrier integrity [62]. Therefore, the disruption of the steady-state balance of the gut microbiota could indirectly influence OM by further aggravating the disruption of intestinal integrity caused by anticancer agents and hence activating

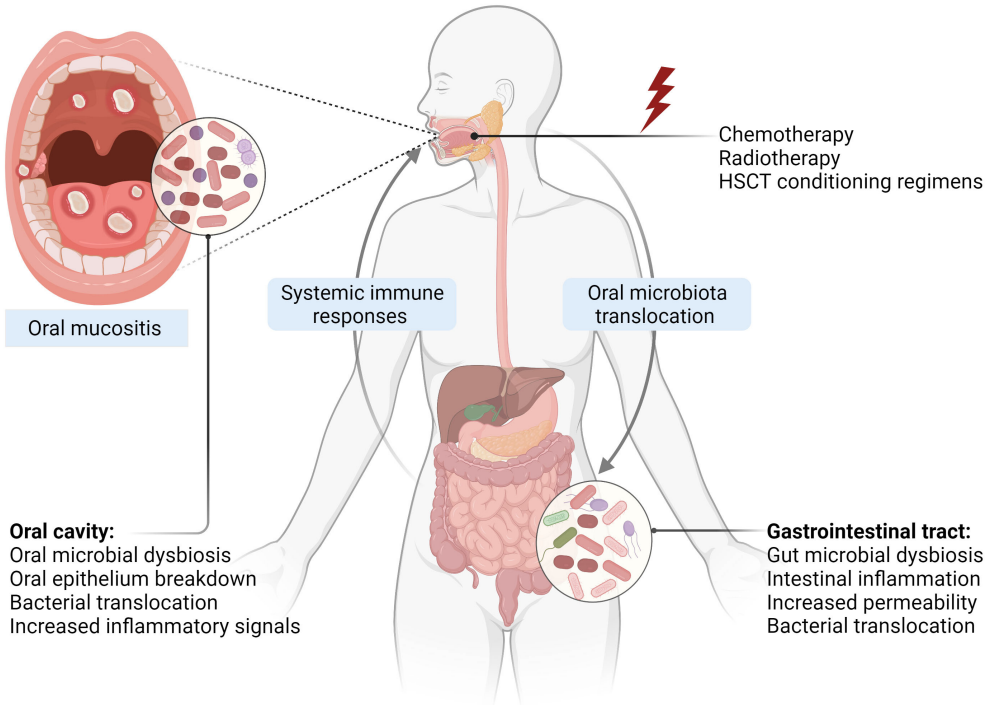

FIGURE 1 | Oral-gut microbiome axis in the development of OM. Exposure to cytotoxic cancer treatments causes direct tissue injury and subsequent inflammatory responses leading to epithelial damage. Changes in the oral environment result in oral microbiota dysbiosis, which can cross through the damaged and ulcerated mucosa, interacting with immune cells and enhancing inflammatory responses. Intestinal pathological changes including gut microbiota dysbiosis, caused by anticancer agents and oral microbiota translocation into the gut, disrupt intestinal homeostasis and facilitate bacterial translocation into circulation and activation of systemic immune responses, which in turn aggravate OM severity (Created with Biorender.com).

systemic immune responses [70]. A recent study demonstrated that the restoration of the gut microbiota using ingested probiotics reduced the severity of OM in patients with nasopharyngeal cancer receiving chemoradiotherapy and in a rat model of radiation-induced OM through reducing of OM-associated inflammation [71]. Collectively, growing research indicates that gut microbiota could play a role in OM pathology (**Figure 1**); however, further research in this field is needed.

Top-Down: Interaction Between the Oral and Gut Microbiota During OM

The oral and gut microbiota are composed of distinctive microbial load and taxa. However, the interconnected nature of the alimentary tract provides a potential route of oral bacteria transfer into the distal digestive tract. It has been hypothesized that oral microbiota can translocate into the gut through either the enteral (gastrointestinal tract) or the hematological route (blood) [72, 73]. Current evidence suggests that more than half of oral microbes are subjected to oral-gut translocation even in healthy individuals [74]. However, more pronounced ectopic displacement occurs under pathological conditions such as periodontitis and severe systemic inflammatory disorders [75]. Oral microbiota colonization of the gut, also known as the oralization of the gut microbiota, has been linked to several conditions including liver cirrhosis [76] and colorectal cancer [77]. The translocation of oral pathobionts could result in gut microbial dysbiosis and potentially disrupt intestinal immune homeostasis, hence affecting gastrointestinal [78] and systemic inflammatory diseases [79]. For instance, the administration of *P. gingivalis* was found to cause a significant gut microbiota dysbiosis, reduce the expression of intestinal tight junction proteins and increase the risk of endotoxemia [80, 81]. Collectively, oral bacteria translocation is increased in pathological conditions and could cause gut microbiota dysbiosis and disruption of intestinal homeostasis.

Oral microbiota translocation during OM is yet to be investigated. Nevertheless, an increase in oral bacteria in the gut has been reported following cancer treatments [82, 83]. It has been demonstrated that oral Firmicutes (*Veillonella parvula* and *Solobacterium moorei*) and Actinobacteria (*Rothia mucilaginosa*) are detected in the stool of patients undergoing HSCT and are associated with the severity of acute graft-vs.-host disease [82, 83]. Since OM is associated with major changes in the oral environment and oral microbial community, translocation of dysbiotic oral bacteria into the gut is likely to occur. This in turn could contribute to pathological changes in the gut and activation of systemic immune responses and hence negatively affect OM (**Figure 1**). As such, further research investigating oral microbial translocation in patients at risk of OM and whether that has any implications in OM pathogenies is warranted.

TARGETING THE ORAL-GUT MICROBIOTA AXIS IN OM

Since the recognition of the potential role of oral bacteria in the pathogenesis of OM, multiple attempts to use antiseptic and antimicrobial agents to treat or prevent OM in patients undergoing cancer treatments have been made with limited success [84–87]. The lack of benefit seen in these studies could be due to the use of non-targeted antimicrobial agents. Further, the use of antibiotics could disrupt the oral microbial ecosystem affecting both commensal and pathobiont microbes and hence may have overall detrimental effects on OM. As such, the use of alternative methods such as probiotics has been explored [21, 88, 89]. In a recent systematic review, which included five clinical trials, probiotics reduced the risk of all OM grades with a more significant result for grade $\geq$3 [90]. Probiotics could be used to manipulate oral and gut microbiota to improve both oral and intestinal homeostasis. For instance, administration of probiotic feed containing *Bacillus subtilis, Bifidobacterium bifidum, Enterococcus faecium, and Lactobacilllus acidophilus,* has been shown to enhance OM regression and reduce both oral and intestinal inflammation and intestinal villus-related damage in a rat model of chemotherapy-induced OM [91]. Probiotics are a safe method for modulating the microbiota; however, the risk of infections should be taken into consideration, especially in immunocompromised patients. Although, it should be appreciated that a damaged microbiota is predictive of infection in immunocompromised patients, and as such, probiotics may counterintuitively serve to reduce infection risk.

Another way to modulate gut microbiota is through diet. Given that reduction of oral intake is one of the main OM complications, changes in dietary habits are likely to have a significant impact on the gut microbiota. Andersen et al. demonstrated that reduced oral intake post hematopoietic progenitor cell transplantation was associated with a shift in the microbial composition with a lower gut microbial diversity and lower abundance of *Blautia* and Faecalibacterium *prausnitzii* [92]. Furthermore, compared to parenteral nutrition, enteral nutrition was associated higher abundance of short-chain fatty acids-producing *Faecalibacterium* and *Ruminococcus bromii* [92] and faster recovery of the gut microbiota structure [93]. Therefore, further research is needed to determine the best nutritional support that enriches the oral and gut microbiota symbiosis of patients suffering from OM.

Fecal microbiota transplant (FMT) and more recently oral microbiota transplant (OMT) are also possible ways to restore microbial symbiosis. While FMT is a more well-established procedure, it is yet to be investigated for mitigation of OM. Further, only one study has demonstrated that OMT from healthy mice into irradiated mice was able to reduce OM-associated epithelial injury and oral and systemic inflammation by mitigating irradiation-induced alteration in both oral and gut microbiota [69]. Further research is warranted for both FMT and OMT as they hold significant potential as do other emerging strategies such as photobiomodulation [94, 95].

CONCLUSION

Cancer treatment-induced OM remains a major complication with significant personal, clinical, and economic burdens. Growing evidence indicates that the oral microbiota is altered following cancer treatment and may be involved in OM pathogenesis. Further, there is mounting evidence for the role of the gut microbiota contributing to OM pathogenesis through the regulation of systemic immune responses. Moreover, intestinal dysfunction caused by cancer treatment or oralization of gut microbiota could exacerbate the severity of OM. Further research is warranted to further investigate these oral-gut microbiome axis pathways and identify the best targeting intervention to prevent or reduce the severity of OM.

AUTHOR CONTRIBUTIONS

GA-Q conceptualized, wrote, and contributed to editing the manuscript. HW, YV, and JB contributed to drafting and revising the manuscript. All authors contributed to the article and approved the submitted version.

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Dental Evaluation Prior to Cancer Therapy

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A comprehensive oral examination and dental care prior to the start of cancer therapy is the standard of care in many cancer centers. This is because good oral health will likely minimize the undesirable complications such as opportunistic infections during cancer therapy. As the considerations differ between anti-neoplastic regimens, this chapter discusses the indications and rationale when planning and executing a treatment plan for patients undergoing various cancer therapies.

Keywords: radiotherapy, antineoplastic agents, bone density conservation agents, dental care, dental service, hospital

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INTRODUCTION

Many cancer centers routinely recommend that patients undergo a comprehensive oral examination and if necessary, receive dental treatment prior to the commencement of anti-neoplastic therapy [1, 2]. This concept is commonly referred to as "dental clearance" and the rationale for this is based on the assumption that good oral health can likely minimize the undesirable oral sequelae from anti-neoplastic therapy [3, 4]. For instance, basic oral care strategies to improve oral health modifies the oral microbial load, which is proposed to decrease oral mucositis severity via modulation of the host inflammatory response [5]. As there are ethical issues with the conduct of clinical trials evaluating the benefit of dental clearance, the evidence regarding the effectiveness of dental clearance protocols and the extent of clearance needed to prevent or minimize oral complications arising during anti-neoplastic therapy is limited [2]. Thus, dental clearance protocols often vary between cancer centers; especially with regard to the aggressiveness of dental therapy needed (e.g., need for removal of asymptomatic partially impacted third molars). Despite these differences, the majority of dental clearance protocols generally follow these principles: [1] to stabilize and/or remove existing and potential sources of infection and irritation in the oral cavity and [2] to educate patient regarding the acute and chronic oral manifestations associated with anti-neoplastic therapy as well as oral care recommendations throughout their anti-neoplastic therapy [1, 4].

This aim of this chapter is to review the indications, rationale and guiding principles when planning and executing a dental treatment plan for patients undergoing anti-neoplastic therapy.

INDICATIONS

As the considerations differ between anti-neoplastic regimens, dental practitioners should be cognizant of the rationale and objectives for dental clearance for the various anti-neoplastic therapies.

Anti-neoplastic Chemotherapy and Hematopoietic Stem Cell Transplantation

The main mechanism of anti-neoplastic chemotherapeutics is the inhibition of cell proliferation and growth [6]. The majority of these agents do not differentiate between the cancer and healthy tissues; thus rapidly dividing non-cancerous tissues such as the hair follicles, skin or the bone marrow are also affected by anti-neoplastic chemotherapeutics [7]. Of significance to dentistry is the suppression of the bone marrow resulting in immunosuppression, which predisposes the patient to increased risk of opportunistic viral and fungal infections [8, 9]. Exacerbation of pre-existing oral or dental infections can also occur and may be complicated by superinfection and necrosis [10–13]. Oral mucositis, which is associated with the use of certain chemotherapy agents (e.g., methotrexate, doxorubicin, 5-fluorouracil, busulfan, bleomycin, and platinum co-ordination complexes) further increases the risk of a systemic infection from a local site due to the loss of an intact oral mucosal barrier [13–17].

The extent of bone marrow suppression is dependent on the chemotherapeutic regimen. Non-myeloablative regimens are reduced in intensity and do not completely suppress the bone marrow. They are usually used as adjuvant treatment for a variety of solid organ malignancies. High-dose myeloablative chemotherapy regimens are typically indicated for patients with hematological malignancies and are associated with a significant decline in hemoglobin, platelet and neutrophil levels. This occurs about 7 days after the drug administration, with the nadir occurring between 10 and 14 days and recovery in 3–4 weeks. The recovery to functional blood count levels is prolonged in some patients for various reasons such as advanced age, decreased clearance of chemotherapeutic drugs due to renal or liver dysfunction or concurrent radiotherapy to the bone marrow [18–20]. For allogeneic hematopoietic stem cell transplantation recipients, a certain degree of immunosuppression is deliberately maintained for 6–12 months after myeloablative chemotherapy for prophylaxis against graft-vs.-host-disease [21]. For the reasons mentioned above, the primary aim for dental evaluation in patients undergoing anti-neoplastic chemotherapy and hematopoietic stem cell transplantation is to prevent and minimize the occurrence of opportunistic infections and the potential systemic spread of a local infection [22, 23].

Head and Neck Radiation Therapy

Radiation therapy is the use of ionizing radiation to diminish or kill cancer cells. Unlike anti-neoplastic chemotherapy where only rapidly proliferating cells are targeted, radiation therapy affects all structures in the exposed field. The main dental concern with head and neck radiation therapy (HNRT) is the life-long risk of Osteoradionecrosis of the Jaw (ORNJ) development with radiation doses $\geq$ 60 Gy [24–32]. ORNJ is defined as a slow-healing radiation-induced ischemic necrosis of bone with or without associated soft tissue necrosis of variable extent, occurring in the absence of local primary tumor necrosis, recurrence, or metastatic disease [33]. The reported prevalence of ORNJ is ∼3–7% [34, 35]. The mandible, radiation doses $\geq$ 65–70 Gy [25, 26], co-morbidities (e.g., diabetes mellitus, excessive alcohol consumption), poor oral health, invasive dental treatment and ill-fitting prosthesis have been associated with higher risk of ORNJ development [24, 27–32, 36]. The treatment of ORNJ is based on the severity and remains challenging. Current treatment modalities range from antibiotic therapy, combination therapy with pentoxifylline, tocopherol and/or clodronate, hyperbaric oxygen therapy and surgical intervention [37–39]. Other significant oral manifestations arising from HNRT include permanent salivary gland hypofunction and trismus which can occur at radiation doses as low as 20 and 50 Gy, respectively [40–43]. Both conditions exponentially increase the patient's caries risk resulting in rapidly progressing dental decay. In view of the life-long risk of ORNJ and its associated treatment challenges, the main objective of dental evaluation for HNRT patients is to eradicate local risk factors to minimize ORNJ risk. A secondary objective is to provide anticipatory guidance regarding preventive oral care strategies because of the high risk of rapidly progressing dental caries in post-HNRT patients.

Anti-resorptive and Anti-angiogenic Therapy

The first reports of osteonecrosis of the jaw associated with bisphosphonates emerged in the early 2000s and was termed Bisphosphonates-Related Osteonecrosis of the Jaw [44]. This term was changed in 2014 to Medication Related Osteonecrosis of the Jaw (MRONJ) when reports of osteonecrosis of the jaw associated with the use of other anti-resorptive agents (ARAs) and anti-angiogenic agents (AAAs) were published [45]. ARAs are used in cancer therapy to prevent skeletal related events (e.g., pathological fractures, hypercalcemia of malignancy), while AAAs disrupt (neo) angiogenesis which hampers tumor growth and development. MRONJ is defined clinically by 3 criteria: (1) current or previous treatment with ARAs or AAAs; (2) exposed bone or bone that can be probed through an intra-oral or extra-oral fistula(s) in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy or obvious metastatic disease to the jaws [45]. The prevalence of MRONJ in cancer patients on ARAs or AAAs ranges widely between 0 and 18% [45, 46]. Longer duration of therapy, pre-existing inflammatory dental disease (e.g., periodontal disease), ill-fitting dentures, invasive dental procedures, uncontrolled diabetes mellitus, immunocompromised states and tobacco use are associated with higher risk [45–48]. Currently, there is no universally accepted treatment for MRONJ [46, 49, 50]. Treatment options include conservative symptomatic management, pharmacological interventions with pentoxifylline and tocopherol, hyperbaric oxygen therapy or surgical management [46, 49–51]. With the increasing use of ARAs and AAAs for cancer treatment, dental evaluation prior to the initiation of AAA or ARA therapies to address and mitigate modifiable risk factors associated with MRONJ development is considered routine in many cancer centers [45, 49].

GENERAL PRINCIPLES OF DENTAL EVALUATION PRIOR TO ANTI-NEOPLASTIC THERAPY

Clinical Assessment

Thorough medical, dental and social histories as well as patient's dental complaints should be elicited as part of the clinical assessment prior to initiating anti-neoplastic therapy.

A comprehensive clinical examination begins with a thorough assessment of the extra-oral structures to evaluate for any sources of pain or infection. Next, the intraoral examination should include a systematic assessment of the oral mucosal tissues for soft tissue pathologies, opportunistic infections or other abnormalities. This should be followed by the assessment of the teeth for caries and quality of existing restorations. Teeth with large restorations or suspicious for pulpal or periapical pathologies should be further evaluated using adjunctive aids (e.g., pulp sensibility tests) to rule out acute and/or chronic infections. If present, oral prosthesis should be checked and adjusted for any areas that could cause mucosal trauma. A periodontal examination to identify the presence of deep or suppurative periodontal pockets, inflamed gingiva, clinical attachment loss and furcal exposure should be performed [4, 45, 52–58].

For radiographic examination, acquiring a dental panoramic pantogram (DPT) provides an overview of the general oral health status and is useful for identifying pathology (e.g., impacted teeth, cysts) [59, 60]. A baseline DPT should be taken if one is not available within the year, or if there is a clinical suspicion of an intra-bony pathology. Bitewing radiographs should be taken to assess for caries and to check the quality of existing restorations (i.e., recurrent caries) [59, 60]. For patients with bitewings that were done within a year, a new set of bitewing radiographs may not be needed if the suspicion for new caries is low. Periapical radiographs should be captured for both asymptomatic and symptomatic teeth with large cavities and restorations to rule out pulpal or periapical pathologies as well as to assess the periodontal health [59, 60].

TABLE 1 | Summary of complete and partial dental clearance protocols [52, 58, 73, 78–85].

	Complete clearance protocol	Partial clearance protocol
Caries prevention	• Application of professional topical fluoride varnish at least twice yearly • Consider regular use of high fluoride (≥2,800 ppm) toothpaste	
Dental caries	• Extract non-restorable teeth, teeth with guarded or poor prognosis and retained roots	• Treat only large or symptomatic carious teeth
	• Restore all carious teeth	• Restore teeth with mild and moderate caries only if time permits. If not, regular topical fluoride therapy application is advised. Silver diamine fluoride may also be considered
	• Replace all defective restorations	• Treat only defective restorations that are symptomatic
Non carious lesions	• Restore non-carious lesions that affect maintenance of good oral hygiene • Extract large non-carious lesions that approximate the pulp	• Treat only symptomatic non-carious lesions
Pulpal and periapical pathology	• Extract primary teeth with deep caries, pulpal or periapical pathology • Permanent teeth - Symptomatic and asymptomatic non-vital teeth: Initiate root canal treatment at least 1 week before anti-neoplastic therapy to allow for sufficient time to assess treatment success. If not possible, extraction should be considered - Previously root canal treated teeth with apical periodontitis: Retreat, extract or perform apicoectomy	• Treat only symptomatic teeth with apical periodontitis and/or periapical lesion ≥ 5 mm
Periodontal disease	• Professional cleaning	
	• Extract teeth with advanced periodontal disease (probing depth ≥ 6 mm, furcation I, II, III, tooth mobility II-III)	• Extract only teeth with severe periodontal disease (probing depth ≥ 8 mm, mobility III)
Prosthesis and appliances	• Check dentures for irregularities or sharp edges and adjust accordingly • Remove orthodontic appliances that may aggravate mucosal injury	
	• Modify, disassemble or replace fixed prosthesis suspicious of recurrent caries, marginal leakage or affecting maintenance of good oral hygiene	• Modify, disassemble or replace only fixed prosthesis with large or symptomatic caries
Misaligned teeth	• Extract supra-erupted and grossly misaligned teeth	• No recommendation
Exfoliating teeth	• Extract mobile deciduous teeth with >50% physiological root resorption or those that are expected to exfoliate	• Extract only severely mobile deciduous teeth that are expected to exfoliate within a few weeks
Partially impacted third molars	• Extract asymptomatic and symptomatic partially erupted impacted third molars	• Extract only partially erupted impacted third molars with evidence of pericoronitis or purulence

Treatment Planning

Considerations

Treatment planning is directed by the nature and urgency of the dental problem, the time available to complete the treatment, the patient's medical fitness and considerations unique to the type of anti-neoplastic therapy [2].

The dental practitioner should consider the potential for a dental finding to develop into an infection or become a problem in the future, and the consequences of treatment versus no treatment. The considerations differ based on the type of anti-neoplastic therapy planned which has been discussed in the earlier section.

Another consideration is to prioritize and sequence dental procedures to ensure sufficient time for healing. For example, dental extractions should be performed earlier to allow time for wound mucosalization. Typically, the minimum healing durations prior to initiation of chemotherapy and HNRT/ARA/AAA therapies are ∼7–10 days and 10–14 days, respectively [45, 56, 61, 62].

For cancer patients who are immunosuppressed from their underlying illness or as a consequence of their anti-neoplastic therapy, a baseline complete blood count may be necessary to assess the need for antibiotic prophylaxis or blood transfusions prior to invasive dental procedures [63]. Although recommendations may vary across different centers, the common thresholds to determine the need for antibiotic prophylaxis and platelet transfusions are absolute neutrophil count 1×10^9/L ($<1000/mm^3$) and platelet count of 60×10^9/L ($<60{,}000/mm^3$), respectively [35, 64]. Another consideration for necessitating antibiotic prophylaxis is the presence of a central indwelling catheter because of the potential for a distant site infection after an invasive dental procedure. However, evidence supporting this practice is limited [65].

For patients undergoing high dose HNRT, the advent of Intensity Modulated Radiation Therapy (IMRT) has allowed for continued high dose delivery to the tumor bed while reducing the radiation to the adjacent tissues [66–68]. This has resulted in some reduction of the oral toxicities induced by HNRT [28, 69]. Polce et al. had further explored using the IMRT radiation plans to estimate the radiation dose to each tooth or selected area of interest so that decision making during treatment planning can be more precise [66]. Other local measures include fabrication of intra-oral stents to be worn during HNRT treatment sessions to decrease radiation scatter in patients with heavily restored dentition, to displace the tongue or to position the oral structures away from the epicenter where the radiation dose is at the highest [70, 71]. While potentially effective in reducing the oral side effects of HNRT, intra-oral stents are not widely used due to the lack of standardized protocols and limited high-quality evidence [71, 72]. Patients also often find the intra-oral stents bulky and uncomfortable, especially for those experiencing oral pain and trismus [72].

Lastly, while it is ideal to eliminate all dental disease, the clinician must consider the intent of the anti-neoplastic therapy during the treatment planning process. The benefit of total dental

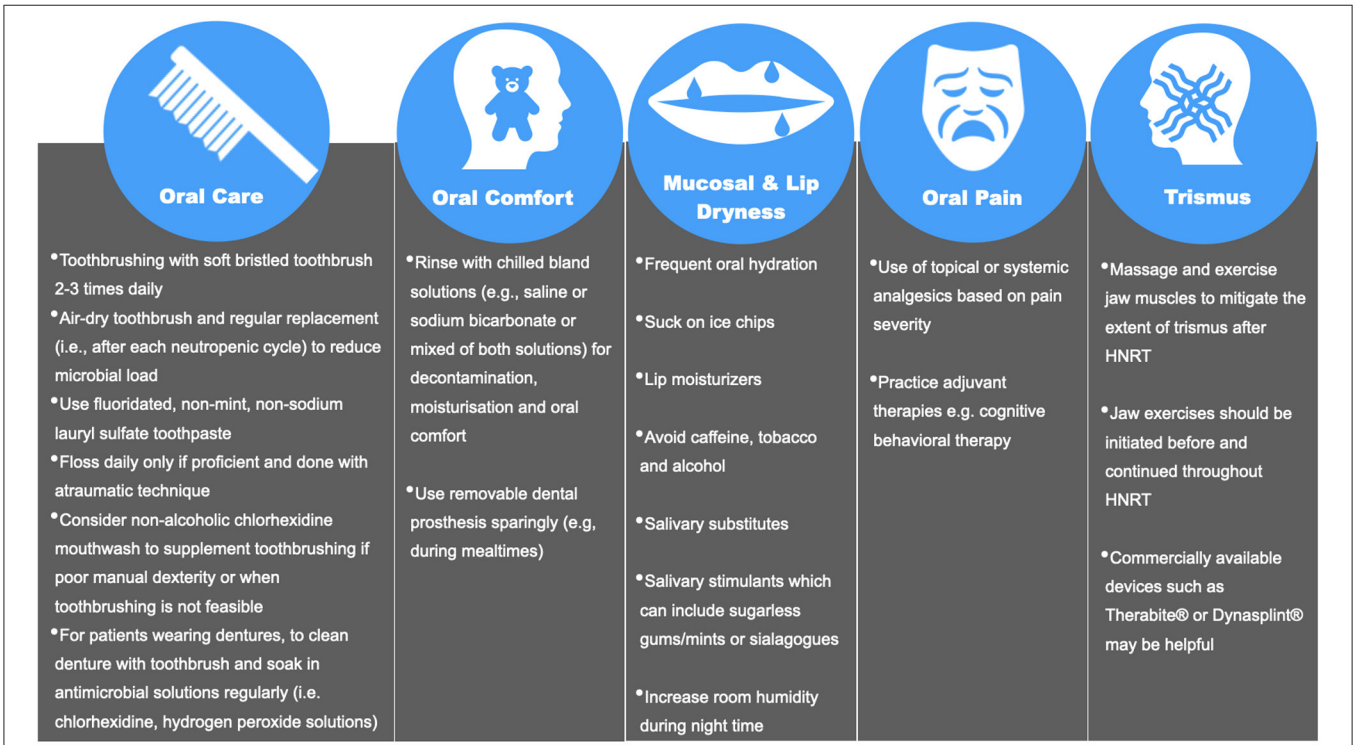

FIGURE 1 | Oral care instructions during and after anti-neoplastic therapy [54, 63, 92–101].

disease eradication in patients undergoing palliative treatment should be balanced against the discomfort and post-operative sequelae of extensive dental procedures.

Dental Clearance Protocols

Conventionally, the objective of dental clearance has been to eliminate all dental pathology prior to anti-neoplastic therapy. However, the complete clearance approach may carry some risk of complications arising from the dental treatment itself [2, 73–75]. Tai et al. reported that 40% of patients who had third molar extractions prior to their anti-neoplastic therapy developed post-operative complications (e.g., alveolar osteitis) [76]. Another consideration is when there is inadequate time to complete all planned treatment, and for treatment to be completed and adequate healing to occur, anti-neoplastic therapy would have to be delayed. This is not ideal because of the well-documented association between delay in anti-neoplastic therapy initiation and poorer survival rates [77].

In recent years, the concept of partial or minimal dental clearance protocols have emerged in the literature [2]. A partial clearance protocol allows for a less aggressive dental clearance and does not require for all dental pathologies to be eliminated prior to the anti-neoplastic therapy. A minimal protocol involves the treatment of only symptomatic oral disease. In a systematic review evaluating the adequacy of the partial and minimal dental clearance protocols prior to chemotherapy and HSCT, the authors recommended that a partial dental clearance protocol may be appropriate when there is insufficient time for complete dental clearance [2]. However, whenever possible, complete treatment clearance protocol is preferred [2]. **Table 1** provides an overview of the typical procedures performed in complete and partial clearance protocol [52, 58, 73, 78–85].

Delivery of Dental Treatment

Dental evaluation and treatment should be ideally performed prior to the initiation of anti-neoplastic therapy. If extractions are required after HNRT, some authors have suggested that atraumatic extractions are best performed within 6 months after HNRT to mitigate the risks of ORNJ [86–88]. This recommendation is based on a landmark histology study by Marx et al. whereby serial biopsies from 64 patients at varying times (unspecified) during and after receiving 72 Gy of HNRT demonstrated hyperemia and endarteritis in the first 6 months post-HNRT [74]. After which, the tissues demonstrated hypovascularity and fibrosis that progressively worsened with time [74]. In a recent systematic review evaluating the incidence of ORNJ in patients who had dental extractions before or after HNRT, authors found no difference in ORNJ incidence between the 2 groups [89]. However, authors cautioned that these results were based on vastly heterogeneous studies that lacked detail regarding the timing of dental procedures in relation to HNRT and recommended the need for larger longitudinal studies [89].

Patient Education

Patient education is an essential element of the dental clearance protocol. The dental professional should communicate with the patient about the rationale for dental evaluation, the potential acute and chronic oral complications and the recommended oral care during anti-neoplastic therapy (**Figure 1**) [54, 63, 90–101]. The recommendations should be customized to the patient's needs, which is dependent on the type of anti-neoplastic therapy as well as their underlying medical and dental conditions.

ORAL CARE DURING AND AFTER ANTI-NEOPLASTIC THERAPY

The objectives of oral care during and immediately after anti-neoplastic therapy are to prevent infections, control pain, maintain function and manage acute and chronic oral complications [4].

During active anti-neoplastic therapy, elective dental treatment should be avoided. In the event of an acute dental infection, pharmacological intervention with antibiotic therapy and analgesics are the preferred management modality [83]. If an emergency dental procedure is required (e.g., severe odontogenic abscess with potential airway embarrassment), the dental practitioner should plan for dental treatment in liaison with the patient's oncologist or medical physician. Specific pre-procedure considerations include the need for antibiotic prophylaxis, replacement of blood products and in some situations, disruption of anti-neoplastic therapy.

After active anti-neoplastic therapy or in patients with a history of cancer, 3–6 monthly routine reviews are recommended, and the interval is based on patient's dental needs. Other than addressing patient's complaints and performing a comprehensive clinical examination at these reviews, the dental professional should carefully evaluate the oral cavity for signs or symptoms of chronic oral manifestations from anti-neoplastic therapies as well as recurrence and occurrence of secondary malignancies. At the review, the importance of maintaining a good oral hygiene homecare program should also be reiterated.

CONCLUSION

Dental clearance prior to anti-neoplastic therapy is routine in many cancer centers. To be able to deliver the best care for the patient, it is essential for the dental practitioner to be aware of the rationale and objectives for dental evaluation as well as the specific considerations unique to the various anti-neoplastic treatment modalities.

AUTHOR CONTRIBUTIONS

CWY contributed to majority of the writing. AR contributed to the framework of the manuscript, provided expertise in the area, and checked the manuscript for accuracy. CH developed the framework for the manuscript and contributed to the writing. All authors contributed to the article and approved the submitted version.

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An Overview of Clinical Oncology and Impact on Oral Health

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As the incidence of cancer continues to increase, so too will the use of various forms of cancer therapeutics and their associated oral and dental complications. Although many of the acute and chronic oral toxicities of cancer therapy are largely unavoidable, appropriate and timely management of these complications has the potential to alleviate morbidity and improve outcomes. Undoubtedly, the substantial short- and long-term impacts of cancer therapy on the health of the oral cavity requires increased awareness, prevention, and treatment by multidisciplinary healthcare teams consisting of medical oncologists, dentists, and other oral healthcare specialists. This mini review provides a brief purview of the current state of clinical oncology and its impact on oral health. The topics introduced here will be further investigated throughout the remainder of the "Oral Complications in Cancer Patients" mini-review series.

Keywords: cancer, clinical oncology, oral health, oral complications, cancer therapy

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INTRODUCTION

Cancer accounted for roughly 10 million deaths in 2020, serving as a leading cause of mortality globally [1]. Cancer incidence is continuing to grow [2], reflecting population growth and aging, as well as the increasing prevalence of cancer risk factors associated with socioeconomic development. In the United States (US), half of men and one-third of women will develop cancer throughout their lifetime [3–5].

Many cancer treatment modalities, such as surgery, radiotherapy, chemotherapy (neoadjuvant, adjuvant, and/or concurrent), and hematopoietic stem cell transplantation, as well as supportive care measures (e.g., antiresorptive therapies) have the potential to cause various oral complications (**Figure 1**) [6]. More novel cancer therapeutics, such as targeted therapies [e.g., epidermal growth factor receptor (EGFR) inhibitors and tyrosine kinase inhibitors (TKI)] and emerging immunotherapies, have also demonstrated oral side effects [7–9]. As the incidence of cancer continues to increase, so too will the use of various forms of cancer therapeutics and their associated oral and dental complications.

This mini review provides a brief purview of the current state of clinical oncology and its impact on oral health. Clinical oncology consists of three primary disciplines: surgical oncology, radiation

oncology, and medical oncology. Basic principles of clinical oncology, recent advancements in cancer therapeutics, and various oral health complications associated with cancer treatment will be discussed. Finally, the authors will consider various approaches to promoting oral health before, during, and after cancer treatment. The topics introduced here will be further investigated throughout the remainder of the "Oral Complications in Cancer Patients" mini-review series.

CANCER EPIDEMIOLOGIC TRENDS

According to the Global Burden of Disease (GBD) study, cancer imposes the largest burden of any disease in the world, exceeding that of ischemic heart disease and stroke [10]. In 2018, over 18 million new cases of cancer were diagnosed; the most prevalent cancers among men were lung (1.37 million cases), prostate (1.28 million cases), and stomach (0.68 million), whereas women were most likely to be diagnosed with cancers of the breast (2.09 million cases), lung (0.72 million cases), and cervix/uterus (0.57 million cases) [11]. After ischemic heart disease, cancer remains the second leading cause of death worldwide, followed by stroke, and chronic obstructive pulmonary disease [12]. Over the last 15 years, the incidence of cancer has increased by 28%, which is 3-fold higher than the increase in mortality over the same period (∼9%) [12]. Overall, individuals between the ages of 0–74 have a 10.6% risk of dying from cancer; men are most likely to die from lung, liver, and stomach cancer, whereas women are most likely to die from breast, lung, and cervix/uterus cancer [12]. By 2030, cancer is projected to be the leading cause of global mortality, surpassing that of ischemic heart disease [13].

Cancers of the head and neck (HNC) are a heterogeneous group of malignancies that comprise the ninth and seventh most common cancer in the US and world, respectively [2, 4]. Each year, head and neck squamous cell carcinoma (HNSCC) is diagnosed in over half a million patients and is responsible for over 380,000 deaths globally [14]. Oral squamous cell carcinoma (OSCC), a major concern among dentists, oral medicine providers, and other oral healthcare specialists, accounted for approximately 145,000 deaths worldwide in 2012 [15]. In the US, OSCC is responsible for roughly 3% of cancers in men and 2% of cancers in women, most of which are diagnosed after the age of 50 [16]. Five-year survival rates for OSCC are ∼70%, although this number fluctuates substantially depending on anatomical/histologic subtype and grade/stage at the time of diagnosis [17].

CANCER THERAPY AND ASSOCIATED ORAL HEALTH COMPLICATIONS

Surgical Management

Surgical management remains a mainstay of modern cancer treatment, including for HNSCC. While removal of simple, early stage tumors may result in minimal side effects, surgical treatment of more advanced stage lesions can produce numerous esthetic, functional, and psychological sequelae. Potential impacts of surgery on oral function include difficulty tasting, speaking, chewing, and swallowing, whereas the excision of mucosal surfaces, loss in soft tissue volume, and removal of bone may result in substantial esthetic deformities [18]. Maxillofacial prosthodontics is an essential component of oral rehabilitation in patients with oral cancer undergoing surgical management.

The primary goals of maxillofacial prosthodontics are to restore oral function, improve facial esthetics, and enhance quality of life [19]. For example, maxillofacial prosthodontists fabricate various appliances, such as obturators, partial bridges, etc., to support ongoing cancer treatment and for patients following surgical procedures [20]. By utilizing computed tomography imaging, medical modeling technology, and virtual surgical planning (VSP), maxillofacial prosthodontists are able to accurately pre-plan the prosthetic and dental rehabilitation of patients undergoing complex surgical reconstruction [21, 22]. Undoubtedly, the maxillofacial prosthodontist is an essential member of the cancer team and plays a vital role in achieving optimal treatment outcomes for cancer patients.

Radiotherapy

Radiotherapy remains one of the primary treatment modalities for both localized and late-stage cancers. Further, various randomized control trials have demonstrated a superior tumor response to radiotherapy and concurrent chemotherapy, rather than radiotherapy alone, for numerous advanced tumors including HNCs [23–25]. The side effects and toxicities related to radiotherapy, however, have the potential to impart a substantial amount of morbidity and worsen quality of life for many patients. Despite recent advances in radiotherapy technique and delivery, many of the dental and oral complications related to head and neck radiation, such as oral mucositis, salivary gland dysfunction, radiation caries, and osteoradionecrosis, are still largely prevalent among this cancer population.

Oral Mucositis

Oral mucositis (OM) is fairly ubiquitous among patients receiving radiation therapy to the head and neck [26]. Symptoms of OM include irritation, discomfort, and pain that often precedes an erythematous mucosal lesion, which may ultimately progress to frank ulceration [27]. OM frequently occurs 2–3 weeks following high-dose radiation therapy to the head and neck (e.g., 60–70 Gy), and symptoms typically worsen with increasing radiation dose. Although any mucosal surface can potentially develop OM, non-keratinized tissues (e.g., buccal mucosa, lateral tongue, soft palate, and floor of mouth) are at a greater risk than keratinized tissues (e.g., attached gingiva, hard palate, dorsal tongue) [28]. The addition of concurrent chemotherapy or targeted therapies with radiation therapy has been shown to increase the severity, duration, and extent of OM [29]. The morbidity associated with OM includes pain, nutritional compromise often necessitating a feeding tube, reduction in quality of life, interruptions in cancer therapy, possible concomitant infections, and increased treatment costs [28]. Photobiomodulation, which uses red or near-infrared light to beneficially influence cellular metabolism to repair tissue damage caused by injury or disease, has been shown to be effective in preventing OM [30, 31].

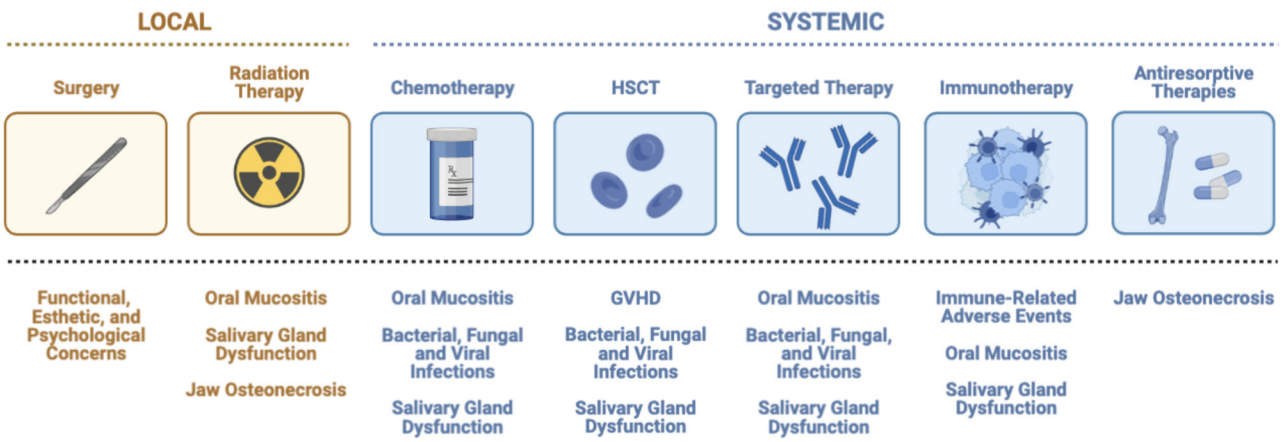

FIGURE 1 | Methods of cancer therapy and oral health considerations. There are many types of possible therapies used to treat cancer, each with their own oral health side effects. For example, chemotherapy and targeted therapy designed to treat both local and systemic cancers carry with them similar concerns for oral mucositis, infection, and salivary gland dysfunction. Antiresorptive therapies may raise the possibility of osteonecrosis, which is also a concern when radiation therapy is used, although the possibility of emergent oral mucositis and salivary gland dysfunction are less prevalent with antiresorptive therapies. HSCT, hematopoietic stem cell transplantation; GVHD, graft-vs.-host disease; HSV, herpes simplex virus.

Salivary Gland Dysfunction and Radiation Caries

Radiotherapy to the head and neck region is a common cause of salivary gland dysfunction, with doses of 50 Gy or higher imparting the highest risk for this complication [32, 33]. Patients may experience xerostomia in as little as 1 week after initiating radiation therapy, with the potential for permanent salivary gland dysfunction with continued exposure [34]. Disruption in the normal salivary flow may result in numerous oral complications, such as dysgeusia, dysphagia, problems with speech, oral candidiasis, and dental caries, while severely diminishing quality of life [35]. The enhanced risk of tooth decay, known as radiation caries, is thought to be a direct result of radiotherapy-induced salivary gland acinar degeneration and interstitial fibrosis [36, 37]. Teeth exposed to radiation may also be more prone to decay due to changes in the composition of dental hard tissue, such as loss of enamel prism structure, degeneration of odontoblast processes, and obliteration of dentinal tubules [38].

While various pharmacologic agents have been suggested as possible interventions for preventing radiation-induced salivary gland dysfunction, such as parasympathomimetic drugs, parasympatholytic drugs, and cytoprotective agents, the evidence to support their efficacy is of admittedly poor quality [34, 39–42]. Some clinicians and patients may opt for non-pharmacologic products such as toothpastes, mouthrinses, mouth sprays, and gels, as well as sugar-free gums and lozenges to reduce symptoms of xerostomia [43]. Fluoride supplementation, varnish, and regular oral hygiene check-ups are also essential to reduce the risk of developing radiation caries. In patients treated with radiotherapy, the daily application of 1% sodium fluoride gel has the potential to significantly reduce the incidence of caries [44].

Osteoradionecrosis

Osteoradionecrosis (ORN) of the jaw is a potentially severe iatrogenic disease of devitalized bone caused by radiation therapy of the head and neck that fails to heal or remodel [45–48]. Early proposed pathophysiologic mechanisms of ORN focused on hypoxic, hypovascular, and hypocellular tissue resulting in tissue breakdown and a non-healing wound [47, 49, 50]. More recent research, however, has favored the radiation-induced fibrosis theory whereby abnormal fibroblast activity leads to inflammation, local tissue injury, and eventually tissue necrosis [46, 51]. Common signs and symptoms of ORN include oral dysesthesia, paresthesia, pain, trismus, ulceration and necrosis of oral mucosa, malodor, pathologic fractures, draining fistulas, and deterioration in dental hygiene practices. Despite conflicting evidence, hyperbaric oxygen therapy (HBO) may be utilized in an attempt to prevent ORN of the jaws in adults receiving radiotherapy to the head and neck [52].

Chemotherapy and Hematopoietic Stem Cell Transplantation

Chemotherapeutic agents comprise a vast group of chemicals designed to halt the growth of cancer cells, either through inducing apoptosis or preventing their replication. These agents produce their toxic effects by targeting rapidly proliferating cells, such as the basal cells of the mucosal layer as well as the acinar and ductal cells of the salivary glands [53]. The oral side effects of chemotherapy are relatively common and may include OM, candidiasis and other oral infections (including bacterial, viral, and fungal infections), xerostomia, oral bleeding, and

potentially periodontal disease [53, 54]. Although concomitant chemotherapy often produces OM, the concomitant use of targeted agents may further alter mucositis risk, severity, and course [55, 56].

Hematopoietic stem cell transplantation (HSCT), on the other hand, involves the transplantation of healthy hematopoietic stem cells to patients with dysfunctional or depleted bone marrow for the treatment of various cancers, immune-deficiency syndromes, and hemoglobinopathies [57]. HSCT carries the risk of numerous acute and chronic complications that may impact the oral cavity, such as OM, oral candidiasis, herpes simplex virus (HSV) recrudescence, and graft-vs.-host disease (GVHD).

Graft-vs.-Host Disease

Graft-vs.-host disease (GVHD) is a major cause of morbidity and non-relapse mortality in patients undergoing allogeneic HSCT, with over 50% of patients developing chronic GVHD [58, 59]. Chronic GVHD is an alloimmune condition caused by donor T-cells recognizing and attacking antigens expressed on normal host tissues [60]. Oral chronic GVHD is characterized by mucosal, lichen planus-like changes presenting as erythematous and/or ulcerative lesions. Patients may experience oral pain, sensitivity to spicy/acidic foods, alcohol, and certain mouthwashes, xerostomia, difficulty speaking/swallowing, and taste changes that may predispose patients to decreased oral intake, nutritional deficiencies, and oral infections [61, 62]. Dentists and oral medicine specialists are important identifiers of this potentially debilitating disease. The most commonly used topical therapies for oral chronic GVHD include high-potency corticosteroids and calcineurin inhibitors, whereas systemic therapy includes corticosteroids, calcineurin inhibitors, and many other immunomodulatory agents [63].

Antiresorptive and Antiangiogenic Therapy

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially debilitating condition characterized by non-healing exposed bone in patients who have used either antiresorptive or antiangiogenic agents [64, 65]. High-dose regimens of antiresorptive medications, like bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors (e.g., denosumab), are frequently used to prevent skeletal-related adverse events in adults with malignancies involving bone [66]. Although the pathophysiology of MRONJ has been greatly debated, most hypotheses suggest the role of altered bone remodeling, oversuppression of bone resorption, and angiogenesis inhibition as key mechanisms resulting in this disease process [67].

Dentists and other oral healthcare specialists play a vital role in preventing or minimizing a patient's risk of developing MRONJ. Dental assessments and the provision of prophylactic dental care prior to initiation of antiangiogenic or antiresorptive therapy have been shown to decrease a patient's chances of developing MRONJ [68]. In patients with MRONJ, treatment is divided into either conservative (such as maintaining optimal oral hygiene, eliminating soft and hard tissue disease, antibiotic therapy, and the use of antibacterial mouthwashes) or surgical management [68]. Although the success rate of surgical treatment for MRONJ has proven to be high [69], the side effects of these invasive resections have the potential to impart a substantial amount of morbidity.

Targeted Therapies and Immunotherapies

Targeted therapies, which target specific genes and proteins involved in the growth and survival of cancer cells, and immunotherapies, which stimulate a patient's own immune system to combat cancer, are quickly becoming central pillars of cancer treatment. Although the introduction of targeted therapies and immunotherapies have revolutionized treatment for numerous types of malignancies, they have also produced novel side effects known as immune-related adverse events (irAE). While these adverse events have been observed in nearly all parts of the body, their impact on the oral cavity is notable [70].

Immune-Related Adverse Events

Although immunotherapy has made an indelible mark on the field of cancer therapeutics, irAEs associated with their use are unfortunately commonplace [71]. These adverse events are thought to arise from a loss of tolerance to self-antigens, which results in organ toxicity [72]. irAEs are found in nearly every organ, including the oral cavity where they primarily affect the oral mucosa, salivary glands, and sense of taste [73]. Numerous authors have reported an association between immunotherapy use and numerous oral complications, such as lichenoid reactions, sicca syndrome, vesiculobullous disorders, erythema multiforme (EM), and Steven-Johnson syndrome (SJS) [74–78]. Despite these observations, little is known regarding the etiology, underlying pathophysiology, and appropriate management for these conditions. Nevertheless, appropriate referrals to multidisciplinary teams composed of oncologists, rheumatologists, and oral healthcare specialists should be made to ensure proper case management for this complex patient population.

PROMOTING ORAL HEALTH WITH CANCER TREATMENT

Before Cancer Treatment

Obtaining dental clearance is an essential step prior to the initiation of cancer treatment, particularly for patients to be exposed to radiation to the head and neck. The rationale for dental screening prior to cancer therapy derives from numerous studies linking an increased incidence of intra-therapy complications, such as acute dental infections, with poor oral health [79–81].

A complete oral evaluation prior to the initiation of cancer treatment should elucidate the following information: presence of a dental home, date of last dental visit, recognition of past and current dental problems, an oral/dental evidence-based risk assessment such as CAMBRA (caries management by risk assessment), and an evaluation of past and current medication use.

Additionally, the patient should receive oral prophylaxis including professional hygiene therapy as well as eliminate any

existing low-grade infections and possible sources of trauma (e.g., trauma from denture or fixed orthodontic appliances) [82]. The National Institute for Dental and Craniofacial Research recommends that elective surgical procedures be postponed until the cessation of cancer therapy, while invasive procedures be completed at least 14 days prior to the initiation of head and/or neck radiation and 7–10 days prior to myelosuppressive chemotherapy [83]. Finally, patients should be educated in proper oral hygiene techniques for the prevention of future dental caries and oral disease that may impact cancer treatment.

During Cancer Treatment

The increased risk of acute oral complications resulting from radiation and/or chemotherapy highlights the importance of continued proper oral hygiene practices and maintenance. Patients should continue to use the modified Bass brushing method with fluoride toothpaste at least two times per day [84], floss one time per day, avoid the use of alcoholic mouthwashes, and remain on a regular hygiene recall schedule with their dentist. The use of removable appliances and prostheses, especially those with the potential to cause hard and soft tissue damage, should be limited. Stimulation of salivary production in those patients demonstrating hyposalivation can be achieved either through the use of sugar-free lozenges or gums (e.g., xylitol) [85, 86].

It is crucial that dentists and other oral healthcare specialists maintain communication with the oncologist throughout the duration of cancer therapy and obtain proper consultation with the oncologist prior to any dental procedures, including prophylaxis. A blood sample should be obtained from patients undergoing chemotherapy roughly 24 h prior to any invasive oral surgical procedures and postponed when the following are present: platelet counts $<75{,}000/mm^3$; abnormal clotting factors present; and/or absolute neutrophil count of $<1{,}000/mm^3$ [83].

After Cancer Treatment

Following the completion of cancer therapy, patients should remain on a regular recall schedule as recommended by their dentist and continue practicing proper oral hygiene including the use of fluoride toothpaste and varnish. In patients at higher risk for dental caries (especially post-allogeneic HSCT/GVHD) as well as those with a history of oral malignancy (such as OSCC), a more intensive and frequent recall schedule may be necessary. Further, a patient's hematologic status, such as the resolution of immunosuppression and/or thrombocytopenia following the cessation of cancer therapy, should be assessed prior to dental treatment. Furthermore, the dentist should update the patient's medication list and assess for any anti-resorptive and/or anti-angiogenic medications used throughout the duration of cancer treatment.

Finally, childhood cancer therapy has the potential to result in numerous dental, craniofacial, and soft tissue complications. Children are particularly susceptible to the long-term effects of cancer therapy as treatment typically occurs during the most active stage of growth and organ development [87]. For example, these patients are at an increased risk for dental caries, abnormalities in tooth morphology and composition, hyposalivation, maxillary and mandibular growth disturbances, and temporomandibular dysfunction (TMD) [88, 89]. As such, pediatric and general dentists should be aware of these potential complications and monitor for any abnormal deviations in craniofacial and/or dental growth and development [83].

CONCLUSION

Innovations and improvements in cancer therapy have substantially increased survivorship in recent years. As a result, there is a growing need for continuing management of the oral health needs of this population. Although many of the acute and chronic oral toxicities of cancer therapy are largely unavoidable, appropriate and timely management of these complications has the potential to alleviate a considerable amount of morbidity. Further, with advances in computational modeling and "Deep Learning" protocols, individuals at risk for developing drug toxicities may be identified and providers may be better equipped to predict which patients and drugs are most likely to induce oral side effects. Finally, the successful management of this complex patient population requires interprofessional collaboration and the utilization of a comprehensive, patient-centered approach with an emphasis on oral health.

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JH and GO wrote the first draft of the manuscript. GH guided and revised the manuscript. NT conceptualized and guided the project. All authors contributed to the article and approved the submitted version.

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Oral Complications in Cancer Patients–Medication-Related Osteonecrosis of the Jaw (MRONJ)

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Medication-Related Osteonecrosis of the Jaw (MRONJ) was first reported in 2003. Despite the progress in the understanding of this oral complication in cancer patients for the past 18 years, there is still discussion about the best way to define MRONJ, prevent the complication, how to diagnose, and the options of treatment available. The initial reports associated MRONJ to bisphosphonates and denosumab, medications that work as bone-modifying agents. Later, other agents such as the antiangiogenics, have also been reported to cause the oral complication, either alone or in combination with antiresorptives. Initially, these medications were prescribed to patients with osteoporosis and cancers patients with bone metastasis. Today, because of the effect of the medications in the bone remodeling system, patients with several other diseases such as giant cell tumors, rheumatoid arthritis, Paget's disease of bone, fibrous dysplasia, osteogenesis imperfecta, are managed with these medications, significantly increasing the population of individuals at risk for developing MRONJ. This mini review focused on the cancer patient. It updates the dental clinician on the recent scientific literature about MRONJ and provides information on how to diagnose and manage patients being treated with these medications, suggests protocols to prevent the development of MRONJ, and present ways to manage those patients who develop the oral complication.

Keywords: ONJ, MRONJ, osteonecrosis of the jaw, osteonecrosis, oral complications, cancer therapy

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INTRODUCTION

The history of MRONJ started about 18 years ago when it was first reported [1–3]. After many suggestions to name the complication, including ONJ, BON, BIONJ, ostechemonecrosis, BONJ, and many others, the final universal agreement came with a proposal from the clinical guidelines article from the American Academy of Oral and Maxillofacial Surgeons (AAOMS) in 2014 that named it "medication-related osteonecrosis of the jaws, or MRONJ" [4] due to its association with medications. This is the terminology we will use throughout this mini review. Despite the progress in the understanding of this oral complication in patients with cancer, there is still discussion about the best way to define, diagnose, and stage MRONJ, the mechanisms that lead to the development of the oral complication, management alternatives with medical or surgical interventions, and best prevention measures. We will discuss current knowledge about patient management, with the goal of assisting the dental provider when treating patients, taking drugs reported to be associated with MRONJ and those patients who develop the complication.

METHODS

We conducted a brief PubMed review of the recent literature, addressing MRONJ in patients with cancer. Using the key words bisphosphonates and osteonecrosis, the initial search revealed 3,635 publications from 2003 through 2021. From this search, relevant articles written in English were reviewed, and pertinent information was collected. When available, clinical trials were used as the main source of information. Otherwise, important research and personal expert experience developed during the past 18 years will be used. A recent joint clinical practice guidelines manuscript published by the Multinational Association of Supportive Care in Cancer, the International Society of Oral Oncology and the American Society of Clinical Oncology (MASCC/ISOO/ASCO) has revealed a lack of robust clinical trials, making difficult to produce guidelines based solely on scientific evidence [5].

Mini-Review Results

Definition, Diagnosis, and Clinical Staging

MRONJ is an oral manifestation characterized by exposed necrotic jawbone of patients who are using one of the medications that have been associated with the complication. To diagnose this condition, the clinician should confirm the presence of the three following criteria [4, 5]:

- Current or previous treatment with bone-modifying agents, such as a bisphosphonate, denosumab, or an antiangiogenic.
- The presence of an exposed necrotic bone or a bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks.
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

In addition to a precise definition and diagnosis, one should stage the complication before management is proposed (**Figure 1**). Staging of MRONJ is of importance in the decision-making process on how to manage each of the patients. The staging classification proposed in 2014 by the AAOMS guidelines article established the following staging criteria (updated based on new evidence):

At Risk

No apparent necrotic bone in patients who have been or who are being treated with oral or intravenous antiresorptives and or antiangiogenics.

Stage Zero

No clinical evidence of a necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms. This staging terminology is controversial and may lead to under or overdiagnosis MRONJ. Clinicians should be aware of this possibility when diagnosing patients at risk for MRONJ [6–8].

Stage 1

Exposed and necrotic bones or fistulas that probe to be bones in patients who are asymptomatic and have no evidence of infection.

Stage 2

Exposed and necrotic bones or fistulas that probe to be bones associated with infection as evidenced by pain and erythema in the region of exposed bones with or without purulent drainage.

Stage 3

Exposed and necrotic bones or a fistula that probes to be a bone in patients with pain, infection, and ≥ 1 of the following: exposed and necrotic bones extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla), resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

An important aspect of the staging system is presented by the Italian consortium on MRONJ, stating that imaging examination is necessary to precisely diagnose and stage the oral complication [9]. Areas of osteosclerosis and bone changes can assist the clinician in determining the real extension of the complication and help in the planning of management [10, 11].

Prevalence of MRONJ

How prevalent is MRONJ among patients being treated with one of the drugs associated with the oral complication? The prevalence is small. For the dental provider, it is important to know that patients with cancer have a higher risk of developing the complication than patients who use the medications for osteoporosis. A prospective controlled study compared zoledronic acid (ZA) and denosumab use in 5,723 patients with cancer. The overall risk of MRONJ was 1.6%. In patients being treated with zoledronic acid, 1.3% developed MRONJ, whereas 1.8% of patients treated with denosumab developed MRONJ [12]. A review from 2008 to 2015 suggested that the frequency of MRONJ is about 1% (range, 2–6.7%) [13]. The recommendation for the clinician is to consider that any patients exposed to the medications are at risk to develop the complication.

What Are the Drugs That Have Been Reported to Be Associated With MRONJ?

The first group of drugs associated with MRONJ were the bisphosphonates Pamidronate (Aredia®) and zoledronic acid (Zometa®). These drugs inhibit osteoclasts and are used to treat patients with cancer with malignancies that metastasized to bones, such as multiple myeloma, breast, prostate, and lung [1, 2, 14]. Following, with the development of denosumab (XGeva®), a humanized monoclonal antibody with similar action over osteoclasts, new cases of MRONJ were reported. Currently, several other drug groups have been associated with MRONJ, including the antiangiogenics, targeted therapy, and biologic immunomodulators [15–17]. The use of these drugs places individuals at risk for the development of MRONJ. The clinician must certify if a patient is being treated with one of the drugs when reviewing medical history so a prevention protocol can be used during patient care. It has been proposed that patients with cancer being treated with a combination of bisphosphonates and antiangiogenics may be at increased risk for MRONJ [18].

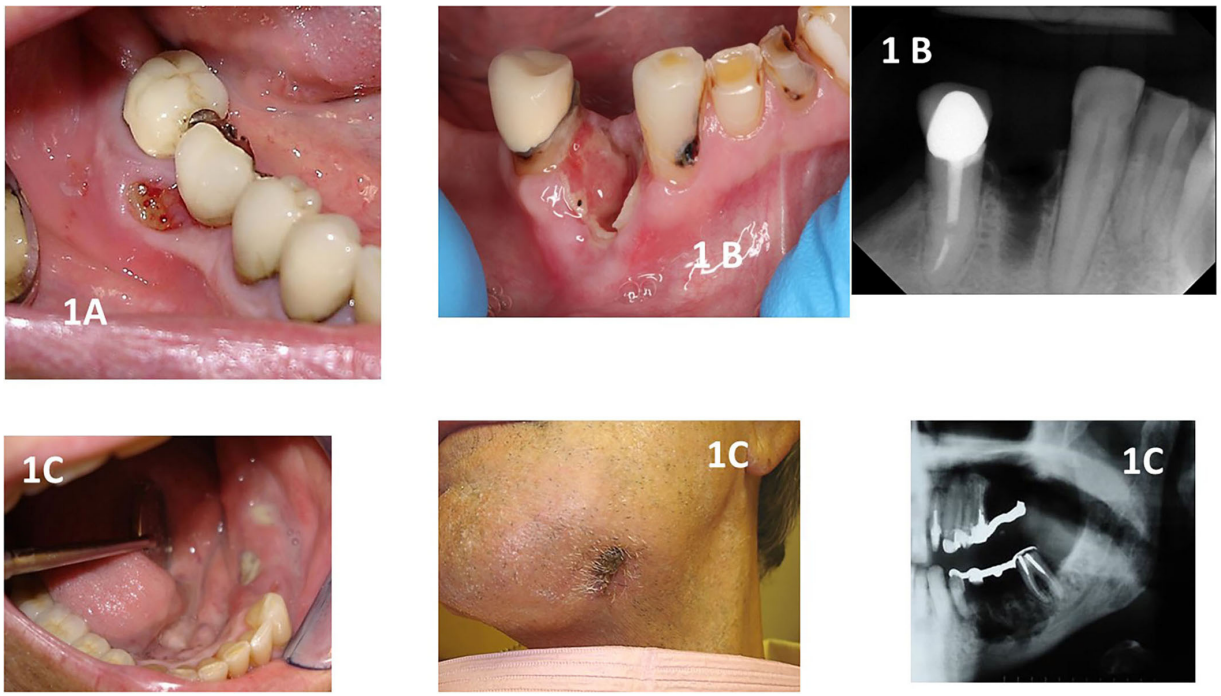

FIGURE 1 | Shows clinical and radiographical images of different stages of MRONJ. **(A)**: stage 1 showing a patient with breast cancer taking zoledronic acid with a small asymptomatic area of exposed necrotic bone that was affecting the use of a removable prosthodontic appliance. **(B)**: shows a patient taking denosumab who had a recent dental extraction. The site was not healing, and exposed alveolar bone could be seen. The patient was in pain and did not respond to antibiotics. The radiographical image shows the non-healing alveolus. **(C)**: shows a patient with multiple myeloma with Stage 3 MRONJ. The patient was in pain and presented to the clinic with swelling of the alveolar mucosa and several areas of infected and exposed bone with pus drainage. The patient complained of paresthesia in the area and had a strong mal odor. One can observe an extraoral fistula on the left submandibular area. The radiograph shows the extensive area of bone destruction, placing the patient at risk for a pathological fracture. Note that the fixed prosthodontic appliance was removed, revealing the exposed bone seen in this figure.

Common Signs and Symptoms Associated With MRONJ

The most common signs and symptoms associated with MRONJ observed in patients who have developed the complication include pain, infection with purulent secretion, general jaw discomfort, paresthesia, mal odor, a non-healing extraction site, or a sore associated with an ill-fitting denture [4, 5]. Of major importance is the presence of exposed necrotic bone or bone that could be probed through a fistula, according to the currently accepted definition of MRONJ [4].

It has been postulated that clinicians who manage patients considered at risk for MRONJ would benefit from having a diagnostic test that would indicate increased risk for MRONJ prior to doing invasive dental care. A study has hypothesized that bone remodeling markers may be indicators of the risk of development of MRONJ [19]. However, there is controversy in the literature whether or not such bone remodeling markers may, indeed, indicate risk [20]. A more recent study using different markers of bone changes in patients taking an antiresorptive medications [21] has evaluated 12 different biomarkers in patients with and without MRONJ. They suggested that tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) levels were significantly lower, and the mean Dickkopf-related protein 1 (DKK1) levels were significantly higher than the corresponding values for the control group (without MRONJ). This indicates the need to carefully follow patients with these abnormal biomarkers before and after dental extractions. However, one must always consider the availability of such tests and the cost of running them.

What Is the Mechanism That Leads to MRONJ?

A large body of research has been published in order to establish the mechanism that leads to the formation of MRONJ. The current evidence is that MRONJ is a multifactorial complication resulting from the effect of antiresorptive drugs-inhibiting osteoclasts and altering the bone remodeling system [22], the presence of dental infection both in the periodontium and the periapical areas [23, 24], chronic inflammation and acidic environment [25], dental trauma from dental extractions or invasive surgery [26], diabetes and other chronic disease [27], the use of corticosteroids, and altered local immunity [28]. This continues to be researched with the goal of determining the precise mechanism that results in MRONJ. However, there is no doubt that the antiresorptives and the antiangiogenics play a very important role. There is also evidence that the combined use of bisphosphonates and antiangiogenics in certain types of cancer increases the risk for the complication [29].

Suggestions of Management Protocols

Patients at Risk for MRONJ and Prevention Protocols

Patients who will be prescribed medications associated with MRONJ should have their oral health stabilized as soon as possible, preferably prior to the start of the drug therapy. A complete evaluation of teeth, periodontium and radiographic examination should be done. The dentist should perform dental extractions of hopeless teeth, scaling and root planning, dental restorations, and implement good oral hygiene. There is evidence that this may prevent or decrease the risk of MRONJ development [5, 6, 30, 31]. A periodic follow-up could be planned, depending on the oral health of each of the patients. If the drug therapy has started, dental procedures can be planned together with the patient's physician. Patients with complex medical conditions may not be exposed to invasive surgical procedures, and a more conservative dental care should be done. One must always consider the best alternative for the overall health of the patient. Although MRONJ is a severe complication, the risk is relatively small. Patients with active dental and periodontal infections may benefit from local treatment to control the infection associated with antibiotic therapy and topical antiseptic rinses [5, 32].

Patients With MRONJ

Dental professionals with expertise in managing MRONJ should be the ones to treat patients with this complication [5]. It is recommended that the decision on how to treat the patient should be done by a multiprofessional team. MRONJ must be staged, the overall medical health status evaluated, and the prognosis of the cancer should be considered. In general, experts propose two modalities of therapy: medical and surgical treatments. However, controversy exists in the literature about which is the best approach [17, 33].

Medical treatment is a more conservative approach. Minor local debridement of areas of exposed necrotic bone can be performed, sharp edges of bone can be eliminated, and active infection managed with antibiotics and topical antibacterial rinses. Some have proposed the use of a combination of pentoxifylline and tocopherol (vitamin E) such as it is done with patients with osteoradionecrosis [34]. However, clinical and radiographic results may take months or years to happen [35, 36]. Patients who cannot use pentoxifylline, cilostasol can be an alternative [37]. Conservative therapy can also be of value to treat patients ineligible to surgery [38].

Surgical treatment as the first choice for the treatment of MRONJ has been proposed regardless of staging [39]. The surgical approach must aim to the removal of all necrotic bones and closure by primary intention [40]. Several studies have shown improvement and resolution of MRONJ with surgical management [41, 42]. Surgical lasers have been used with reasonable success [43, 44].

DISCUSSION

MRONJ is a relatively new oral complication in patients with cancer being treated with medications used in cancer care. We provided current information that may be used by the clinician when managing patients at risk or with MRONJ. However, professional expertise in the diagnosis, staging, and management of patients with MRONJ is of importance for the success of the treatment [5].

It is suggested that a team of medical and dental providers must make all decisions about the best way to manage patients at risk for MRONJ. The idea of the patient discontinuing drug therapy is always present in the clinician's mind. However, the evidence available about a drug holiday prior to invasive dental procedures is not robust [45]. Discontinuation of antiresorptives may lead to more serious complications, such as skeletal-related fractures.

We revised information on the important aspects of taking complete dental and medical histories, detecting signs and symptoms that lead to the suspicion of MRONJ diagnosis and a patient's characteristics that help to determine risk of MRONJ development. We provided basic guidance for the clinician on current proposed prevention and management protocols.

Research Gaps and Future Research Needs

There still exist research gaps that are being investigated by several authors. These gaps provide future research ideas in the field of MRONJ. For example, we still do not know the exact mechanism that leads to the formation of MRONJ. There are several suggestions, but the only thing that can be stated is that it is a multifactorial process [28]. However, what starts MRONJ and how the many mechanisms interact have not been established. There is a lack of information about the mechanisms involved in MRONJ with new, non-antiresorptive drugs that are being reported to be associated with the complication [16]. None of the proposed treatment protocols have been demonstrated to have complete success, but only partial resolution of MRONJ cases [17, 46]. There is a need to better understand the role that osteoimmunity plays [28] and whether or not a genetic predisposition exists among populations [47].

The final take-home message is that patients with cancer are prescribed drugs that help mitigate the burden of oncological disease. As any drug, some are associated with the development of MRONJ but have other beneficial effects. Individual patients have different kinds of cancer staging and prognosis, and only their oncologists can determine the risk of discontinuing a medication or of doing an invasive procedure in the oral cavity. It is common for patients with cancer to have additional comorbidities that may preclude invasive surgical procedures. The recommendation for the clinicians is to work in collaboration with the oncology team when making decisions to treat dental disease in this population of patients.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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Oral Chronic Graft-Versus-Host Disease

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Chronic oral graft-versus-host disease (cGVHD) is a complex, frequent, and highly impactful complication of allogeneic hematopoietic cell transplantation (alloHCT). It represents the leading cause of morbidity and mortality in long-term alloHCT survivors. cGVHD can affect almost any visceral organ system and commonly affects the skin, eyes and mouth, manifesting with signs and symptoms similar to other known immune-mediated and autoimmune diseases. Oral manifestations of GVHD include inflammation, thinning, and ulceration of oral mucosal tissues (similar to lichen planus), lymphocyte-mediated salivary gland dysfunction (similar to Sjögren/Sicca Syndrome), and decreased oral opening (trismus) secondary to sclerosis of oral and perioral tissues (analogous to limitation in scleroderma). Potential sequelae include severe mucosal pain, compromised nutrition, weight loss, limitation in opening, and sometimes irreversible fibrosis of the salivary glands. While some cases can be managed with topical therapies, management may also require long-term targeted immunosuppressive and/or corticosteroid therapy with associated risk of local and systemic infection, hyperglycemia, kidney dysfunction, osteopenia/osteoporosis, and possibly secondary malignancies. The aim of this mini-review is to provide an up-to-date review of literature related to the diagnosis and management of oral cGVHD to aid dental and medical clinicians in optimizing oral cGVHD therapy while minimizing potential adverse effects.

Keywords: chronic GVHD, hematopoietic cell transplantation, oral medicine, dental, supportive care

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a common, pleotropic disorder with distinct manifestations throughout the body. cGVHD is diagnosed in 30–50% of allogeneic hematopoietic cell transplantation (alloHCT) recipients with more than 90% diagnosed within 12 months [1–3]. Incidence is increasing due to greater frequency of alloHCT, improved survivorship, and trends in donor selection, graft source, and other factors [2, 4]. It represents the leading cause of morbidity and mortality in long-term survivors otherwise in remission from their hematological disease [5–11].

ORAL cGVHD

Oral cGVHD is characterized by lichenoid mucositis, immune-mediate salivary dysfunction, and tissue sclerosis. Recent studies suggest that each represents a discrete clinical entity with little interrelationship [12, 13]. Though oral cGVHD is not independently associated with mortality, it may cause significant morbidity, making oral therapy an important component in comprehensive management [13–18].

Symptoms in mucosal cGVHD range from asymptomatic lichenoid changes to severely painful ulcerations which can be disabling (**Figures 1A,B**). Often minimal pain is reported at rest, though thinning and ulceration of the oral mucosa regularly cause sensitivity to previously tolerated stimuli [19, 20]. Common triggers include acidic, spicy or highly seasoned foods, carbonated beverages, alcohol/alcohol-based products, and flavoring agents such as mint in toothpaste [14, 19–22]. Tissue irritation may compromise nutrition, mastication, speech, swallowing, social interactions, and ability to perform effective oral hygiene, particularly when salivary dysfunction is also present [13, 23]. Mucosal ulceration compromises barrier function increasing risk for oral-sourced bacteremia [24].

Oral health and health-related quality of life are further impaired by immune-mediated salivary dysfunction which is especially impactful [12, 13]. Dysfunction is associated with xerostomia (the subjective impression of dry mouth), increased adherence of bacterial plaque and debris, difficulty swallowing, and decreased ability to clear viscous secretions. Qualitative and quantitative changes in saliva increase susceptibility to dental caries, oral candidiasis, and mucosal breakdown [25–28]. Dry mouth exacerbates mucosal symptoms while independently decreasing quality of life [13]. Mucoceles, dome-shaped fluid-filled "blisters" arising from minor salivary glands, are also common in cGVHD, though not specific to the disease [19, 22] (**Figure 1C**).

Function may also be limited by trismus resulting from oral sclerosis which has been described as a late effect of oral cGVHD. Pathophysiology is not well-understood [14, 20, 29]. Recent work found association between limited mouth opening and skin sclerosis, but not lichenoid mucositis suggesting a cutaneous rather than mucosal process [12]; however, limitation may be multifactorial as chronic inflammation can cause mucosal scarring [19, 22]. Trismus can impact nutrition, oral hygiene, and ability to comfortably complete dental procedures [22].

Taste-alterations have been described [30–32].

DIAGNOSIS AND STAGING OF cGVHD

In 2014 the NIH Diagnosis and Staging Working Group revised standards established in 2005 [33] to clarify enrollment criteria for clinical trials, align disease staging with treatment prognosis, and aid in treatment selection [34]. Diagnostic criteria were updated for the skin, mouth, lungs, and genitalia and organ severity scores revised in eight organs to improve global severity scoring. Diagnostic and distinctive features are defined for each system with diagnosis confirmed by the presence of one diagnostic feature, or one distinctive feature supported by a confirmatory test (e.g., biopsy). Conversely, acute GVHD, which was initially defined by time of occurrence (<100 days post-alloHCT), is now diagnosed and staged based on rash, total bilirubin elevation, and diarrhea. Overlap of acute and chronic GVHD can be seen and may relate to worse clinical outcome [3]. Though diagnostic criteria are foundational, some patients with equivocal diagnoses may also require therapy to minimize adverse effects of alloimmunity [3].

Diagnosis of Oral cGVHD

The mouth is commonly affected by cGVHD with up to 83% of cGVHD patients meeting diagnostic criteria [35, 36]. Oral cGVHD may co-occur with disease in other visceral organs or present as the initial or only site of involvement [14, 16, 22, 37]. The high incidence and ease of oral examination may aid in diagnosis of emerging disease [37]. Diagnosis is based on visual examination supplemented by history and global health status [14, 19]. Pathophysiology of oral cGVHD is not fully characterized, though findings of inflammation and fibrosis mirror other systems [3, 14]. Lichen planus-like changes are diagnostic and do not require confirmational biopsy. They may present as Wickham striae, lichenoid patches, or plaques. The 2014 NIH criteria replaced the term "hyperkeratotic plaques" [33] with "lichen-like changes" to differentiate from other causes of oral hyperkeratosis which may be reactive (frictional or chemical induced), infectious (pseudomembranous and hyperplastic candidiasis), or potentially malignant (idiopathic leukoplakia) [34]. Distinguishing cGVHD from idiopathic leukoplakia is especially important given increased risk of oral malignancy after alloHCT [38–43].

Distinctive features include mucosal atrophy, pseudomembranes, ulcers, mucoceles, and xerostomia. Distinctive features must be differentiated from other conditions common in the AlloHCT population including candidiasis, recurrent herpetic infection, drug reaction, mucosal trauma, recurrent or primary malignancy, and salivary dysfunction secondary to xerogenic medications and/or polypharmacy [19, 29, 34]. Biopsy, culture, viral PCR, and sialometry may be valuable in confirming diagnosis [32]. When cGVHD is suspected, biopsy should be obtained from non-ulcerated tissue and reviewed by an experienced pathologist [22, 44].

Severity Scoring and Response Criteria

Severity scores are used to quantify organs affected by cGVHD and resulting level of functional impairment [34]. Global and organ-specific scores are used in treatment planning which is strongly influenced by extent and severity of disease [34, 45, 46]. Topical and local therapies are favored in mild cases (confined to $\leq$ 2 non-respiratory organs each with a maximum score of 1) [3, 45] while systemic therapy is often required in moderate to severe disease. The NIH Global Severity Score is a simple instrument that can be used by non-specialists to assess functional impact of cGVHD [34]. Eight organs are scored from 0 to 3 with higher scores indicating greater disability [34, 36]. An oral score of 1 reflects disease that is not significantly impacting nutritional intake while a 3 indicates major dietary limitations caused by oral symptoms [34]. Asymptomatic oral lichenoid changes do not impact global scoring as they do not affect nutrition [34]. Patients should also rate their peak sensitivity (i.e., irritation from normally tolerated stimuli) over the past week using a 0 to 10 scale either alone or in combination with the oral questions on the Lee cGVHD symptom scale [46, 47].

Organ-specific response criteria are intended for use by specialists to capture higher level detail [46]. The preferred oral instrument is the NIH Modified Oral Mucosa Score (OMRS) which assigns scores for mucosal erythema (0–3), lichen-like

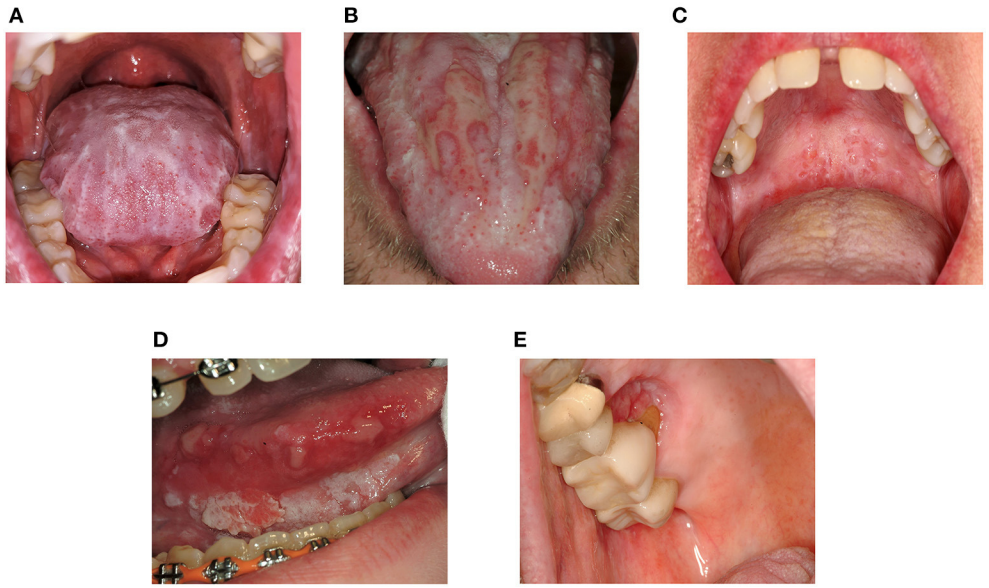

FIGURE 1 | Clinical features of oral mucosal cGVHD and Oral Squamous Cell Carcinoma. **(A)** Dense lichenoid reticulations involving the dorsal tongue **(B)** Pseudomembrane-covered ulcerations of the dorsal tongue surrounded by lichen-like changes (lichenoid hyperkeratosis) **(C)** Superficial mucoceles of the left soft palate. Note the prominent minor salivary glands and thin lichenoid striations affecting the hard and soft palates **(D)** Squamous cell carcinoma of the right ventrolateral tongue in a patient with longstanding oral cGVHD **(E)** Squamous cell carcinoma of the right hard palate at a site of persistent cGVHD involvement.

changes (0–3), and tissue ulceration [0–6] based on severity and surface area affected. Final scores range from 0 to 12 with scores of $\geq$2 representing clinically significant disease. Score change of $\geq$2 indicates disease progression (if increasing) or response to therapy (if decreasing) [46, 48, 49]. Mucoceles have been removed from the scale due to challenges in reporting and lack of correlation with clinical outcomes [18, 46, 50, 51]. Lichenoid changes, erythema, and symptoms scores are most strongly associated with perceived change in disease status [37].

PROPHYLAXIS AND MANAGEMENT

GVHD prophylaxis and treatment are complex and determined by extent of disease, co-occurrence of acute and chronic GVHD, degree of functional impairment, and patient specific factors including likelihood of end organ damage [45, 46, 52]. Therapy must balance GVHD-associated morbidity against the benefit of the graft-versus-leukemia (GVL) effect which decreases risk for relapse [53–55]. Standard prophylaxis includes a calcineurin inhibitor and an antimetabolite (most commonly methotrexate) [45]. Systemic corticosteroids, specifically prednisone 1 mg/kg, is well-established as first-line therapy [3, 45], though mild localized disease may be limited to topical or local corticosteroids. Addition of a non-steroidal agent in initial therapy has not shown additional benefit in patients with standard risk GVHD [56–58]. Non-steroidal immunomodulatory medication should be added in in severe GVHD to limit end organ damage and adverse effects associated with extended systemic corticosteroid use [45, 59]. Second-line therapy varies widely. Choice is often center-specific as studies comparing relative effectiveness are lacking [45]. Sirolimus, tacrolimus, cyclosporine, mycophenolate mofetil, pentostatin, and extracorporeal photopheresis are commonly used off-label [52]. The FDA has only been recently approved ibrutinib (2017) [60], ruxolitinib (2021) [61] and belumosudil (2021) [62] in the treatment of cGVHD.

While systemic immunomodulating medications are essential in treatment, they are associated with a variety of adverse effects including impaired immune function, decreased bone density, diabetes, renal dysfunction, neurologic side effects, and in some cases secondary malignancy [32, 63]. Risk mitigation is critical as most patients require systemic therapy beyond 2 years with up to 15% extending past 7 years [14, 56, 64]. Optimizing non-systemic therapies may help to limit prolonged use, particularly when the oral cavity is the primary site of involvement [16, 23, 32, 65, 66].

Oral Mucosal cGVHD

Topical therapies are the cornerstone of oral cGVHD management and are valuable even when systemic treatment is required as combined therapy has greater effect than systemic alone [32, 65–68] (**Table 1**). Furthermore, the mouth is one of few organs in which aggressive topical therapy may successfully manage moderate-to-severe disease [65]. Oral cGVHD should be treated when there is loss of barrier function and/or when oral sensitivity is negatively affecting quality of life [14, 20, 32, 67]. Asymptomatic lichenoid changes do not require therapy as treating to "disease resolution" has limited clinical benefit. This practice is consistent with treatment approaches in other organs [69]. Data from cGVHD Consortium sites has confirmed that treatment behavior follows these recommendations with topical therapies more likely to be used in patients reporting pain and

TABLE 1 | Topical therapies for oral mucosal cGVHD.

Topical Therapies	Standard Instructions:
Rinses: • Budesonide 0.03%* • Dexamethasone 0.01%* • Clobetasol propionate 0.05%* • Tacrolimus solution 0.1%* • Cyclosporine 100 mg/ml# • Azathioprine 5 mg/ml#	Rinse and hold 5 to 10 mL for 3 to 5 min and spit out. Repeat 1 to 4 times daily. Rinses are followed by a 20 to 30-min period of no food or fluid intake.
Ointments/gels • Tacrolimus ointment 0.1%* • Clobetasol propionate gel 0.05%* • Fluocinonide gel 0.05%* • Azathioprine gel (5 mg/ml in methylcellulose base)#	Apply a small amount of ointment/gel ("pea size") directly to the lesion (s) for 10 to 15 min. Gauze occlusion may help to hold in place. Trays for gingival application can be fabricated. Applications are followed by a 20 to 30-min period of no food or fluid intake.

*Supported by prospective clinical trial.
#Supported by case series or retrospective studies.

decreased oral function [70]. Follow-up is recommended to confirm symptom control and restoration of mucosal integrity. Therapy should be tapered over time to the lowest frequency (and potency) required to maintain effectiveness in symptomatic mitigation [16, 23].

Medication selection is based on the extent of oral lesions, medication potency, cost, availability, and patient preference [19, 23]. There are currently no FDA-approved topical therapies for oral cGVHD, though corticosteroids and calcineurin-inhibitors are regularly used in practice. Rinses are recommended when lesions are widespread to facilitate application to all sites. Localized lesions may be treated with higher potency gels or ointments which can be applied under gauze occlusion to maximize local effect. Numerous topical steroids, topical non-steroidal agents (e.g., tacrolimus [71–75], cyclosporine [76], sirolimus [77], azathioprine [78, 79], thalidomide [80]), and phototherapies (Photobiomodulation [81], PUVA [82, 83], UVB [84]) have been used in clinical practice and excellent evidence summaries have been previously published in national and international consensus documents [32, 65, 85, 86] and comprehensive reviews [14, 22, 66]. Surveys indicates that over 90% of specialists initially favor topical steroids with tacrolimus the preferred second-line alternative [87]. Among topical therapies only clobetasol, dexamethasone, tacrolimus solution and budesonide effervescence tablets have been analyzed in randomized trials [68, 72, 88]. Evidence-based practice is hindered by availability as only dexamethasone and prednisolone solutions are commercially manufactured in the United States [23, 65]. Other agents may be compounded; however, this increases cost to the patient as compounded medications are unlikely to be covered by insurance [23].

Topical steroids are generally well-tolerated, but patients must be monitored for potential adverse effects. Secondary candidiasis with topical steroids is not uncommon and [63, 88, 89] and prophylactic antifungal coverage is often used in clinical practice [16, 65, 87]. Risk factors for oral candidiasis, including immunosuppression, altered quantity and composition of saliva, and the use of medications that alter the normal oral flora (e.g., antibiotics, steroid inhalers), are common in people living with cGVHD. Candidiasis should therefore be considered when presumed oral cGVHD is not responsive to topical steroids. Whereas systemic uptake of tacrolimus has been described in case series and blood levels should be periodically monitored to rule it out [75]. Limited data is available for topical steroid absorption in the cGVHD population. Nonetheless patients should be monitored for cushingoid features or other signs of adrenal suppression [22]. The best available evidence is a study of 62 patients with severe erosive lichen planus treated with clobetasol propionate 0.05% rinse (10 mL for 5 min TID for 2 to 6 weeks based on response). Plasma cortisol levels showed signs of suppression in 85.5% of patients during initial therapy with only 4% of patients effected in the maintenance phase (suggesting lower systemic absorption after mucosal integrity is reestablished [90]. There were no major adverse events and dose reduction was effective in reversing cushingoid features and capillary fragility. Topical budesonide has been proposed as a preferred alternative for extended use due to low transmucosal absorption and poor systemic bioavailability [68].

Topical therapies may also be useful adjuncts in lesion assessment, though biopsy is required for definitive diagnosis. For example, short (e.g., 2 week) therapeutic trials of high potency topical steroids have been recommended in differentiation of lichenoid hyperkeratosis from leukoplakia. Immune-mediated lesions, such as cGVHD, are likely to respond to topical therapy while oral potentially malignant lesions will not. Non-responsive lesions should be biopsied to rule out epithelial dysplasia and/or squamous cell carcinoma [32, 65]. Intralesional injections with triamcinolone acetonide (40 mg/mL) have also shown value in treatment of persistent oral ulcerations which must also be differentiated from oral malignancy [91].

Salivary Dysfunction

Treatment of salivary dysfunction focuses on reestablishing oral lubrication to improve comfort and function while simultaneously minimizing risk of dental sequelae related to hyposalivation. Patients are encouraged to take frequent sips of water to moisten the mouth and maintain hydration. Liquid intake during mealtime, or when swallowing medications, can help to limit dysphagia if swallowing function is otherwise normal. Sugar-free candy, mints, and chewing gum can provide gustatory and masticatory stimulation to glands to increase salivary flow during the day [92]. All are inexpensive and widely available without a prescription. Normal saline rinses, over-the-counter coating agents, in the form of rinses, sprays, and gels, and artificial saliva may temporarily reduce xerostomia, but must be regularly reapplied [16, 32, 65]. Adhesive tablets, such as XyliMelts®, slowly dissolve over time while simultaneously stimulating flow. They may be especially useful during sleep along with other longer lasting agents (e.g., gels, oil-based products).

Systemic sialagogues are commonly used off-label in the treatment of severe cGVHD-related salivary dysfunction.

Pilocarpine is FDA-approved for the treatment of radiation-induced dry mouth in head and neck cancer patients and the treatment of dry mouth and dry eyes in Sjögren syndrome, while Cevimeline is approved in Sjögren syndrome only. Data in the cGVHD population is limited [93, 94]. Daily use of pilocarpine has been associated with increased salivary output, improved oral function, and restoration of normal sialometric properties, though data is limited to one randomized trial and several open enrollment studies [95–98]. Cevimeline has shown similar safety and efficacy in other populations [99, 100], and case series suggest it is an effective alternative in cGVHD [101]. A survey of practitioners in specialty health centers confirmed pilocarpine as the most common first-line therapy for salivary dysfunction in cGVHD (41.7%) with saliva substitutes favored as first-line palliative therapy [102]. The FDA cites hypersensitivity, uncontrolled asthma, acute iritis, and narrow angle glaucoma as contraindications [103] while consensus guidelines in cGVHD also advise against use in patients with cardiac disease and obstructive pulmonary disease (including pulmonary GVHD) [65]. Preexisting pulmonary and gastrointestinal GVHD may be exacerbated due to increase in bronchial and gastric secretions [16, 19, 87]. Sweating and flushing, commonly reported in other populations, is reported to be uncommon in the cGVHD population [19]. Titration of the medication over 2 weeks can be helpful in mitigating this effect when present. Side effect profiles are similar, and choice may be based on relative out of pocket cost [19].

Oral Sclerosis

Stretching and physical therapy are the most common therapies for oral and perioral sclerosis. Use of long-term, sequential intralesional steroid injections have also been described [65].

Palliative and Ancillary Therapy

During active therapy, palliative and ancillary therapies can be helpful to decrease pain, mucosal trauma, secondary infection, and dental sequelae. Dietary modifications, favoring bland and soft foods, and adjustments to oral hygiene practices (e.g., soft bristle toothbrush, non-mint and sodium lauryl sulfate-free toothpaste, non-alcohol-based rinses) can help to decrease mucosal sensitivity [19, 20]. Topical adhesive agents, such as ZilactinB® or Orabase®, can be applied to localized ulcerations to decrease pain and recurrent trauma while occlusal guards or Essix retainers can minimize frictional irritation from sharp or malpositioned teeth. Effective plaque control and judicious use of topical antimicrobials, such as chlorhexidine gluconate, can decrease gingivitis improving gingival comfort and decreasing risk for secondary infection [20].

Topical anesthetics, such as lidocaine or benzocaine, are recommended if soft tissue pain is limiting ability to eat or perform effective oral hygiene. Numerous preparations are available, though 2% viscous lidocaine is favored in consensus documents [32, 65, 67]. Care should be taken to avoid trauma after application, particularly in pediatric patients [65]. Gargling and swallowing should be avoided to decrease risk for aspiration [65]. Studies in oral mucositis patients have shown low systemic absorption and risk is low with oral application when used as directed [104]. Methemoglobinemia has been described after application to large mucosal surfaces (e.g., bronchoscopy) and with excessive oral use [105–108].

LATE ORAL COMPLICATIONS

Dental Caries

Patients with salivary cGVHD are at high risk for dental caries. Extensive caries has been described within 2 years of diagnosis [27]. Prevention is paramount as progressive caries increases risk for oral-source infection, the need for invasive dental procedures, and overall cost of care. Dietary counseling is recommended to limit refined sugar and other fermentable carbohydrates [109, 110]. Daily application of prescription fluoride gel is recommended and may be supplemented by professional fluoride application and shorter recall intervals in cases of severe hyposalivation [20, 32, 65, 87].

Second Malignancy

NIH consensus recommendations call for annual oral examinations in AlloHCT patients surviving beyond 1 year [111] due to increased risk for oral cancer [39–43, 112] (**Figures 1D,E**). Elevated risk for oral squamous cell carcinoma in oral cGVHD patients has prompted other groups to recommend more frequent assessment [87] analogous to other oral premalignant disorders [113]. Long-term follow-up is essential as the risk increases over time [114–117].

SUMMARY

Oral cGVHD is a common complication of AlloHCT associated with decreased quality of life. Oral cGVHD includes three distinct manifestations: lichenoid mucositis, salivary gland dysfunction, and tissue sclerosis resulting in trismus. Complications include tissue sensitivity, loss of mucosal integrity, infection risk, xerostomia, and compromised oral function. Topical, intralesional, palliative, and ancillary interventions are essential in managing these complications and may help to limit prolonged use of systemic immunomodulatory agents. Long-term follow-up is essential due to elevated risk for oral cancer which increases with time.

AUTHOR CONTRIBUTIONS

DD drafted and critically revised the manuscript. HS critically revised the manuscript. All authors give final approval and agree to be accountable for all aspects of the work.

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MINI REVIEW
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Salivary Gland Dysfunction Secondary to Cancer Treatment

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The number of cancer survivors are increasing and so are the oral toxicities from cancer therapy. Most patients receiving treatment for cancer develop some form of oral adverse events including, but not limited to, mucositis, opportunistic infections, dry mouth, and/or osteonecrosis of the jaw. One of the most common complications from head and neck cancer radiation therapy is salivary gland dysfunction (SGD). SGD is an umbrella term that includes the subjective sensation of dry mouth (xerostomia) and hyposalivation (objective reduction of the salivary flow rate). Dry mouth in cancer patients may lead to functional defects (e.g., eating, speaking, and swallowing), increase the risk of dental caries and oral candidiasis, and can have a negative effect on the nutritional and psychological status of the patients. The aim of this mini review was to summarize the current criteria for diagnosis and management of SGD associated with cancer treatment.

Keywords: cancer, dry mouth, xerostomia, hyposalivation, radiotherapy, chemotherapy, management

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INTRODUCTION

Cancer survival rates continues to increase and by 2040, it is estimated that there will be 26 million cancer survivors in the United States [1–3]. Cancer patients may develop acute and chronic oral toxicities from cancer therapy including mucositis, xerostomia, salivary gland dysfunction (SGD), neurosensory disorders, trismus, jaw necrosis, and infections to name a few. Cancer regimen-related toxicities often lead to devastating consequences, reduced function, poor clinical outcomes, and higher health care cost [4].

SGD is one of the most frequent side effects from cancer therapy [5]. Dry mouth in cancer patients may be secondary to chemotherapy, head and neck radiotherapy, dehydration, and chronic graft-vs. host disease (cGVHD). Saliva has important functions including antimicrobial activity, gustatory function, protection and lubrication of the oral mucosa and esophagus, and remineralization and maintenance of hard and soft tissues in the oral cavity; all these functions have the potential to be compromised by cancer therapy [6]. The aim of this mini review was to describe the established causes and guidelines for diagnosis and management options of SGD in cancer patients, as well as the potential new therapeutic approaches that are currently in study and development.

DEFINITIONS AND DIAGNOSTIC TESTS FOR SALIVARY GLAND DYSFUNCTION

SGD has been defined as "any alteration in the qualitative or quantitative output of saliva caused by an increase (hyperfunction) or decrease (hypofunction) in salivary output" [7].

Hyposalivation is assessed by measuring stimulated and unstimulated salivary flow and at times, by individual major gland secretion. Hyposalivation is defined as a resting (unstimulated) whole saliva flow rate of ≤0.1 mL/min and/or a stimulated whole saliva flow rate of ≤0.5 mL/min [8, 9]. Commonly used stimulants to assess stimulated salivary flow rates include sugar free gums, paraffin wax, rubber bands, or citric acid. Hyposalivation may or may not result in xerostomia (the subjective feeling of dry mouth), negative impact on function, including eating, speaking, and swallowing, dysgeusia, and/or a burning sensation of the oral mucosa [10, 11].

Xerostomia in cancer patients is assessed by patient reported outcomes (PROs) [e.g., Xerostomia Inventory (XI)] or by practitioner reported outcomes [e.g., using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (PRO-CTCAE)], where in addition to the patient symptoms, the unstimulated saliva is measured (**Table 1**) [12, 13]. The XI is an 11-item instrument that evaluates and measures the different aspects of xerostomia that are experienced by the patient. A shortened version of XI named Summated Xerostomia Inventory (SXI) comprises five of the original 11 items and was more recently developed to focus on the "experiential aspects of dry mouth" rather than measuring general exocrine gland functions [14].

TABLE 1 | Common Terminology Criteria for Adverse Events (CTCAE) for dry mouth.

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dry mouth	Symptomatic (e.g., dry, or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms: oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	*	*

TNP, Total parental nutrition.

**No applicable. Grade 4 refers to life-threatening consequences; urgent intervention indicated. Grade 5 refers death related to AE.*

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE. Dry mouth is categorized under gastrointestinal disorders with Grade 1–3 severity of symptoms [12].

Excessive salivation is rare, and may occur in cancer patients due to dysphagia, odynophagia, malignancy, or local oral irritation. Non-pharmacologic treatment varies from functional dysphagia therapy to neurosensory approaches. Pharmacologic treatment aims to reduce salivary flow and includes several agents such as glycopyrrolate, scopolamine, atropine, benztropine, and botulinum toxin injection into the salivary glands [15]. Mucolytic agents such as guaifenesin and n-acetylcysteine may decrease the viscosity and volume of mucous secretions and improve comfort [16].

SGD SECONDARY TO CANCER TREATMENT

Radiotherapy- Induced SGD

Dry mouth is one of the most common and dismal effects of radiation therapy (RT) to the head and neck cancer patients. Salivary gland tissue, in particular acinar cells of the serous glands (parotid), is sensitive to RT with permanent salivary gland damage in patients receiving cumulative doses > 30 Gy [17]. RT can also cause dry mouth due to indirect damage to epithelial and connective tissues of the gland including the blood vessels and nerves [4]. When salivary glands are within the field of radiation, irreversible salivary glands damage occurs in 63–93% of the patients [18]. In head and neck cancer patients undergoing RT, the dysfunction is dose dependent; when 40–50 Gy are administered up to 75% of the parotid gland function may be impaired [19]. The effects of RT on SGD are long term and usually irreversible [18].

Preventive strategies of salivary gland hypofunction and dry mouth secondary to RT have focused on the preservation of salivary gland function, primarily the parotid glands, by new advances in radiation techniques, including the appearance and optimizing of 3D treatment planning, conformal radiation techniques, and intensity-modified radiotherapy (IMRT) [20, 21]. Recent studies also showed that the prevention of hyposalivation secondary to RT may be addressed via use of cytoprotective agents (eg. amifostine), the application of lubricating or stimulatory agents, surgical transfer of submandibular glands, and acupuncture during and following cancer treatment [11, 22–24].

Treatment of salivary gland hypofunction secondary to RT includes systemic parasympathomimetic agents with muscarinic action (pilocarpine HCl and cevimeline) [25]. Pilocarpine is recommended to be administered at a dose of 5 mg 3 times a day for at least 3 months [26]. Cevimeline is also recommended for a minimum of 3 months to achieve clinical results, 30 mg 3 times daily [27]. Common side effects for both medications include increased excess of sweating, dyspepsia, nausea, and diarrhea [28]. Topical agents include over-the-counter saliva substitutes and mucosal lubricants, as well as non-pharmacological approaches to mechanically stimulate salivary flow, such as sugar-free lozenges and gums [29]. Acupuncture and hyperbaric oxygen (HBO) therapy have been also used as a possible intervention for the treatment of radiation-induced xerostomia in patients with a residual functional capacity of the

salivary glands with controversial results [11, 30]. Low-level laser therapy (LLLT) has proven effects in promoting biomodulation in the cellular metabolism and has been effectively used as a salivary stimulants in patients with reduce salivary flow rate due to chemotherapy and radiotherapy [31]. More recently, salivary gland transfer and gene therapy, using human aquaporin-1 gene transfer, are strategies that appear potentially useful for preventing salivary gland radiation damage [32, 33]. The regenerative medicine options include adipose tissue–derived mesenchymal stem cell and adult salivary gland–derived stem cells [32].

Graft vs. Host Disease- Induced SGD

Chronic graft vs.-host-disease (cGVHD) is a complication that may occur in 30–70% of patients undergoing allogeneic hematopoietic stem cell transplant (HSCT) [34]. Oral cGVHD is characterized by lichenoid changes, ulcers, erythema, and salivary gland hypofunction [35] Salivary gland involvement is characterized by destruction of secretory acini and ducts, resulting in decreased production of saliva and defense proteins [36]. HSCT patients typically experience dry mouth after receiving conditioning regimens, and this may persist through the period when salivary gland cGVHD develops, making the onset and diagnosis less evident. cGVHD of the salivary glands results in both quantitative and qualitative changes in salivary production, composition, and output [37]. Sialagogues such as pilocarpine and cevimeline have shown to improve symptoms in approximately two thirds of patients and recommended dosing is the same as described for RT-induced hyposalivation [38].

The effects of salivary gland hypofunction in these patients include rampant decay and recurrent oral candidiasis, especially if there is ongoing topical corticosteroid therapy for management of mucosal cGVHD, which suppresses mucosal immunity. An additional feature of oral cGVHD is the development of recurrent superficial mucoceles, suggesting that the underlying inflammation may be secondary to generalized mucosal involvement or because of direct salivary gland tissue targeting [39, 40].

Chemotherapy- Induced SGD

Chemotherapy induced dry mouth is prevalent in 10–80% of patients undergoing treatment, regardless of the type of cancer [41]. The onset of oral symptoms generally begins in the 7th to the 10th day after the administration of chemotherapy and resolves after completion of chemotherapy, unlike radiotherapy-induced SGD, which persists for years after radiation therapy is completed. Symptoms include, but are not limited to, dry oral mucosa with consequential oral pseudomembranous candidiasis, halitosis, oral dysesthesia, hypogeusia, and difficulties in chewing, swallowing, and speaking [41].

Changes in salivary gland function can be caused by several chemotherapeutic agents including doxorubicin, cyclophosphamide, fluorouracil, methotrexate, and vinblastine [42]. Some cancer patients may also be on anticholinergic medications for therapy-induced nausea or diarrhea (e.g., for irinotecan-related early diarrhea) which may contribute to xerostomia [7].

Clinical presentation of chemotherapy induced SGD is variable, with some patients presenting with dry mucous membranes of varying severity, while others complaining of excessive salivation with drooling because of dysphagia or odynophagia. As opposed to RT-induced dry mouth, chemotherapy-related dry mouth is typically reversible. Therefore, management is palliative in nature and aims to relieve the temporary symptoms that manifest during treatment. This includes lifestyle modifications, use of saliva substitutes and mucosal lubricants, and short-term use of non-pharmacologic stimuli (gustatory stimuli, sugarless gum) [43, 44]. Acupuncture, tomotherapy, and 1% malic acid spray are currently under investigation, without published results yet.

Immunotherapy–Induced SGD

Immune checkpoint inhibitors (ICIs) have proven to be an effective treatment option for patients with many forms of advanced cancers by preventing cancer cell evasion mechanisms through the suppression of major immune regulatory pathways, such as PD-1/PD-L1 and CTLA-4 [45]. The introduction of ICI therapy has been accompanied by a constellation of adverse events, likely secondary to T-cell–mediated immune reactions, resulting in increases in proinflammatory cytokines or enhancement of complement and autoantibody-mediated immune injury. Immune-related adverse events (irAEs) may virtually affect every organ system [46, 47], including the salivary glands. The development of ICI-induced sicca syndrome usually develops within the first 3–4 months of treatment [48]. Clinical features include severe hyposalivation with xerostomia, ocular dryness, and in some cases parotid gland swelling. Management depends on the severity of the irAE and is with over-the-counter topical agents, sialagogues, and systemic treatment with prednisone 1–2 mg/kg or hydroxychloroquine for severe cases [49]. ICI treatment interruptions may also help [50].

SGD COMPLICATIONS AND MANAGEMENT

Dental Caries

Patient who develops dry mouth secondary to cancer therapy are at risk of developing dental caries. A literature review conducted by the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) which included 37 head and neck cancer trials, showed that the prevalence of dental caries in head and neck cancer patients treated with radiation was 24% (4 studies) and 21% respectively (9 studies) for those receiving chemoradiation [51]. Patients with oral chronic GVHD also present with a $>$ 50% increased number of cervical and interproximal dental caries [52]. The management and prevention of dental caries for cancer patients include regular dental care, maintenance of meticulous oral hygiene, daily sodium fluoride application for 3–4 min on teeth using a toothbrush or custom trays (patient should be instructed to avoid rinsing or eating for the next 30 min following the application) and dietary modification, minimizing consumption of cariogenic and acidic foods [53].

Oral Candidiasis

Patients with salivary gland hypofunction may develop a secondary Candida infection in 39–62% of cases while receiving cancer treatment [54, 55] Although Candida albicans has been the most common Candida species detected in cancer patients, the prevalence of non-albicans Candida species (NACS) varies from 37% to 51% and is associated with increased drug resistance [56].Treatment of oral candidiasis involves either topical or systemic antifungal drugs; topical agents are considered preferable to systemic agents due to lower risk of side-effects and drug interactions [55]. The Infectious Diseases Society of America (IDSA) guidelines recommend the use of clotrimazole troches or nystatin suspension (easy to use for patient with hyposalivation) as first-line option for the management of mild candidiasis [57]. A common systemic agent as fluconazole is best used for short courses to prevent the development of resistance. Fluconazole was found to be effective in the prevention of clinical oral fungal infection and in the management of moderate to severe fungal colonization in patients receiving cancer therapy [57]. For fluconazole-refractory cases, the IDSA guidelines recommend the use of itraconazole or posaconazole, with voriconazole and amphotericin B and the echinocandins (caspofungin, anidulafungin, and micafungin) [55].

Malnutrition

In cancer patients an average loss of 8 to 10% of body weight is common, even with early nutritional support [58]. SGD can contribute to difficulties in maintaining adequate nutrition during and after chemotherapy and RT. Cancer therapy may also cause dysphagia, odynophagia, loss of taste, dysgeusia and dehydration, all of which may result in malnutrition [59]. Patients on enteral nutrition had significantly less average weight loss during therapy (3.1 vs. 7.0 kg), required significantly fewer hospitalizations for dehydration and malnutrition, and had fewer interruptions in their cancer treatment (0 % vs. 18%) compared to patients on normal oral food intake [60, 61].

Psychological Disorders

Individuals suffering from cancer are at high risk of experiencing major depressive episodes throughout treatment, although this risk appears to be especially prominent within the first year of diagnosis. The estimated prevalence of anxiety and depression among cancer survivors is 17.9% and 11.6%, respectively [62].

As part of the treatment regimen the most commonly prescribed medications include tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). While both classes of medications have been linked to hyposalivation, in a study done on parotid salivary flow rates, TCAs exhibited a 58% reduction in flow compared to 32% with SSRIs [63]. A meta-analysis performed by Capetta *et al.* further looked at selective norepinephrine reuptake inhibitors (SNRIs) and found that they significantly increased the risk of developing dry mouth when compared to SSRIs [64]. These data, when combined with the increased risk that head and neck cancer patients already face from SGD, indicate the need for careful prescription of antidepressants for this patient population [65].

CONCLUSIONS

SGD is a common and debilitating complication that affects almost two-thirds of patients undergoing cancer treatment. Early diagnosis and management may result in decreased morbidity associated with SGD and improve well-being. Dental specialists are integral part of the cancer treatment team, and provide comprehensive education, supportive care, and the therapy of SGD related to cancer treatment. The current management approach of SGD is mostly palliative and aims to increase the amount of saliva and minimize the risk of secondary effects such as dental caries, dysgeusia and fungal infections.

Patients with SGD from cancer therapy should be followed by their dentist regularly for regular checkups and prescribed sodium fluoride 1.1% gel or toothpaste to reduce the risk of rampant decays.

In summary, SGD therapy is an important component of care prior to and during cancer therapy and amongst survivors. A multi-disciplinary approach is fundamental in the successful management of this complication in oncology and bone marrow transplant patients.

AUTHOR CONTRIBUTIONS

AVM is participated in conceptualization of the work, data collection and summary, and wrote the mini review. GP participated in data collection and preparation of the manuscript. VS provided feedback on the manuscript. CS participated as an advisor and in the manuscript preparation. AV supervised the work, participated in the analysis of the data, and manuscript preparation. All authors approved the final version of the manuscript.

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The Potential Contribution of Dental Foci and Oral Mucositis to Febrile Neutropenia in Patients Treated With Myelosuppressive Chemotherapy for Solid Tumors and Lymphoma

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Introduction: Febrile neutropenia (FN) is a potential life-threatening complication of myelosuppressive chemotherapy, particularly when induced by infection. There is evidence that FN can originate from the oral cavity, but its contribution to FN is largely understudied in patients treated for solid tumors. The aim of this study was to assess the prevalence of FN in these patients and to evaluate its relation with dental foci and oral mucositis.

Material and Methods: A prospective longitudinal observational study was conducted. Patients diagnosed with solid tumors and lymphoma scheduled to be treated with myelosuppressive chemotherapy with an intermediate risk of developing FN were included. A pre-chemotherapy dental examination was performed and patients were followed during and after chemotherapy regimen. During subsequent hospital visits for chemotherapy administration, the oral cavity was inspected and oral mucositis (OM) was scored using the CTC-AE version 3.0. When patients presented with fever, a comprehensive full body examination including laboratory/microbiological/imaging investigation was performed.

Results: Eighty-eight patients were included. Pre-chemotherapy, 39 patients (44.3%) were diagnosed with a dental focus. During chemotherapy, 46 patients developed OM (53.4%), of which 15 patients had a maximum score of grade II (ulcerative mucositis). Ten patients developed FN during the follow-up period. Patients with FN more often suffered from ulcerative OM compared to patients without FN; both FN and mucositis risk was associated with the myelotoxicity of chemotherapy. However, no relation could be established between the presence of dental foci prior to chemotherapy and the development of FN ($p > 0.05$).

Conclusion: A significant relation was identified between ulcerative OM and FN, but no robust conclusions could be drawn with respect to a relationship between the presence of dental foci and FN.

Keywords: febrile neutropenia, dental infection, oral mucositis, myelosuppressive chemotherapy, solid tumor

INTRODUCTION

Myelosuppressive chemotherapy (CT) is one of the modalities for treating solid tumors and lymphomas. Side effects include severe neutropenia during which patients are unable to mount a robust inflammatory response and are therefore at risk for infectious complications. Fever developing concurrently with neutropenia is classified as febrile neutropenia (FN) [1]. Depending on the degree of myelotoxicity of the CT regimen, patients have a low-, intermediate- or high risk of developing FN. Most CT regimens used for the treatment of solid tumors have an intermediate risk for FN development [1].

FN can prelude a life-threatening complication, particularly when caused by infection and should therefore be recognized at an early stage [2]. If a neutropenic patient presents with fever, a search for its cause should be performed consisting of history taking, physical examination and additional laboratory/microbiological/imaging investigation [3]. Non-infectious causes of FN include transfusion reactions, medication allergies and toxicities, vasculitis or other inflammatory conditions, and tumor(lysis)-related fever. Common sources of infection include the skin, urinary tract or lungs. However, as an infectious cause is documented clinically in only 20–30% of FN episodes and <30% of blood cultures is positive for microbial growth [4–11], the majority of fevers is classified as "fever of unknown origin". Therefore, it is important to also consider other potential causes of FN, such as oral infection and inflammation.

The oral cavity contains teeth, periodontium, mucosa, and salivary glands, which may all act as foci of infection and inflammation and thus may induce FN. An oral focus is defined as a pathologic process in the oral cavity that does not cause major infectious problems in healthy individuals, but can lead to severe local or systemic infection under certain circumstances [12]. Pericoronitis, dental abscesses, infections associated with retained root tips, and apical periodontitis are potential dental foci. Apical periodontitis is a periradicular infection due to profound caries, with a reported prevalence of 52% in the general population [13]. Periodontal diseases are common chronic inflammatory diseases of the tissues supporting the teeth. Gingivitis is characterized by inflammation of the gingiva without loss of periodontal attachment, whereas periodontitis affects the deeper parts of the periodontium and is associated with alveolar bone loss [14]. Chronic gingivitis is seen in 40–50% of the population [15], whereas severe periodontitis is present in 7.0–10.8% of the population of Western countries [16]. These chronic infections may become acute and present with pain, redness and swelling, but during myelosuppression these signs and symptoms can be muted and may remain undiagnosed. Nevertheless, periodontal foci can be a cause of FN and infectious complications in myelosuppressed cancer patients [17, 18].

Furthermore, patients may have dental implants and develop peri-implant mucositis and peri-implantitis, which may have systemic implications similar to periodontal diseases [19].

A common side effect of CT and another possible oral cause of FN is oral mucositis (OM). OM is defined as mucosal inflammatory changes induced by cancer therapies, ranging from erythema to extensive ulcerations most often manifesting at the buccal and labial mucosa, ventral tongue, floor of mouth and soft palate [14]. Ulcerative OM may act as a portal of entry for oral microorganisms and inflammatory products into the bloodstream and may therefore contribute to FN (reviewed in 14).

A pre-transplant oral examination and elimination of oral foci is standard of care in high risk patients treated with myeloablative CT followed by stem cell transplantation or in patients diagnosed with head and neck cancer. However, in many cancer centers, pre-treatment screening for dental foci is not systematically performed in patients diagnosed with a solid tumor scheduled for CT regimens with an intermediate risk of developing (febrile) neutropenia. Since the cause of FN often remains unidentified and oral foci may be easily overlooked, oral examination before the start of CT may also be indicated in these patients as this may contribute to FN diagnosis and management. Yet, the evidence for a relationship between oral foci and FN in chemotherapy patients with intermediate FN risk is scarce. Therefore, the present study was aimed to assess the prevalence of FN and to evaluate its relation with dental foci and oral mucositis in patients treated with myelosuppressive chemotherapy for solid tumors or lymphoma.

MATERIALS AND METHODS

This study was performed according to the principles stated in the World Medical Association declaration of Helsinki 2018, at the Department of Oral and Maxillofacial Surgery and the Department of Oncology of the Amsterdam University Medical Center, location AMC. The Institutional Review Board approved this study (NL53440.018.15).

All participants received comprehensive information of the study aims and design and were informed when foci were diagnosed and advised to see their dentist after completion of CT when blood cell counts had normalized. All potential oral foci were noted on the medical records. This study had a prospective longitudinal observational design and took place between December 2015 and December 2020.

Patients ≥18 years, with a (partial) natural dentition and/or dental implants, no prior head and neck radiotherapy, diagnosed

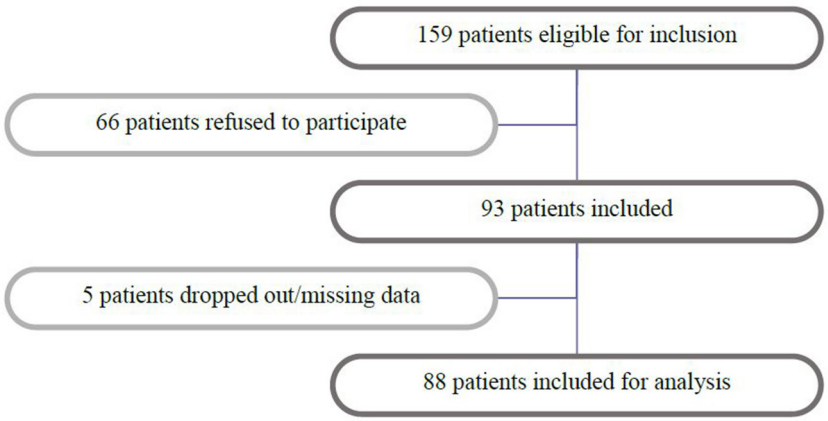

FIGURE 1 | Patient inclusion.

with a solid tumor (outside of the head and neck region) or lymphoma and scheduled for CT treatment with an intermediate risk of FN [1] were eligible for inclusion. Patient demographics including gender, age, body mass index (BMI), intoxications, American Society of Anesthesiologists (ASA) classification, World Health Organization (WHO) performance status and cancer diagnosis were retrieved from the medical files.

Chemotherapy Regimens and Supportive Care Measures

Chemotherapy regimens were noted, including the number of planned CT cycles and supportive care measures (i.e., granulocyte colony stimulating factor, antibiotics, and anti-fungal/viral therapy). Adaptations to this treatment plan were also registered. Dose delay was defined as a delay of planned chemotherapy for more than 3 days; dose reduction was defined as one dose or more administered that was 85% or less of the initially planned dose [20]. A chemotherapy cancellation was defined as a initially planned dose that was not given at all.

Despite the strict inclusion criteria for FN risk [1], the actual risk of neutropenia varied. We therefore divided the group in relatively low- and relatively high risk of myelotoxicity (see **Appendix 1**). This classification was performed by an experienced oncologist (AW).

Pre-chemotherapy Oral Screening

Prior to the start of CT an oral examination took place consisting of the following:

- Evaluation of dental mindedness (dental visits, oral hygiene habits) and oral complaints over the last 3 months
- Intra-oral screening for dental and/or mucosal pathology
- Periodontal screening using the Dutch Periodontal Screening Index [21].
- Screening for peri-implant mucositis and peri-implantitis
- Panoramic radiograph and selective peri-apical radiographs

All pre-existing dental and oral pathology that may contribute to the development of FN and infectious complications, was noted as an oral focus in accordance with the guidelines of the Dutch Association of Maxillofacial Surgery [22]. These included:

- Periodontal disease (DPSI 4; periodontal probing depth of >5 mm); (peri-implantitis was also considered as a focus)
- Profound dental caries
- Periapical pathology due to an infection of the root canal
- (Partially) impacted teeth
- Retained roots with surrounding pathology

Treatment of foci was only considered when symptomatic.

Febrile Neutropenia

Febrile neutropenia was defined as: temperature > 38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count < 500/μL or expected to fall below this threshold [3, 9]. When FN was diagnosed, laboratory- and/or radiological-results (including hematological full blood count, infection panel, urine sediment and chest X-ray) working diagnosis and treatment were noted. Blood cultures were checked for the presence of microbial growth after 2 days. Sepsis/septic shock and/or death was also noted.

Assessment of Oral Mucositis and Other Oral Pathology During Chemotherapy Regimen

Oral mucositis was scored according to the CTC-AEv3.0 [23], during and after the planned CT regimen. All examiners were trained in reliable and consistent OM scoring and received an instruction card. The highest OM score during the observation period was used for analysis. When a patient presented with fever, OM was also assessed. Moreover, patients were examined for oral fungal and recrudescent herpes simplex virus infection and acute exacerbations of dental infection. The diagnosis was made on clinical findings, when deemed necessary microbiological investigations were performed.

TABLE 1 | Patient demographics, tumor and treatment characteristics.

		No. of patients (*N*)	Percentage (%)
Patient demographics (*N* = 88)			
Gender	Male	26	29.5
	Female	62	70.5
Age	Mean 53.5 years		
	Range 18–78 years		
	SD 15.0		
BMI	Mean 25.4		
	Range 16.8–44.3		
	SD 5.6		
Smoking	Yes	14	15.9
	No	53	60.2
	Quit	21	23.9
Alcohol use	Yes	29	33
	No	59	67
ASA classification	ASA I	50	56.8
	ASA II	33	37.5
	ASA III	5	5.7
WHO performance status	WHO 0	53	60.2
	WHO 1	32	36.4
	WHO 2	3	3.4
Tumor and treatment characteristics (*N* = 88)			
Tumor subgroup	Gynecological	42	47.7
	Upper GI tract	18	20.5
	Sarcoma	11	12.5
	Urinary tract	6	6.8
	Lymphoma	5	5.7
	Breast	4	4.5
	Lower GI tract	2	2.3
CT-regimen	Relatively high risk	34	38.6
	Relatively low risk	54	61.4
Treatment goal	Curative	59	67
	Palliative	29	33
Prophylactic G-CSF	Yes	16	18.2
	No	72	81.8
Dose reduction	Yes	19	21.6
	No	69	78.4
CT cycles alterations	Delay	20	22.7
	Cancellation	20	22.7
	No alterations	48	54.5

BMI, Body Mass Index; ASA, American Society of Anesthesiologists; WHO, World Health Organization; GI, Gastro Intestinal; CT, chemotherapy; G-CSF, Granulocyte-colony stimulating factor.

Statistical Analysis

The data were analyzed using the statistical package IBM SPSS for Windows (Version 26.0, IBM Corp, Armonk, NY, USA). Patients were divided into two groups; patients who developed FN and patients who did not develop FN. Differences between both groups and relations between the presence of FN, dental foci and OM were calculated using the Chi-Square test. A p-value < 0.05 was considered significantly different.

TABLE 2 | Oral mindedness and dental visits.

		No. of patients (*N*) & No. of smokers (*n*)	Percentage (%)
Oral mindedness (*N* = 88, *n* = 14)			
Brushing	>Twice a day	6 (3)	6.8
	Twice a day	67 (7)	76.1
	Daily	14 (4)	15.9
	Unknown	1 (0)	1.1
Tooth picks	Daily	21 (2)	23.9
	Weekly	15 (2)	17
	Monthly	3 (0)	3.4
	Never	49 (10)	55.7
Flossing	Daily	7 (0)	8
	Weekly	10 (0)	11.4
	Monthly	1 (0)	1.1
	Never	70 (14)	79.5
Interdental brushes	Daily	24 (2)	27.3
	Weekly	10 (1)	11.4
	Monthly	1 (0)	1.1
	Never	53 (11)	60.2
Mouthwash	Daily	4 (0)	4.5
	Weekly	6 (1)	6.8
	Monthly	2 (0)	2.3
	Never	76 (13)	86.4
Dental visits (*N* = 88, *n* = 14)			
Dentist	Twice a year	56 (6)	63.6
	Once a year	21 (4)	23.9
	Sporadically	7 (2)	8
	Never	4 (2)	4.5
Oral hygienist	Twice a year or more	36 (4)	40.9
	Once a year	14 (2)	15.9
	Sporadically	6 (2)	6.8
	Never	29 (6)	33
	Unknown	3 (0)	3.4

RESULTS

A total of 159 patients was eligible for inclusion. Of these, 93 patients agreed to participate and signed informed consent. Reasons for not participating included: the study was too burdensome ($n = 9$), logistical reasons (e.g., participating in other trials, already started with CT, not reachable) ($n = 14$), not eligible according to inclusion criteria ($n = 5$)„ dental anxiety ($n = 5$) or no reason recorded ($n = 33$).

In five patients OM scores were missing; one patient did not want to participate any longer, and four patients had progressive illness or no response to CT and started palliative care without any hospital visits. Finally, 88 patients were included for analysis (**Figure 1**).

Patient demographics are summarized in **Table 1** and in **Appendix 2** the patient group is divided in non FN and FN. Sixty-two patients (71%) were female and the mean age was 53.5 (±15.0) years. The majority of patients had a WHO performance

status score of 0 prior to the start of CT. Gynecologic tumors were most frequently diagnosed (48%), followed by upper GI tract tumors (20.5%). The CT regimens were reviewed and divided in two subgroups based on myelotoxicity risk as described earlier (**Appendix 1**). Fifty-four patients had a CT regimen classified as having a relatively low risk for FN (61.4%), and 34 as having a relatively high FN risk (38.6%). A statistical difference was seen in CT-regimen and dose reduction between the FN-group and non FN-group.

The mean follow up time was 94 days (range 15–200). Patients received on average five CT cycles (range 1–10). Twenty patients received less CT cycles than planned. Reasons included progressive illness, complications due to CT toxicity, surgical intervention and death.

TABLE 3 | Dental foci pre-chemotherapy, oral mucositis and oral mucosal infections during the course of chemotherapy ($N = 88$).

		No. of patients	Percentage (%)
Dental foci prior to the start of chemotherapy			
Yes		39	44.3
	Periodontal	25	28.4
	Peri-apical	25	28.4
	Profound caries	6	6.8
	Retained root tips	7	8
	Partial impacted teeth	2	2.3
	Peri-implantitis	1	1.1
	Multiple dental foci	16	18.2
No		49	55.7
Total		88	100
Oral mucositis and oral mucosal infections during chemotherapy cycles			
Oral Mucositis	Grade I	32	36.4
	Grade II	15	17
	No mucositis	41	46.6
Oral mucosal infections	Oral fungal infection	8	9.1
	Oral herpes simplex infection	1	1.1
	Other	20	22.7
	None	58	65.9

Oral Assessment Pre-chemotherapy

At the pre-chemotherapy oral screening, 64% of the patients reported visiting the dentist twice a year, 23.9% once a year and 12.5% visited the dentist never or sporadically. All patients but one, reported performing oral hygiene measures at least once daily. None of the patients reported having any acute oral complaints. See **Table 2** for additional information about oral mindedness.

Thirty-nine patients (44.3%) had a dental focus at the pre-chemotherapy evaluation. Dental foci were significantly more present in smokers (Chi-square, $p = 0.03$).

Of these, 25 had a periodontal focus, 25 had peri-apical pathology and one patient had peri-implantitis. Sixteen patients had more than one oral focus (**Table 3**). No dental interventions prior to the start of the CT were performed.

TABLE 4 | Characteristics of patients ($n = 10$), in which 11 episodes of febrile neutropenia developed during chemotherapy cycles.

		No. of patients	Percentage (%)
Gender	Male	3	30
	Female	7	70
Age	Mean: 46.9 years (range 18–78)		
Tumor subgroup	Gynecological	1	10
	Upper GI tract	2	20
	Sarcoma	4	40
	Urinary tract	1	10
	Lymphoma	1	10
	Breast	1	10
	Lower GI tract	–	–
CT-regimen	Relative low myelosuppression risk	1	10
	Relative high myelosuppression risk	9	90
CT-cycles	Mean: 2 cycles (range 1-6)		
Temperature	Mean: 39.0°C (range 38.4–40.6°C)		
Neutrophil count	Mean: 0.11 × 109/L (range 0.00–0.33)		
Source of infection (per episode)	Urinary tract	2	18.2
	Airway	2	18.2
	Fever of unknown origin	7	63.6
Blood cultures (per episode)	Positive	1	9.1
	Negative	10	90.9
Treatment (per episode)	Intravenous antibiotics	10	90.9
	Oral antibiotics	1	9.1

GI, gastrointestinal; CT, chemotherapy.

TABLE 5 | Dental foci, oral mucositis, febrile neutropenia and unplanned CT modifications ($N = 88$).

	OM—Grade 0	OM—Grade I	OM—Grade II	Total
FN	1	4	5	10
No FN	40	28	10	78
Total	41	32	15	88
Chi-square: $p = 0.005$				
	High risk CT-regimen	Low risk CT-regimen	Total	
FN	9	1	10	
No FN	25	53	78	
Total	34	54	88	
Chi-square: $p = 0.000$				
	Dose reduction	No dose reduction	Total	
FN	5	5	10	
No FN	14	64	78	
Total	19	69	88	
Chi-square: p = 0.02				
	Dental focus	No dental focus	Total	
FN	3	7	10	
No FN	36	42	78	
Total	39	49	88	
Chi-square: $p = 0.333$				
	CT delay	CT cancellation	No alterations	Total
FN	3	2	5	10
No FN	17	18	43	78
Total	20	20	48	88
Chi-square: $p = 0.843$				

OM, oral mucositis; FN, febrile neutropenia; CT, chemotherapy.

Febrile Neutropenia

Sixteen patients developed febrile episodes during CT treatment, of which 10 met the criteria of FN diagnosis. Six patients developed fever but were not neutropenic; in two of these patients the fever was diagnosed as a reaction to medication, whereas three patients developed non-neutropenic fever induced by a clinically-documented non-oral infection (i.e., pneumonia, pleura empyema and influenza), and one had fever of unknown origin.

In patients who developed FN ($n = 10$), 11 FN episodes were further analyzed (**Table 4**). The median number of CT cycles before developing FN was two and FN occurred 9.8 days after the most recent cycle was given. The mean neutrophil count was 0.11×10^9/L; the median temperature was 39.0°C. None of the patients developed sepsis/septic shock or died as a result of FN.

In seven out of these 11 FN episodes no clinical non-oral infection could be identified. In case an infection was documented, it was either a urinary tract infection (18.2%) or an airway infection (18.2%). In all but one patient, the blood cultures were negative. In one patient *Staphylococcus epidermidis* was cultured. This patient had no pre-existent oral foci or OM at the time of the FN episode and a clinical infection was not identified. Nine of the 10 FN patients were treated with intravenous antibiotics, Augmentin + Ceftazidim being the first choice.

Oral Mucositis, Dental Foci, and Febrile Neutropenia

During CT cycles, OM was recorded six times per patient on average (range 2–15). We followed a standardized protocol to score OM. Nevertheless, the length of the CT treatment varied among patients. This explains the wide range of number of OM evaluations. Overall, 47 patients developed OM (53.4%), of which 15 patients (17.0%) had a maximum score of grade II (**Table 3**). No grade III and IV OM were observed. In the majority of patients, OM occurred for the first time after administration of the first CT cycle (51.1%). Of patients receiving a relatively high risk CT regimen, 67.5% developed OM during any of the CT cycles, of which 22.4% developed ulcerative (grade II) OM.

Of the 10 patients who developed FN, four patients had OM during the FN episode of which one had grade II OM. In three patients the OM score was not noted during the FN episode. Patients with FN had a significantly higher chance of having more severe OM at any time during the course of their treatment (Chi-square, $p = 0.005$), a relatively higher myelotoxic CT regimen (Chi-square, $p = 0.000$), and more dose reductions (Chi-square, $p = 0.02$) compared to patients without FN. No significant relation was found between the development of FN and CT delays/cancellations (Chi-square, $p > 0.05$), **Table 5**.

A dental focus was identified before the start of CT in three patients who presented with FN, however no significant relation could be identified between developing FN and the presence of a dental focus before CT (Chi-square, $p > 0.05$) (**Table 5**). Nevertheless, in one of these patients an asymptomatic partially impacted wisdom tooth became acutely painful during the FN episode. In another patient with FN without an evident non-oral cause, multiple periodontal and periapical foci were present prior to the start of the CT regimen. These oral sources of infection and inflammation may have induced fever.

Patients receiving CT-regimens classified with a relative high myelosuppression risk developed significantly more severe OM, compared to patients that underwent low-risk CT (Chi-square, $p = 0.001$). No significant relation was found between OM and dose reductions, delay or cancellation of CT (Chi-square, $p = 0.580$, $p = 0.449$). No significant relation was identified between the presence of an oral focus before CT and the development of OM during CT (Chi-square, $p = 0.714$), see **Table 6**.

DISCUSSION

The aim of the study was to assess the prevalence of FN in patients treated with myelosuppressive chemotherapy for a solid tumor or lymphoma and to evaluate its relation with dental foci and oral mucositis. Prior to the start of CT, 44.1% of patients had one or more dental foci. During CT, ten patients (11.4%) developed FN, and 15 patients (17.0%) developed ulcerative OM.

A statistically significant relation was found between the presence and severity of OM and developing FN, suggesting that patients with ulcerative OM are also at risk for developing FN. Patients treated with CT regimens with a relatively high risk of myelosuppression had a significant higher risk of developing OM compared to those treated with relatively low risk CT

TABLE 6 | Oral mucositis, dental foci and unplanned CT modifications ($N = 88$).

		OM—Grade 0	OM—Grade I	OM—Grade II	Total
CT-regimen	High risk	8	15	11	34
	Low risk	33	17	4	54
	Total	41	32	15	88
Chi-square: $p = 0.001$					
Dose reduction	Yes	10	5	4	19
	No	31	27	11	69
	Total	41	32	15	88
Chi-square: $p = 0.580$					
CT cycle alterations	Delay	7	8	5	20
	Cancellation	11	8	1	20
	No alterations	23	16	9	48
	Total	41	32	15	88
Chi-square: $p = 0.449$					
Dental focus	Yes	18	13	8	39
	No	23	19	7	49
	Total	41	32	15	88
Chi-square: $p = 0.714$					

OM, oral mucositis; CT, chemotherapy.

regimens. We found no statistically significant relation between the presence of dental foci before the start of CT and the development of FN or OM during CT.

In this study, a total of 53.4% of patients developed OM (grade I and II), which is higher than reported in the literature, in which an incidence of 15.0–42.3% (all mucositis grades) was reported in patients treated for solid tumors and lymphoma [24–29]. Nevertheless, Jones et al. [26] reported an OM rate of 60% in patients receiving TAC (Taxotere-Adriamycin-Cyclophosphamide) chemotherapy for breast cancer. Raber-Durlacher et al. [30] found an incidence of OM in 31%, of which 16.7% had OM grade II in a retrospective study in patients treated with CT for solid tumors. Whereas the overall incidence in the present prospective study was higher, the incidence of OM grade II is in accordance with our results. OM grade II is likely less underscored as it is painful and characterized by ulcerations, facilitating its identification [28].

A relationship between the incidence and severity of OM and the development of fever has been reported in several studies [11, 28, 29], similar to our findings. van der Velden et al. [11] introduced the term "febrile mucositis" based on their observations in stem cell transplantation recipients; the mucosal barrier may be damaged due to CT leading to the generation of inflammatory cytokines (IL-1 and IL-6) and a disturbed host-microbe interaction may arise, which may lead to fever. Our study provides additional support for a link between OM and FN in patients with solid tumors. It should be noted, however that mucosal injury may occur throughout the whole gastrointestinal tract and our study was only directed to oral mucosal injury.

Among other risk factors, the prevalence of OM is related to the CT regimen administered [14, 28, 31]. Kishimoto et al. [31] found a significant higher rate of OM in patients receiving CT regimens causing more severe myelosuppression. Although a direct relationship between peripheral neutrophil numbers and OM risk was not established, their study confirmed that the higher the myelotoxicity of CT regimens, the higher the risk to develop OM. Our study population falls within an intermediate risk of myelosuppression [1], but there was also differentiation possible in this group based on myelosuppression risk. Thus, in order to estimate OM risk, it is advisable to look more closely at the myelotoxicity of the intended CT regimen.

Even though most of the patients visited the dentist on a regular base, a high percentage (44.3%) of patients had an oral focus prior to the start of the chemotherapy, although lower than reported in the literature [13, 15, 32]. In most cases, asymptomatic chronic dental foci seem not to cause infectious problems in healthy individuals [12]. However, patients who become myelosuppressed may be at risk for exacerbation of an asymptomatic infection, which may lead to local or systemic inflammation and infection [12]. In our study, one patient with FN developed an acute exacerbation of a dental focus, while in another patient with FN without an evident non-oral cause, multiple periodontal and periapical foci were present. Nevertheless, we found no statistically significant relation between the presence of dental foci and FN during CT, which may be explained by the relatively small number of included patients.

In patients receiving intensive CT for hematologic malignancies, Spijkervet et al. [12] and Schuurhuis et al. [33] proposed to only eliminate oral foci with acute signs/symptoms or chronic infections with an exacerbation during the previous 3 months. In contrast, Kishimoto et al. [31] reported a significantly higher incidence of odontogenic infections during CT regimens in patients treated with CT for hematologic malignancies who did not complete their dental treatment prior to the start of CT, however this incidence was not related to the grade of myelosuppression. This suggests that odontogenic infections can

occur in any kind of myelosuppressive CT. Raber-Durlacher et al. [17] suggested that both chronic and exacerbating periodontal diseases may induce fever and infectious complications in patients receiving intensive high-dose CT regimens, but clinical studies aimed to identify such relationships are difficult to perform.

Nevertheless, more large prospective studies are necessary to allow any definitive conclusions about management recommendations on the treatment of oral foci in patients scheduled for myelosuppressive CT.

Our study had several limitations as we evaluated a relatively small number of patients and did not include age, comorbitities and performance status [1] in our analyses. Another limitation of the study is the low incidence of positive blood cultures in the patients who developed FN. Therefore, assessment of the potential contribution of the oral flora to bacteremia was not possibible.

Our group [14] conducted a review about the impact of the oral cavity in febrile neutropenia and infectious complications in patients treated with myelosuppressive CT. This may serve as a guidance in the management and prevention of oral complications in these patients. However, as concluded in this review, limited evidence is present about the implications of oral foci in patients treated with myelosuppressive CT for solid tumors and lymphoma. The present study may serve as a first step for further research in this area.

Although the number of included patients was not sufficient to draw robust conclusions, we identified a significant relation between the presence and severity of ulcerative OM and developing FN, suggesting that patients with ulcerative OM are also at risk for developing FN. Furthermore, we did not find a statistically significant relation between the presence of dental foci and FN during CT, pointing to the notion that chronic dental foci may not have to be aggressively eliminated before the initiation of CT in patients with solid tumors. Nevertheless, it is advisable to encourage patients to maintain good oral hygiene during CT, particularly when they will receive CT with a relatively high risk of myelosuppression. In order to draw robust conclusions about the potential role of dental foci and oral mucositis in the development of FN, larger prospective studies are needed.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Amsterdam University Medical Centers. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ, JR-D, and AL contributed to conception and design of the study. JZ organized the database and wrote the first draft of the manuscript. JZ and AL performed the statistical analysis. JR-D and AL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/froh.2022.940044/full#supplementary-material

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MINI REVIEW
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Quality Assessment of PBM Protocols for Oral Complications in Head and Neck Cancer Patients: Part 1

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Background: Radiotherapy and chemotherapy are frequently employed in head and neck cancer (HNC) patients causing significant side effects that impair life quality and prognosis. Photobiomodulation (PBM) has become a growing approach to managing such oral complications. Despite its proven efficacy and absence of contraindications, there is still a lack of universally accepted disease-specific PBM protocols.

Objective: A narrative review was conducted to identify the current proposals relating to the use of PBM to treat complications of oncological treatments in HNC patients.

Methods: An electronic search in PubMed and Scopus databases was performed with the following keywords: ("photobiomodulation" OR "PBM" OR "laser therapy" OR "LLLT" OR "laser") AND ("head and neck cancer" OR "oral cancer") AND ("mucositis" OR "oral mucositis" OR "dysgeusia" OR "oedema" OR "xerostomia" OR "dermatitis" OR "trismus") until October 2021.

Results: A total of 35 papers were included in the narrative review. Oral mucositis was the most studied complication, and advisable protocols are conceivable. Although there is a growing interest in PBM to manage of xerostomia, radiodermatitis, pain, and trismus, literature is still scarce to propose a universally feasible protocol.

Conclusions: PBM therapy could significantly prevent or reduce the severity of many side effects related to cancer therapies. More research is needed to obtain recommendations over the preferable parameters.

Keywords: oral cancer, photobiomodulation, oral mucositis, dysgeusia, xerostomia, dermatitis, trismus, oedema

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INTRODUCTION

Head and neck cancer (HNC) is primarily treated with surgery in combination with radiotherapy (RT) and/or chemotherapy (CT). RT and/or CT in the head and neck region (HNR) have several side effects that can be debilitating and heavily affect patients' quality of life (QoL) and prognosis. The most common side effects include

oral mucositis (OM), xerostomia, dysgeusia, oedema, radiation caries, radiodermatitis, and trismus [1]. These spectra of ailments share a common etiopathology of these complications involving sensitization and tissue damage by the oncotherapy agent. Photobiomodulation (PBM) is a non-invasive light therapy increasingly being applied in supportive care for cancer patients. Its main properties cover the field of wound healing and inflammation. However, there is still no clear consensus over the standard protocols and devices to employ. Recent insights have been made about molecular mechanisms, biological responses, and biomarkers for safe and effective PBM treatments [2, 3]. Concurrently, there have been significant advancements with device technologies, increasing availability of wavelengths, and precise control of the beam and output parameters [4]. Therefore, the objective of the present paper was to produce a narrative review of the available scientific evidence to identify the current proposals and related protocols of PBM to manage the most prevalent complications of oncological treatments in the HNR.

METHODS

An electronic search in the PubMed and Scopus databases was conducted with the following keywords: ("photobiomodulation" OR "PBM" OR "laser therapy" OR "LLLT" OR "laser") AND ("head and neck cancer" OR "oral cancer") AND ("mucositis" OR "oral mucositis" OR "dysgeusia" OR "oedema" OR "xerostomia" OR "dermatitis" OR trismus) until October 2021. Papers in languages different from English, Italian, Spanish, Portuguese, and French were excluded. Only original articles and reviews were initially included, excluding short reports and case reports. Further, articles not specifying laser protocol were also excluded. A global group of experts in oral medicine, oncology, radiation biology, and PBM examined and discussed this literature to further develop consensus.

RESULTS

A total of 148 studies were obtained after the electronic search. Two different reviewers read all abstracts. After the abstract screening, 58 were excluded, and 90 were subdivided among reviewers' full-text analyses performed independently by two reviewers. After the full-text screening, 35 papers were included in the narrative review. The majority of papers were about preventing or treating more than one side-effect. Twenty-seven studies dealt with OM, 10 with xerostomia, 4 with radiodermatitis, and 2 with pain and trismus. Other interesting topics included the evaluation of QoL outcomes, systemic analgesia, functional impairment, nutritional status, survival, interruption of RT, adherence, cost-effectiveness, safety, feasibility, and tolerability of PBM. In general, no adverse effects were reported, and all authors supported safety and tolerability. Although clinical time constraints and patient compliance were often considered limitations to PBM therapy, feasibility was high. Further detailed analysis of these results will be conducted in another review by our group. In the phase of full-text screening, reviews and systematic reviews were excluded as they did not mention detailed laser parameters.

Study Characteristics

Overall, 7 papers were published between 1999 and 2010, 19 papers between 2011 and 2019, and 9 papers in the last 2 years, witnessing the increasing interest in the field of PBM applied to supportive care in cancer patients (**Table 1**). A total of 14 studies investigated the role of PBM in preventing the onset of the side effect, 13 in treating the complications, and 8 studies mentioned both protocols. Twenty-two studies included HNC patients subjected to RT sessions alone or combined with surgery, whereas 13 studies included HNC patients subdued to combined CT and RT, with exclusive regimens or as adjuvants to surgical treatments.

Light Parameters

Detailed characteristics of PBM protocols in included studies are outlined in **Table 2**. We noted considerable variations in the types of used lasers, mode of application, frequency of treatment, and treatment parameters. Our analysis precludes robust clinical guidelines. Nonetheless, an overview of the most relevant protocols for each category is outlined to assist clinical implementation.

PBM for Oral Mucositis

The results for OM management were consistent, and guidelines for both prevention and treatment could be outlined in the current narrative review (**Supplementary Table 1**). All Authors choose diode lasers, more often indium gallium aluminum phosphide (InGaAlP) diode laser, and Helium-Neon (He/Ne) laser. The most preferred wavelength was red (632–660 nm) for both prevention and treatment protocols in continuous wave (CW) mode using fiber in contact or reduced (<1 cm) distance. Power output reported varied (5–5,000 mW), but most papers did not discriminate between nominal and effective, resulting in overestimated values, especially in non-contact protocols. A suggestion could be between 10 and 100 mW effective power. While some Authors mention irradiance per treatment point, others suggest a defocused beam ranging between 0.024 and 150 mW/cm^2. As per the new PBM dosing, the most effective preventive protocol would use a total dose of 1.2 Einstein (photon fluence at 650 nm = 5.7 p.J/cm^2). The data suggests successive intraoral applications on single spots on the oral cavity, rather than a scanning motion over the entire mucosal surface, may offer the most predictable outcomes. Also, the time of application was very variable, ranging from sessions of 270 s to 25 min. A minimum of 30 s per point with three (up to 5) sessions a week is recommended in preventive and treatment protocols. Overall, preventive protocols need more repetitions per week than treatment protocols.

PBM for Xerostomia

All authors employed diode lasers, specifically indium gallium aluminum phosphide (InGaAlP) or Gallium Aluminum Arsenide (GaAlAs), preferring low power protocols (**Supplementary Table 2**). Both visible red (650–660 nm)

TABLE 1 | Characteristics of studies included in the narrative review.

References	Sample size	Type of study	Cancer treatment	Topics	Synthesis of main results
Bensadoun et al. [5]	PBM group: 15 patients Placebo group: 15 patients Mean age: 60.4 (36–78) years	Multi-center double blind randomized controlled trial Preventive PBM	CT/RT	Oral mucositis Nutritional status	PBM therapy reduced severity and duration of OM associated with RT. In addition, there is a tremendous potential for using PBM in combined treatment protocols utilizing concomitant CT and RT
Arun Maiya et al. [6]	PBM group: 25 patients, 54 ± 1 years Control group: 25 patients, 53 ± 1 years Gender ratio M:F = 2:1	Prospective randomized blind controlled study Preventive and therapeutic PBM	RT	Oral mucositis	PBM delayed the time of onset, attenuated the peak severity and shortened the duration of OM and pain, controls had more feeding tubes
Lopes et al. [7]	PBM group: 25M, 6F Placebo group: 25M, 4F Mean age: 57.4 ± 13.9 (28–88) years	Randomized clinical trial Preventive PBM	RT	Oral mucositis Xerostomia	The group of patients submitted to RT and PBM had lower incidence of xerostomia, OM and pain when compared to the group treated with RT without PBM
Arora et al. [8]	PBM group: 11 patients Control group: 13 patients Age range: 55–59 years Gender ratio M:F = 1:1	Single-center, prospective, controlled study Preventive PBM	RT	Oral mucositis Systemic analgesia Functional impairment	PBM applied prophylactically during RT can reduce the severity of OM, the severity of pain, and the functional impairment
Simões et al. [9]	39 patients divided in 3 groups Ages range: 15–79 years	Prospective non-controlled study Therapeutic PBM	RT	Oral mucositis	PBM 3×/week was better than one and the combination of low power laser with high power laser is more effective for pain relief but prolongs healing time. For improving the patient's QoL, the most significant effect is the control of pain observed when high power laser was used
Zanin et al. [10]	PBM group: 31M, 5F Control group: 29M, 7F Age range: 34–80 years	Randomized, double-blinded, placebo-controlled clinical trial Preventive and therapeutic PBM	CT/RT	Oral mucositis Quality of life	A 660-nm diode laser was effective in the prevention and treatment of OM in patients undergoing RT and CT, providing them more comfort and a better QoL
Lima et al. [11]	PBM group: 12 patients AH: 13 patients Mean age: 55.82 (33–80) years Male 90.91%, female 9.08%	PBM vs. aluminum hydroxide Preventive PBM	CT/RT	Oral mucositis Quality of life	The prophylactic use of both treatments seems to reduce the incidence of severe OM lesions. However, the PBM was more effective in delaying the appearance of severe OM
Carvalho et al. [12]	PBM group: 25M, 10F Mean age: 56.2 ± 14.5 (22–94) years Control group: 21M, 14F Mean age: 58.1 ± 10.9 (35–79) years	Double blind randomized controlled study Preventive and therapeutic PBM	CT/RT	Oral mucositis	PBM appears to present promising results, both in controlling OM intensity and pain-related
Oton-Leite et al. [13]	PBM group: 22M, 8F Placebo group: 27M, 3F Median age: 55.6 (30–80) years	Therapeutic PBM	RT	Oral mucositis Quality of life	PBM improves OM and consequently the QoL of patients with head and neck cancer undergoing RT and justifies the adoption of PBM in association with conventional cancer treatment
Gautam et al. [14]	PBM group: 97M (87.4%), 14F (12.6%) Mean age: 55.18 ± 11.70 years Placebo group: 92M (83.6%), 18F (16.4%) Mean age: 55.95 ± 11.61 years	Prospective, single centered, triple blinded, randomized controlled trial Preventive PBM	CT/RT	Xerostomia Quality of life Systemic analgesia and functional impairment	Preventive PBM decreased the incidence of CT/RT severe OM and pain, dysphagia and opioid analgesics use and unplanned treatment interruption. It can be considered as non-traumatic modality for the treatment of OM and its associated morbidity
*Gouvêa de Lima et al. [15]	PBM: 27M, 10F Mean age: 53.1 ± 9.4 years Placebo: 30M, 8F Mean age: 53.2 ± 10.3 years	Phase III, randomized, double-blind study Preventive PBM	CT/RT	Xerostomia Systemic analgesia and functional impairment RT interruption	PBM did not improve pain control and it was not effective in reducing grade 3 and 4 OM, although a marginal benefit could not be excluded. It reduced RT interruptions in HNC patients, which might translate into improved CRT efficacy

(Continued)

TABLE 1 | Continued

References	Sample size	Type of study	Cancer treatment	Topics	Synthesis of main results
Gautam et al. [16]	PBM group: 50M (91%), 5F (9%) Mean age: 51.71 ± 11.94 years Placebo group: 48M (87%), 7F (13%) Mean age: 52.60 ± 12.51 years	Prospective, unicentric, double blinded, randomized controlled trial Preventive and therapeutic PBM	CT/RT	Oral mucositis Nutritional status Systemic analgesia and functional impairment	PBM showed better treatment outcomes in preventing and treating the CT/RT induced severe OM than placebo in HNC patients. Incidence of severe oral pain, opioid analgesics use and total parenteral nutrition was less in laser than placebo patients. Hence, it can be considered as a therapeutic modality for improving OM associated decreased oral functions and QoL in these patients
Oton-Leite et al. [17]	PBM group: 30 patients Control group: 30 patients Male: 81.6% Mean age: 56.1 ± 12.4 (30–81) years	Prospective randomized controlled trial Preventive and therapeutic PBM	RT	Oral mucositis Xerostomia	Greater pain scores and lower salivary flows (stimulated and unstimulated) were observed in the follow-up periods in the control group. Better outcomes were observed in the PBM group indicating lower degrees of OM, pain and higher salivary flow ($p < 0.05$)
Antunes et al. [18]	PBM group: 42M, 5F Mean age: 53.5 ± 6.9 years Control group: 40M, 7F Mean age: 55.7 ± 8.6 years	Prospective, randomized, double-blind, placebo-controlled phase III trial Preventive PBM	CT/RT	Oral mucositis	PBM is effective in preventing CT/RT-induced grades 3–4 OM in HNC patients
Gautam et al. [19]	PBM group: 97M (88%); 13F (12%) Mean age: 55 ± 11.52 years Control group: 92M (84%); 18F (16%) Mean age: 56 ± 11.80 years	PBM vs. placebo Therapeutic PBM	CT/RT	Oral mucositis Quality of life	PBM was effective in improving the patient's subjective experience of OM and QoL in HNC patients receiving CT/RT
Gobbo et al. [20]	PBM group: 29M, 13F Control group: 14M, 7F Mean age: 65.4 ± 10.3 (43–89) years	Case-control retrospective Therapeutic PBM	RT	Oral mucositis Nutritional status	PBM has to be considered as a powerful weapon in practitioners' hands and should become part of everyday practice and strategy for oncological patients
Oton-Leite et al. [21]	PBM group: 9M, 3F Control group: 12M, 1F	Original study Therapeutic PBM	CT/RT	Oral mucositis Xerostomia Salivary mediators	PBM brought a clinical improvement in OM in HNC patients undergoing CT/RT. This resulted in the attenuation of the inflammatory process and less required repair
Gautam et al. [22]	PBM group: 22 patients Mean age: 71.57 ± 7.27 years Placebo group: 24 patients Mean age: 69.67 ± 8.68 years	A randomized, double blinded, placebo-controlled trial Therapeutic PBM	RT	Oral mucositis Nutritional status Systemic analgesia and functional impairment	PBM was effective in reducing the severity and duration of RT induced OM and oral pain in elderly HNC patients. Also need for opioid analgesics, total parenteral nutrition and radiation break was less in laser treated patients. PBM can be considered a therapeutic modality against RT-induced OM in elderly HNC patients
Gonnelli et al. [23]	PBM group: 15M, 2F Mean age: 56.6 (35–74) years Control group: 9M, 1F Mean age: 58.5 (51–68) years	Prospective randomized study Therapeutic PBM	RT	Xerostomia	PBM seems to be an efficient tool for mitigation of salivary hypofunction in patients undergoing RT for HNC
Palma et al. [24]	PBM group: 21M, 8F Mean age: 61 (48–74) years	Prospective non-controlled study Therapeutic PBM	RT	Xerostomia	PBM seems to be effective to mitigate salivary hypofunction and increase salivary pH of patients submitted to RT for HNC treatment. As a final result, an evident improvement in QoL could be achieved
Elgohary et al. [25]	Group A (LIUS and TET): 11M, 9F; 61.00 ± 6.16 years Group B (LLLT and TET): 10M, 10F; 60.75 ± 5.09 years Group C (TET): 12M, 8F; 62.85 ± 5.77 years	Original study Traditional Exercise Therapy (TET) vs. LLLT and Low Intensity UltraSound (LIUS) Therapeutic PBM	RT	Pain and trismus Quality of life	All the three approaches were beneficial in managing TMJ dysfunctions. LIUS has a more superior effect when combined with the TET program in comparison to LLLT when combined with the same types of exercises in the treatment of trismus and its related pain among patients with HNC

(Continued)

TABLE 1 | Continued

References	Sample size	Type of study	Cancer treatment	Topics	Synthesis of main results
González-Arriagada et al. [26]	PBM group: 87M, 21F Control group: 86M, 22F	Case-control study Therapeutic PBM	RT	Oral mucositis Xerostomia Pain and trismus Dermatitis RT interruption	PBM and the inclusion of oral care professionals in the multidisciplinary oncologic team contribute to reducing the morbidity resulting from OM and other collateral effects and would increase the QoL of RT HNC patients
Guedes et al. [27]	PBM group: 58 patients (88% M, 12% F) Median age: 59.5 (30–85) years	Prospective cohort study Therapeutic PBM	RT	Oral mucositis Survival/recurrence	PBM with high doses of laser energy produces a small improvement in the prevention of RT-induced OM and did not significantly increase the risk of neoplastic recurrence
Legouté et al. [28]	PBM group: 37M, 5F Mean age: 58 (53–62) years Placebo group: 38M, 3F Mean age: 58 (53–68) years	Prospective randomized study Preventive PBM	CT/RT	Oral mucositis Systemic analgesia and functional impairment Safety	PBM was well-tolerated with a good safety profile, which promotes its use in clinical routine for severe OM treatment
Rezk-Allah et al. [29]	PBM group: 80 patients Median age: 55.2 years	Original study Therapeutic PBM	CT/RT	Oral mucositis Cytokines	PBM is well-tolerated and improves OM. It may be useful to improve the symptoms of CT-induced OM
Bourbonne et al. [30]	PBM group: 31M, 9F Median age: 61 (45–76) years	Prospective not controlled study Therapeutic PBM	RT	Oral mucositis RT interruption	The surface laser applied transcutaneously seems to allow patients to tolerate treatment without interruption and to develop low mucosal toxicity rates
Morais et al. [31]	PBM group: 49M (80.3%); 22F (19.7%) Mean age: 58.6 ± 9.9 years	Original Prospective study Preventive PBM	RT	Oral mucositis Xerostomia Quality of life Survival RT interruption	The PBM associated with a rigorous and well-controlled preventive oral care protocol resulted in satisfactory control of oral adverse effects, reduction of QoL impacts, and interruption of RT regimen due to severe OM
*Dantas et al. [32]	PBM group: 23M, 7F Mean age: 55.9 ± 11.1 years Control group: 24M, 2F Mean age: 57.9 ± 9.5 years	Case control prospective study Preventive PBM	CT/RT	Oral mucositis Xerostomia	PBM was not effective for the prevention of OM, salivary stimulation, or pain management in oral cavity cancer patients undergoing CT/RT of the head and neck region
Park et al. [33]	PBM group: 42 patients Mean age: 55.61 ± 9.84 (19–79) years	Prospective, pilot study Preventive PBM	RT	Dermatitis Safety	PBM is safe and feasible. It might be effective to reduce the severity of acute RD in patients receiving 60 Gy or higher dose of RT in the head and neck area
De Carvalho et al. [34]	PBM group: 56M, 17F Mean age: 55.8 ± 11.9 (29–79) years	Double-blind, randomized prospective study Preventive and therapeutic PBM	RT	Oral mucositis	PBM protocol used in group 1 (660 nm, 15 mW, 3.8 J/cm^2) presented better ability to delay grade II OM and lower pain scores. The protocol used in group 2 presented similar results to group 3 for the management of RT-induced OM
*Ribeiro et al. [35]	PBM group: 14M, 6F Mean age: 64 ± 10.3 years	Analytical cross-sectional Preventive PBM	RT	Xerostomia	The use of PBM did not prevent the reduction of salivary flow associated with RT, but it did appear to prevent patients from progressing to higher degrees
de Pauli Paglioni et al. [36]	PBM group: 107M (73.8%), 38F (26.2%) Mean age: 58.9 ± 10.19 years	Retrospective, cohort study Preventive PBM	RT	Oral mucositis Nutritional status	PBMT may offer the potential to reduce the occurrence and severity of OM and associated pain and reducing the use of enteral feeding and opioid analgesic use
Martins et al. [37]	PBM group: 20M, 5F Mean age: 60.32 ± 9.76 years Control group: 21M, 2F Mean age: 59.13 ± 13.68 years	Double-blind randomized controlled trial Preventive and therapeutic PBM	RT	Oral mucositis	PBMT is effective in the prevention and treatment of severe OM

(Continued)

TABLE 1 | Continued

References	Sample size	Type of study	Cancer treatment	Topics	Synthesis of main results
Robijns et al. [38]	PBM group: 23M, 5F Mean age: 64.06 ± 11.78 years Placebo group: 16M, 2F Mean age: 65.06 ± 10.37 years	Randomized, placebo-controlled trial Preventive PBM	RT	Dermatitis	PBM significantly reduces the severity of RD and improves the patients' QoL during their RT course
Bensadoun et al. [39]	72 patients (A1: 17M, 5F; A2: 8M, 1F; A3: 23F; A4: 18F) Median age: 61.4 years	Multicentric, prospective, non-comparative study Preventive and therapeutic PBM	RT	Oral mucositis Dermatitis Safety	CareMin650 is feasible, safe, and well-tolerated for preventive or curative treatment of OM and RD in cancer patients treated with RT. Preliminary efficacy results are promising

*Topics in black color: theme discussed in the present review, topics in gray color: theme not considered in the present review. M, male; F, female; PBM, photobiomodulation; RT, radiotherapy; CT, chemotherapy; OM, oral mucositis; QoL, quality of life; HNC, head and neck cancer; TET, traditional exercise therapy; LLLT, low level laser therapy; LIUS, low intensity ultrasound; TMJ, temporomandibular joint; RD, radiodermatitis. *Lack of reported benefits after PBM therapy.*

and infrared (780–808 nm) wavelengths were used in CW mode. In two cases, the application was both intraoral and extraoral. Output power varied consistently, ranging from 10 to 100 mW for intraoral to 15–30 mW for extraoral applications. Also, time per site reported significantly gone from 3 to 400 s. Fluence went between 2 and 60 J/cm^2, equating to 3.8–114 p.J/cm^2 (photon fluence at 650 nm) or 0.8–25 Einstein. Sessions should be repeated at least twice a week but would be best effective if performed each day of RT (5-day per week), both in preventive and therapeutic protocols.

PBM for Radiodermatitis

Among the four papers dealing with PBM for dermatitis management, two proposed a red wavelength, while the other used infrared (**Supplementary Table 3**). All Authors employed very heterogeneous diode devices (e.g., He/Ne, InGaAlP). Only Robjins et al. studied dermatitis specifically, while other authors did not distinguish between prevention or treatment of specific side effects [38]. Outputs varied between 100 and 2,500 mW and irradiance between 100 and 168 mW/cm^2 when mentioned. The fluence varied between 2 and 60 J/cm^2, equating to 3.8 to 114 p.J/cm^2 (photon fluence at 650 nm) or 0.8 to 25 Einstein. Treatment time per session varied from 270 to 720 s while repetitions varied between 2 and 5 times a week for the whole course of RT. Although the publications on this topic are scarce and heterogeneous, there is a feeling toward the appropriateness of 2 or 3-weekly applications instead of daily sessions, preferring a preventive or combined strategy rather than just using PBM in a curative way. DeLand et al. reported that LED treatments immediately after RT reduces dermatitis incidence in breast cancer patients. These findings may inspire a protocol for HNC subjects. Despite the variability of the parameters, a general recommendation can be hypothesized [40].

PBM for Pain and Trismus

PBM treatments for the management of pain and trismus induced by RT were assessed by two papers (**Supplementary Table 4**) [26]. While both protocols were focused on treatment, and the parameters were too heterogeneous for comparison, such as wavelength (660 red vs. 950 infrared), output powers (100 vs. 15 mW), and fluences (60 vs. 7.6 J/cm^2 per session). Further, Elgohary et al. compared various techniques, including PBM, that were not the study's primary objective [25]. Based on our clinical experience, we recommend using a combination of 660 and 810 nm PBM devices, both intraoral and extraoral, at 50 mW/cm^2 for 30 s per site, treating multiple areas in a scanning motion for a total fluence of 6 J/cm^2 which equates to 9 p.J/cm^2 at 810 nm or 2 Einstein. Treatments should be repeated up to 3 times per week for at least 3–4 weeks.

DISCUSSION

The present review offers an overview of the literature on PBM therapy in HNC patients with RT-related side effects, specifically OM, xerostomia, dermatitis, pain, and trismus. The most studied side effect of cancer treatments remains OM [41]. Literature has increased substantially, outlining preventive, therapeutic, or combined protocols [42]. The results section of our literature review has provided reliable suggestions for creating an effective protocol. PBM biological responses depend on the treatment parameters, delivery protocols, and redox state of the cells. It is well-established that PBM dosing is biphasic and relies on the underlying pathology and patient-associated factors that may affect individual outcomes. Further, inappropriate dosing may result in poor or adverse therapeutic effects. The PBM dose window is defined by correct treatment timing, the number of repetitions, and specific adaptation of protocols for each indication [43].

In general, PBM was noted to be effective in both the prevention and treatment of OM [27, 32]. It is almost universally accepted that the primary goal of treatment is reducing pain and improving QoL; most studies confirmed this regardless of the protocol. Even the low PBM efficacy papers noted reduced severity of OM grades (scores 3 and 4 according to the World Health Organization scale) and fewer treatment interruptions during RT. Most of the papers included in our systematic review used CW protocols. This contrasts with prior reports that pulsed,

TABLE 2 | Laser parameters of the studies included in the narrative review.

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Bensadoun et al. [5]	Low-energy He-Ne laser (Fradama Geneva, Switzerland)	632.8 nm	CW	Fiber	0.5 mm	60 mW	NS	1 cm^2/point 9 points	33 s per spot (Nice and Marseilles) 80 s per spot (Reims)	5 min/session (Nice and Marseilles) 12 min/session (Reims)	5 days/week (Monday to Friday) for 7 consecutive weeks	2 J/cm^2	18 J	3 J/cm^2
Arun Maiya et al. [6]	He-Ne laser (Electro care Ltd. Laser 2001, India)	632.8 nm	NS	Fiber	NS	10 mW	NS	NS	NS	3 min/session	5 days/week	1.8 J/cm^2	NS	NS
Lopes et al. [7]	InGaAlP laser	685 nm	NS	Fiber	Contact	50 mW (nominal power) 35 mW (real power)	Diameter of 400 μm	0.028 cm^2 19 points	ns	58 s	10 days	2 J/point	NS	70 J/cm^2
Arora et al. [8]	He-Ne laser (Electro Care Ltd, Laser 2001, Chennai, India)	632.8 nm	Pulse (10 Hz) for 8 days, then CW for 25 days	Scanner for 8 days, fiber for the following 25 days	Distance	10 mW	NS	NS	5 min/site on 6 sites	First 8 days: 5 mins supine position, following 25 days: 30 min	33 sessions	1.8 J/cm^2	NS	NS
Simões et al. [9]	Low Power Laser: InGaAlP diode laser (Twin Flex III Evolution, MMOptics® Ltda, São Carlos, Brazil) Combined Low/High Power Lasers: GaAlAs diode laser (Soft Lase, Zap Laser Ltd, Pleasant Hill, CA)	Low Power Laser: 660 nm Combined Low/High Power Lasers: 808 nm	CW	Fiber	Non-contact 1 cm from the lesion	40 mW	Low Power Laser: 40 mW/cm^2 Combined Low/High Power Lasers: 1 W/cm^2	0.036 cm2	Low Power Laser: 6 s per 62 points Combined Low/High Power Lasers: 10 s on ulcers	Low Power Laser: 372 s Combined Low/High Power Lasers: ns	1–3 times/week for 8 months	Low Power Laser: 0.24 J/point	Low Power Laser: 6 J/cm^2	Low Power Laser: 3.8 J/cm^2
Zanin et al. [10]	AlGaInP diode laser (Bio Wave-Kondortech, São Carlos, Brazil)	660 nm	CW	Fiber	Contact	30 mW	NS	1 cm^2, 18 points	NS	NS	Twice weekly	2 J/cm^2	NS	NS

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TABLE 2 | Continued

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Lima et al. [11]	Diode laser (Laser Unit KM 3000; DMC, São Carlos, SP, Brazil)	830 nm	CW	Fiber	NS	Nominal: 60 mW Effective: 15 mW	75 mW/cm^2	0.2 cm^2	160 s 12 sites	NS	Daily session (Monday–Friday) since the first day up to the end of RT	12 J/cm^2	28.8 J/session	NS
Carvalho et al. [12]	InGaAlP diode laser (Twin laser MMOptics, MMOptics Ltda., São Carlos, São Paulo, Brazil)	660 nm	CW	Fiber	NS	G1: 15 mW G2: 5 mW	G1: 375 mW/cm^2 G2: 125 mW/cm^2	0.04 cm^2	G1: 10 s G2: 10 s	NS	Daily session (Monday–Friday) since the first day up to the end of RT	G1: 3.8 J/cm^2; G2: 1.3 J/cm^2	NS	NS
Oton-Leite et al. [13]	InGaAlP diode laser (Thera Lase; DMC Equipments Ltda, Sao Carlos, Brazil)	685 nm	CW	Fiber	Contact	35 mW	NS	59 points	NS	NS	1/day for 5 consecutive days on 59 sites (a week before the beginning of RT/CT until the end of the treatment)	2 J/cm^2	NS	NS
Gautam et al. [14]	Low level He–Ne laser (Technomed Electronics: Advanced Laser Therapy 1000)	632.8 nm	CW	Fiber	Non-contact	24 mW	24 mW/cm^2	Spot size: 1 cm^2	150–200 s 6 points	15–20 min/session 45 sessions	5 times/week prior to RT for 45 days	3 J/point	36–40 J/session	1,620–1,800 J/cm^2
Gouvêa de Lima et al. [15]	GaAlAr diode laser (Twin Flex, MMOptics, São Carlos, Brazil)	660 nm	CW	Fiber	ns	10 mW	2.5 J/cm^2	4 mm^2	10 s per point	90 s	5 consecutive days (Monday–Friday) during all RT sessions	0.1 J	0.9 J	2.5 J/cm^2
Gautam et al. [16]	He/Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India)	632.8 nm	CW	Fiber	Non-contact (<1 cm)	24 mW	2.12 W/cm^2	0.6 mm 6 sites	14.5 min	145 s	Daily for 6.5 weeks	NS	NS	3.5 J/cm^2

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TABLE 2 | Continued

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Oton-Leite et al. [17]	InGaAlP diode laser (Thera Laser, DMC Equipments Ltd., Sao Carlos, Brazil)	685 nm	CW	Fiber	2 mm distant from the tissue	35 mW	NS	60 points 0.028 cm^2	25 s/point	25 min/session	Start a week before the RT, daily for 5 consecutive days until the end of the RT	0.8 J per point	48 J/session	Min: 1,416 J Max: 1,888 J
Antunes et al. [18]	InGaAlP diode laser (DMC, São Carlos, São Paulo, Brazil)	660 nm	CW	Fiber	Contact	100 mW	NS	0.24 cm^2 9 areas	10 s	12 min	Once daily, 5 times/week	4 J/cm^2	72 J/session	NS
Gautam et al. [19]	He-Ne laser (Technomed Electronics Advanced Laser Therapy 1000)	632.8 nm	NS	Fiber	NS	24 mW	24 mW/cm^2	1 cm^2	125 s on 6 sites	750 s/session	5 times/week	3 J/cm^2	18 J/session	NS
Gobbo et al. [20]	Eltech.S.r.l. GaAlAs diode laser	970 nm	2 Hz, 50% duty cycle	Fiber	Distance	5,000 mW	NS	1 cm^2 9 sites	26 s/site on 9 sites	234 s	2/day for 4 consecutive days	NS	NS	NS
Oton-Leite et al. [21]	InGaAlP diode laser (Twin Flex Evolution, MMOptics Ltda, Sao Carlos, Brazil)	660 nm	CW	Fiber	Contact	25 mW	NS	61 points 0.04 cm^2	10 s	610 s	3/week on alternate days for 7 weeks	6.2 J/cm^2	15.13 J/session	317.69 J
Gautam et al. [22]	He/Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India)	632.8 nm	CW	Fiber	Non-contact (<1 cm)	NS	0.024 mW/cm^2	0.6 mm Spot size 1 cm^2	125 s per 12 locations	NS	5 times a week	3 J/point	36 J/session	NS
Gonnelli et al. [23]	InGaAlP diode laser (Twin Laser—MMOptics® Ltda, São Carlos, SP, Brazil)	Extraoral application: 780 nm Intraoral application: 660 nm	CW	Fiber Array	Contact	Extraoral: 15 mW Intraoral: 40 mW	NS	0.04 cm^2	Extraoral: 10 s per 16 points Intraoral: 10 s per 24 points	Extraoral: 160s Intraoral: 240s	3 times/week 21 sessions	Extraoral: 3.8 J/cm2 per point Intraoral: 10 J/cm^2 per point	Extraoral: 2.432 J per session Intraoral: 9.6 J per session	3.8 J/cm^2

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TABLE 2 | Continued

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Palma et al. [24]	InGaAlP diode laser device (Twin Flex III Evolution, MMOptics® Ltda, São Carlos, Brazil)	808 nm	CW	Fiber	Contact	30 mW	0.75 mW/cm^2	Spot size 0.04 cm^2	10 s per 22 points	3.6 min	24 sessions Twice/week for 3 months	0.3 J/point	6.6 J/session	7.5 J/cm^2
Elgohary et al. [25]	Laser equipment (Electro Medical Supplies, Greenham Ltd., Wantage, Oxford-shire, UK)	950 nm	Pulsed 80%	Fiber	NS	15 mW	NS	NS	NS	6 min	5 times/week for 4 consecutive weeks	NS	4.3 J/cm^2	86 J
González-Arriagada et al. [26]	Diode InGaAlP Photon Lase III (DMC Odontológica, São Carlos, Brazil)	660 nm	NS	Fiber	NS	100 mW	NS	NS	10 s 27 points	270 s	3 times/week since the first day up to the end of RT	60 J/cm^2	NS	NS
Guedes et al. [27]	InGaArP Twin Flex Evolution (MM Optics Ltda, São Carlos, São Paulo, Brazil) and Laser Duo (MM Optics Ltda, São Carlos, São Paulo, Brazil)	660 nm	CW	Fiber	Contact	25 mW 100 mW	625 mW/cm^2 3,333 mW/cm^2	4 mm^2 3 mm^2	10 s/point 28 points	280 s	7 weeks	6.3 J/cm^2 33 J/cm2	7 J/session 28 J/session	NS
Legouté et al. [28]	He-Ne laser HETSCHL®	658 nm	Pulsed (50 Hz)	Fiber	0.5 mm	100 mW	100 mW/cm^2	1 cm^2 per application	40 s/cm^2	NS	1 session/day, 5 sessions/week from day of OM grade II till the resolution OM	4 J	NS	4 J/cm^2
Rezk-Allah et al. [29]	Infrared GaAs laser Phyaction CL- 904 device (Uniphy technology, Belgium)	904 nm	Pulse (200 ns)	Fiber	NS	25 W	NS	NS	60 s	NS	6 days/week from the start of OM till the end of CT	1 J/cm^2	NS	NS

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TABLE 2 | Continued

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Bourbonne et al. [30]	Laser Heltschl FL 3500 ME-TL 10 000 SK (Schlüßlberg, Austria)	660 nm 658 nm	CW	Array	External: non-contact (1 cm) Intraoral: ns	External: 350 mW Intraoral: 100 mW	ns	External: 2 points Intraoral: 1 point	External: 4 mins Intraoral: ns	External: 8 mins Intraoral: ns	3 times/week for 7 weeks	6 J/cm^2	12 J/cm^2 6 J/cm^2	252 J 126 J
Morais et al. [31]	InGaAlP laser (Twin Flex Evolution, MM Optics Ltd., São Paulo, Brazil)	660 nm	CW	Fiber	1 cm distance	25 mW	NS	62 spots/0.04 mm^2	10 s/site	620 s/session	5 days/week	6.2 J/cm^2	14.88 J/day	446.4 J
Dantas et al. [32]	InGaAlP diode, Twin Flex (MM Optics, São Carlos, Brazil)	660 nm	CW	Fiber	Distance	86.7 mW	690 mW/cm^2	0.1256 cm^2	3 s	84 s (28 areas)	3x/week (Monday, Wednesday, Friday) from first day of RT	2 J/cm^2	56 J/session	NS
Park et al. [33]	HEALITE II® 1800 light-emitting diodes (Lutronic Corp., Boston, MA, USA and Goyang, South Korea)	830 ± 7 nm	ns	Fiber	Contact	ns	100 mW/cm^2	ns	660 s	660 s	3 times/week from the first week of RT. In average, 14.97 times (range from 12 to 18 times)	60 J/cm^2	NS	37.80 J
De Carvalho et al. [34]	InGaAlP diode laser (Twin laser MMOptics, MMOptics Ltda., São Carlos, São Paulo, Brazil)	660 nm	CW	Fiber	Contact	15 mW 25 mW	375 mW/cm^2 625 mW/cm^2	0.4 cm^2/point 40 points	10 s	400 s	5 times/week from the first day until the end of RT	3.8 J/cm^2 6.3 J/cm^2	152 J/cm^2 252 J/cm^2	4,560 J/cm^2 7,560 J/cm^2
Ribeiro et al. [35]	Flash AsGaAl Laser III (DMC, São Paulo Brazil)	808 nm	CW	Fiber	Distance	Intraoral: 15 mW External: 30 mW	NS	Intraoral: 0.028 cm^2 21 points Extraoral: 0.028 cm^2 18 points	10 s/point	Intraoral: 210s Extraoral: 180s	3 times/week on alternate days throughout the RT	Intraoral: 12 J/cm^2 Extraoral: 7.5 J/cm2	50.4 J	NS
de Pauli Paglioni et al. [36]	Diode laser (Twin Flex, MM Optics Equipment, São Paulo, Brazil)	660 nm	CW	Fiber	Contact	40 mW	1,000 mW/cm^2	0.04 cm2	Preventive:10 s Treatment:60 s	ns	Daily for 5 consecutive days/week from day 1 until the end of RT	Preventive: 10 J/cm^2 Treatment: 60 J/cm^2	600 J/cm^2 for 10 sites	ns

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TABLE 2 | Continued

References	Type brand	Wavelength	Mode (CW/Pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/ session	Repetitions	Fluence/site	Fluence/ session	Total fluence
Martins et al. [37]	Diode laser (Twin Flex Evolution, MM Optics Equipment, São Paulo, Brazil)	660 nm	CW	Fiber	Contact	25 mW	625 mW/cm^2	0.04 cm^2 61 points	10 s	610 s	5 times/week from the first RT dose until the last one	0.25 J	6.2J/cm^2	NS
Robijns et al. [38]	MLS® M6 diode laser (ASA Srl, Vicenza, Italy)	808 nm 905 nm	Continuous + pulsed wave mode 90 KHz	Array	5 cm above	1,100–2,500 mW (mean 3,300 mW)	168 mW/cm^2	2 cm aperture, 3.14 cm^2 at target	NS	300–600 s	Biweekly for 7 weeks	4 J/cm^2	NS	NS
Bensadoun et al. [39]	Caremin 650	650 nm	CW	Array	Contact	NS	28 mW/cm^2 for oral pads 21 mW/cm^2 for derma pads	NS	NS	Prophylactic: 1 min 47 s (oral pads), 2 min 23 s (derma pads) Curative: 3 min 34 s (oral pads), 4 min 46 s (derma pads)	At least 3 sessions/week (5 sessions/week recommended) immediately before or after RT	NS	NS	3J/cm^2 (prophylactic) 6 J/cm^2 (curative)

low-frequency (<100 Hz) may be superior for wound healing or the damage prevention. Moreover, while most studies used intraoral PBM treatments, there is evidence for extra-orally administered PBM that appears to be more effective for managing of OM of the buccal mucosa, vestibule, and inner lips when combined with an intraoral approach [44, 45].

The PBM studies on salivary glands after RT employed combined external and intraoral applications with both infrared and visible red wavelengths [17, 23]. There appears to be a dose-effect relationship for PBM on reduction of hyposalivation after RT, especially after 15 sessions with red or combined red and infra-red wavelengths [46]. For example, Ribeiro et al. conducted a cross-sectional study with a quantitative approach applying extraoral infrared PBM during the whole course of RT. They demonstrated unchanged unstimulated salivary flow during RT but decreased saliva quantity 1 month after the end of cancer treatment. Despite not corroborating the role of PBM in modulating hyposalivation and salivary gland damage, a concomitant intraoral, lower dose protocol was used for OM that was not the main objective of the study confounding the interpretations of their results [35]. Interestingly, the control of hyposalivation induced by RT seems to be positively affected by PBM treatment strategies [47]. On the contrary, the effect was not marked in preventive protocols. Three studies did not evidence a beneficial impact of PBM in reducing salivary flow connected to RT or combined CT/RT [15, 32, 35]. Note that only one of them is a randomized clinical trial and they all include a limited number of subjects. Moreover, there was no specific protocol for salivary complications that can be distinguished from other side effects, such as OM.

All the publications included in this narrative review suggest that PBM is a safe and valuable strategy for cutaneous complications in the HNR. Encouraging results were noted for PBM management or prevention of radiodermatitis. Many papers have been published regarding radiodermatitis in other body districts, breast *in primis*. However, little has been investigated in the cervical and facial sites, although it is associated with significant pain, disfigurement, risk of RT interruption, and poor cancer prognosis [38]. For cutaneous areas other than the HNR, the literature suggests that preventive PBM application, starting concomitantly or even before RT or combined CT/RT, may not only mitigate the severity of dermatitis but also positively impact the onset and severity of late complications, *via* the mechanisms of tissue repair and regeneration. For example, a study on pigs suggested that combined wavelengths positively influence the development of late radiation damage to the skin. This indicates that this approach may also be applied in the HNR [48]. The fact that all the included publications were very recent (2018–2022) indicates increased interest and recognition of the efficacy of this treatment, together with its proven safety, suggesting that a universal protocol may be feasible shortly.

Specific interest has emerged in this review in trismus management, which is not corroborated by previous literature work. HNC patients are often subdued to destructive surgery, which provokes muscle spasms and reduced mouth opening. The evidence that PBM reduces fibrosis and promotes muscle regeneration could be the primary rationale for the clinical benefit looked for by the Authors, even if it is evident that this topic needs further clinical research [45].

In summary, the available evidence shows that PBM was satisfactory in managing complications related to cancer therapies, both in the prevention of onset and in the reduction of severity and duration, especially for OM. Objective and subjective parameters were studied with comparable rates of success, and the favorable implications on QoL outcomes and wellbeing accounted for most of the positive results expressed by the authors [37]. PBM generates beneficial effects, including reducing of inflammation and pain [49], promoting tissue repair, reducing fibrosis, and favoring nerve regeneration. Therefore, it is clear why studies on PBM application cover a vast range of acute and chronic cancer-related complications in HNC patients.

Moreover, there is growing evidence that PBM is cost-effective both in preventing and treating cancer treatment-related toxicities, such as OM and breast cancer-related lymphedema. This scenario may provide a wider acceptance of PBM at cancer treatment centers, especially if fomented by additional clinical studies to validate cost-effectiveness for preventing and managing cancer treatment-related toxicities other than OM [50].

PBM dosimetry has raised significant interest in recent years, primarily due to its efficacy in a broad range of clinical applications, regardless of the underlying pathology and varying protocols. But since Mester's first description of its benefits, PBM has been used rather empirically as a magic wand, without actual knowledge of photobiological, molecular, and intercellular mechanisms of laser-tissue interaction that cannot be ignored [51]. The absence of clear guides for standardizing protocols description and data presentation remains an issue that can limit comparison among studies and the creation of coherent clinical practice guidelines. Inconsistencies in clinical outcomes are mainly due to problems in reporting PBM dosing and delivery. For the latter, using "*treatment surface irradiance*" rather than laser irradiance alone is expected to reduce confusion about power output, spot size, and distance, especially when using contact and defocused (distant) PBM treatments [24]. This should assist in significantly improving dose reproducibility. The availability of large arrays has encouraged defocused, large treatment areas that reduce treatment time and thermal damage in tissues. Eventually, disease-focused protocols could be created as specific wavelengths target biological chromophores at varying penetration depths and evoke discrete biological responses. Universal protocols may seem convenient and somewhat effective, they are likely to generate inconsistent or irreproducible results [52].

Even in the case of different protocols applied to the same condition, the evoked PBM responses may vary. The absorption of light by a chromophore depends on the affinity with the used wavelength. Even if the wavelength falls within the correct absorption spectrum, low doses of energy are insufficient to start the biological effect, and excessive dosages can result in inhibitory. Moreover, therapeutic responses are restricted to a limited therapeutic dose window termed the Arndt Schultz curve [53]. Recent papers emerged in the literature regarding the possibility of enabling comparisons between protocols, creating a system of "dosing consistency," which is effective

with multiple combined wavelengths. Young et al. suggested using the terms photonic fluence (p.J/cm^2) and "Einstein" (photonic fluence at 810 nm as a reference wavelength) [51]. This enables easy, universal interoperability between dose recommendations with different wavelengths. This novel dose system has been recently applied to the dosing recommendations by the World Association for Photobiomodulation Therapy (WALT) to increase practical implementation irrespective of individual wavelengths or devices that are available globally while preventing overdosing and enabling dose combination with various wavelengths [51].

The similarities of the pathophysiology in different complications and the fact that the same patients may suffer from more than one side effect represent a clear clinical challenge. Moreover, based on the logical extension of acute complications as precursors for chronic ones, preventive ("pre-conditioning") PBM protocols could effectively reduce early and late complications [54]. PBM should be applied using the optimal parameters based on the biological target, device parameters, and delivery technique. Therefore, it is rational to posit that optimal protocols could maximize clinical efficacy, creating a reproducible, and consistent treatment irrespective of the device being used. This work attempts to outlining some of these parameters to pave the way for universal PBM protocols.

CONCLUSION

PBM seems to be an efficacious intervention for several complications of cancer therapy. Robust evidence of the clinical benefit elicited by the correct biological and molecular patterns of light stimulation exists. There is a strong perception that multiple protocols may be applied to similar conditions but to maximize the effect on specific tissue targets, there is an urgent need for standardization and reproducibility of dosages. The increasing number of papers regarding the management of HNC complications *via* PBM witnesses a strong interest in the field. The very recent publications proposing dosage standardization indicate we are moving in the right direction.

AUTHOR CONTRIBUTIONS

GO and MG contributed to conception and design of the study. MG, EM, PA, R-JB, AS-S, LG, and GO performed the articles screening and data collection. MG wrote the first draft of the manuscript. EM, PA, R-JB, AS-S, LG, and GO wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/froh.2022.945718/full#supplementary-material

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Over 300 Radiation Caries Papers: Reflections From the Rearview Mirror

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Radiation caries (RC) is an aggressive oral toxicity in head and neck cancer survivors, which develops 6 to 12 months after head and neck radiotherapy. It initially affects the tooth cervical/incisal surfaces, and if not promptly diagnosed/managed, progresses to dental crown amputation and risk of osteoradionecrosis. It results from a multidimensional cluster of treatment-induced oral symptoms, including hyposalivation, dietary changes, and oral hygiene impairment. Although recognized as a frequent complication of radiotherapy and extensively assessed by a myriad of retrospective, *in vitro,* and *in situ* studies, RC patients are still orphans of clinically validated methods for risk prediction, prevention, and treatment of early lesions. This review provides a historical overview of science-based concepts regarding RC pathogenesis and treatment, emphasizing the growing demand for interventional clinical studies (randomized trials).

Keywords: radiation caries, radiotherapy, radiation, dental caries, dental demineralization, head and neck cancer

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INTRODUCTION

Head and neck cancer (HNC) represent 6% of all malignancies affecting the world population, with over 500,000 new cases worldwide per year. More than half of the patients are diagnosed in advanced stage of disease, leading to the need for multimodal treatment including surgery followed by radiotherapy, chemoradiotherapy, and, more recently, molecular targeted therapy (immunotherapy) for advanced/recurrent/metastatic disease [1]. In this context, head and neck radiotherapy (HNRT) is a locoregional therapy that involves radiation to treat the primary tumor, and regional lymphatic drainage. Although fractionation is performed, acute and late oral complications occur in virtually all patients during and after treatment, including oral mucositis, hyposalivation, sensory changes (mucosal pain, dysgeusia), dysphagia, trismus, radiation caries (RC), and osteoradionecrosis ORN [2].

RC is a complex chronic oral complication of cancer therapy that affects up to 30% of patients within 12 months following the conclusion of HNRT [3], and risk continues indefinitely. The indirect effects of HNRT, validated by the identification of HNRT-specific cluster of symptoms, are the most accepted hypothesis for RC onset and progression [4]. Additionally, poor oral health status, lack of access to dental care before HNRT, primary oral care during and post-radiation treatment, HNRT plans and dosimetric parameters due to tumor location and stage of disease are also some of the well-recognized risk factors for RC development [5].

Despite being well recognized as an oral complication in HNC patients, RC still poses a clinical challenge in terms of risk prediction, clinically validated protocols for prevention, early diagnosis strategies, and optimal treatment interventions. These challenges negatively impact the quality of life of HNC survivors, leading to generalized tooth destruction, loss of masticatory efficiency, persistent chronic oral infections, pain, increased risk of ORN and may impact speech, diet, and esthetics [5, 6]. This review focuses on a historical assessment of RC knowledge as well as on emerging concepts regarding its management.

METHODS

To provide a focused investigation concerning RC outcomes, searches were performed in PubMed/Medline, Scopus, Embase, and Web of Science (**Supplementary Table 1**). Moreover, a search was performed in the Index-Catalog of the Library of the Surgeon-General's Office (US National Library of Medicine), and Medical Heritage Library, both historical research tools concerning RC. The reference lists within selected articles were manually assessed for additional studies that might have been missed during the initial search. The electronic search was performed with using following the keywords: "radiation caries" OR "radiation-related caries" OR "radiation-related dental caries" OR "radiation dental caries" OR "radiation-induced dental caries" OR "post-radiation caries". The search was not limited by year limitations and language restrictions. We include all types of primary and secondary studies that comprised RC concepts, diagnostic and clinical features, prevention, pathogenesis, risk factors, prevention strategies, and treatment. Exclusion criteria were: (1) abstracts, book chapters, editorials, letters to the Editor, notes, commentaries, or images; (2) studies that were not associated with RC outcome; (3) studies that included non-ionizing radiation; (4) studies that assessed dental care pre-HNRT; (5) studies that assessed other oral complication of HNRT than RC; (6) abstract or full-text not accessible. EndNote® (Clarivate Analytics, Philadelphia, USA) and Rayyan software were used for reports screening, exclusion of duplicates, and registration of reason for exclusion (**Supplementary Table 2**).

OVERVIEW

Definitions and the "History" of RC

Based on the current literature, more than three hundred articles related to RC outcomes were published over the years (**Figure 1**). Most of the included articles were preclinical studies (32%) followed by narrative reviews (30%), cohort studies (12%), and

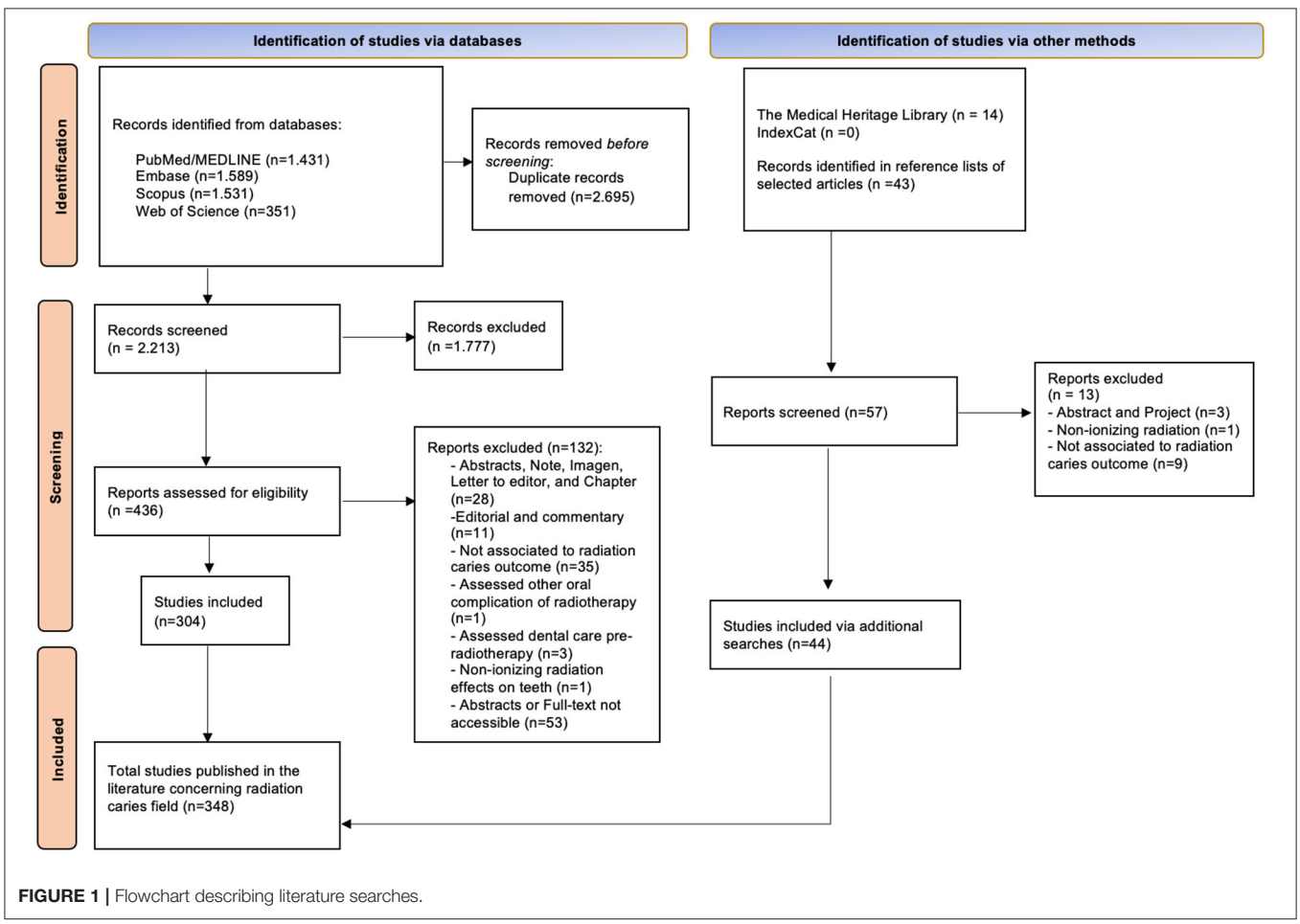

FIGURE 1 | Flowchart describing literature searches.

TABLE 1 | Difference between clinical conditions of conventional and radiation caries.

Conventional active caries	Radiation caries
Clinical appearance	
Frosty/rough appearance of the whitish enamel surface	Brownish pigmentation on smooth surfaces
Microcavities on pits and fissures or white-spots lesions on the smooth surface	Enamel craze lines
White-brown discoloration in the enamel	Enamel delamination
Broken enamel surface and soft dentin	Crown amputation

clinical trials (3%) (**Supplementary Table 3**). Over 82 years since the first report, the evidence levels of studies remain low, which contribute to the lack of well-designed clinical protocols for RC diagnosis and treatment.

The term "radiation caries" describes rampant caries following HNRT [7]. Additionally, another term described as "radiation-related caries" (RRC) has been used to refer mainly to caries associated with indirect effects of HNRT [5]. In the first half of the 20th century, RC was initially reported as an aggressive type of tooth decay with peculiar features that affect HNC patients after an oncologic treatment setting. In the early 1940s, RC lesions were found in the cervical, incisal areas and cusp tips that can lead to dental crown amputation [8] and dental abscess formation. Long-standing RC definitions concepts reported by several authors remain similar in contemporary times, especially regarding the main areas of teeth affected and fast progression patterns. The main areas of teeth affected by RC lesions are the cervical areas surrounding teeth and the lingual surfaces of the anterior mandibular teeth [5] and often extend to involve the entire dentition. Initial stage features of dental demineralization have been described over time, facilitating the recognition of the lesions.

RC Diagnosis

Recognition of RC, to date, has no clinically validated diagnostic criteria or methods that consider classifying RC according to clinical patterns. The RC clinical presentation differs from conventional caries (**Table 1**). Dental indexes have been developed to help clinicians in RC diagnosis [9, 10]; however, several limitations in these indexes are observed, which cannot be clinically representative. The ICDAS and Post-radiation dental index (PRDI) scores, methods utilized for decay diagnosis, are not practical for RC use because both methods do not consider clinical progression patterns [11], which represents key clinical patterns.

With the lack of a systematic method for RC diagnosis, Palmier et al. [11] proposed a clinical guide to diagnosis, management, and treatment according to the clinical stage [5]. In the initial stage, RC lesions usually start with superficial enamel changes with demineralization, leading to brown/blackish pigmentation on the smooth surfaces of teeth (**Figures 2A,B**). Furthermore, enamel craze lines may be observed in the early stage that tend to extend from the cervical to the incisal area (**Figure 2B**). In the second stage, the clinical features are represented by minor demineralized spots and enamel delamination areas (**Figure 2C**). Posteriorly, this delamination tends to advance with extensive areas, leading to crown amputation (**Figure 2D**) [5]. The recognition of RC clinical features, especially in the early stages, impacts a favorable prognosis in dental restorative treatment.

Recently, with the advance in machine learning use, artificial intelligence (AI) has enabled computers to perform diagnoses and predict RC in HNC patients [12]. The use of a clinical data setting, clinical imaging, or panoramic radiography can be utilized to train AI models to predict before HNRT whether HNC patients will develop RC after treatment. Based on clinical images, AI may become an adjunct to predict clinical features of RC risk, in which the dental status before HNRT could be directly associated with the risk of developing RC.

Pathogenesis

RC pathogenesis has been classified according to the direct and indirect effects of HNRT. The indirect effects, recently named as a "cluster of oral symptoms", are pivotal events for the initiation of RC that leads to alterations in teeth structure. The theory of symptoms clustered is represented by hyposalivation, a highly cariogenic diet, inadequate oral hygiene, oral microbial shift, and lower pH value [4]. Recent studies reported that a decrease in oral salivary pH values causes a loss of saliva buffer capacity and biofilm accumulation that increases the cariogenic oral microbiota [13, 14]. Furthermore, alterations in the oral microbiome are a variable that may explain dental caries after radiotherapy treatment, in which the population of Streptococcus *mutans* species tends to increase 6 months after HNRT and lead to demineralization of the dental structure [15]. *In vitro* studies have reported that hotspot mutations in Streptococcus *mutans* caused by radiation doses might be among the reasons for radiation caries [16].

The hypothesis of direct effects of radiation remains unclear once this is divergent between preclinical studies that investigate RC as an outcome. Several *in vitro* studies reported that direct radiation might alter the chemical and biochemical composition of the teeth [17–19]. A decrease in enamel microhardness has been reported, which clinically might be represented as enamel craze lines and enamel delamination [20, 21]. Additionally, chemical elements (not clearly identified yet) that compose the enamel and dentin structure tend to decrease after radiation and cause teeth demineralization [21]. Although the literature suggests that direct radiation may cause morphological changes in dentition, preclinical studies have heterogeneity in the way their methodology, dosimetric parameters, and outcomes are analyzed. The heterogeneity observed implies conflicting results between preclinical studies and, to date, cannot be assumed to be a valid hypothesis exclusively related to RC pathogenesis.

In terms of pathogenesis, it is relevant to highlight that RC development at early stages is frankly asymptomatic and even when progressive may not cause pulp necrosis. A systematic review revealed that HNRT did not induce pulp necrosis [22], and recent *ex vivo* studies hypothetically affirmed that the direct effect of radiation did not impair the microvasculature

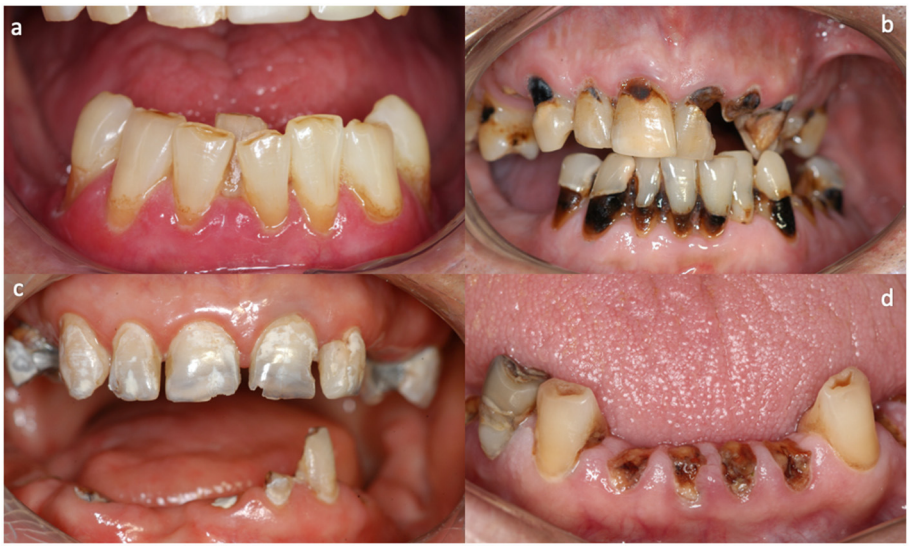

FIGURE 2 | Radiation caries clinical stages. **(A,B)** Representation of incipient radiation caries with presence of superficial enamel changes with brownish pigmentation on the smooth surfaces. **(C)** Demineralization and delamination enamel spots representing the second stage. **(D)** Crown amputation is the last stage of radiation caries with progressively faster pattern.

or innervation of the dentin-pulp complex permanently after ionizing radiation [23, 24], which was validated by clinical studies [25, 26]. This silent progression of RC with absence of pain, particularly at early phases is an important feature to be elucidated, to better understand the mechanisms and pulpal effects caused by HNRT on the dentin-pulpal complex. Therefore, the so-called "inside out" effects of ionizing radiation on the dentin-pulp complex might impact on pulp vitality but still underexplored [26].

Risk Prediction

RC risk predictions are generally related to dental status and HNRT dosimetric parameters. The presence of tooth decay before HNRT, due to poor oral health, smoking habits [27] and dietary changes increases the risk of RC development and tooth extraction. The extractions of teeth with RC may be necessary in advanced cases, and most of the teeth extracted after HNRT are due to RC progression and represent a significant risk factor for ORN [28]. When RC-related tooth extraction is recommended, it should involve minor trauma with minimal flap surgery whenever possible [5]. If extraction can be avoided, with restoration placed in tooth and on residual root tip, and endodontics of residual roots if needed, risk of ORN is reduced.

A previous cohort study reported that an average of eight teeth of HNC patients are decayed before the start of cancer therapy, and about 41% of teeth are a potential candidate to be extracted before or after HNRT [29]. The dental status assessed before starting HNRT is necessary to predict each patient's risk and provide urgent dental treatment. To predict lesions of RC, a first study in the literature utilized the artificial neural network based on panoramic radiographs as an option for RC detection, which showed an accuracy of 99.2% [12]. This methodology shows that further studies can be helpful in RC detection and prediction to improve the dental care of HNC patients. This could guide the selection of dosimetric parameters utilized in the oncologic setting. Dosimetric dental maps have contributed to assessing the prediction of doses in individual teeth and helped improve clinical workflow efficiency [30]. Therefore, radiation oncologists should recognize the challenges faced by dental oncologists in HNC patients adapting their radiation fields to minimize dental and salivary glands exposure [29].

High radiation doses may negatively impact HNC patient dentition with a significant risk of ORN, in which the teeth tend to be extracted early when they receive radiation doses >60 Gy [28]. It is worth mentioning that the increase in tooth loss due to RC is not a prediction related to radiation doses applied directly to the surface of the teeth and includes the significant impact of hyposalivation upon the dentition. Radiation and other events, such as salivary changes and oral microbiome shifts related to saliva functions, are related to RC pathogenesis [28]. Clinicians should consider these events when creating prevention strategies and decreasing the progression of RC lesions.

RC Prevention Strategies

Prevention is the key to decreasing the risks of RC. HNC patients must be constantly educated about the importance of using fluoride, dental hygiene maintenance, and management of hyposalivation pre-, during, and post-HNRT [5], in addition remineralization product use. The use of intraoral positioning appliances (stents) during HNRT which when effective in reducing direct RT salivary gland exposure can reduce salivary changes and reduce caries risk [31]. Although caries rates in HNC patients were not associated simply with salivary flow reduction, the presence of residual saliva is crucial in RC prevention together with other remineralizing

products. Some remineralizing products can support tooth remineralization and caries control, such as casein phosphate polypeptide-amorphous calcium phosphate in toothpaste and resin-modified glass ionomer cement [32]. In addition, fluoride and chlorhexidine varnishes should be considered once the demineralization/remineralization process protects the tooth surfaces against the oral acid environment.

Furthermore, HNC patients must be instructed about oral hygiene and RC concepts before the start of HNRT and this must be reinforced during the follow-up appointments. Previous knowledge of RC concepts by HNC patients before treatment is an excellent step in RC prevention. HNC patients' awareness of the effect of HNRT toxicities is directly related to their lower education level. Evidence shows that 75% of HNC patients do not know about the RC concepts impacting prevention [33]. HNC patient survivors who have not been assessed and provided with oral care before HNRT tend to have a high score of teeth decay after 1 year of treatment. Moreover, the greatest tooth failure occurred in HNC patients who were noncompliant before treatment and during the follow-up [27] which should be carefully considered in pretreatment dental care and prevention protocol.

Although pre-HNRT dental prevention has been performed, there is a risk of substantial tooth failure occurring within 2 years after treatment [28]. Therefore, patients should be provided with written and verbal instructions regarding oral care before, during, and after treatment, and prevention must be reinforced. They should be educated about risk factors to decrease the impact of the cluster of oral symptoms on the dentition. In addition to written and verbal orientations, educational videos have been demonstrated to be a useful audiovisual tool for understanding radiation-related side effects [34]. The audiovisual tool may be periodically presented during dental consultation, validating it as a prevention strategy to decrease the harmful dental conditions found in HNC patients.

Treatment of Dental Damage

When there is the presence of harmful clinical conditions in dentition after HNRT, the management of RC becomes a challenge for dental clinicians. Aggressive RC progression, represented by irregular delamination of enamel and crown amputation, makes difficult the use of routine dental restoration techniques to acquire better mechanical retention [5]. Dental adhesive materials such as resin-modified glass ionomer cement (RMGIC), composite resins (CR), and glass ionomer cement (GIC) are dental materials that are often used in the treatment of structural damage of RC worldwide. The literature supports this indication, emphasizing the fact that these materials improve mechanical properties. Nevertheless, GIC and RMGIC longevity are affected by radiation-related hyposalivation because they are soluble materials, leading to higher restorative failure rates [5]. However, it is critical that the demineralization and caries process be addressed, or new and progressive dental damage will recur even after structural repair of tooth structure.

To date, few clinical trials have assessed the long-term efficiency of dental restoration with these dental adhesive materials. The chance of restoration failure is highly possible due to the deterioration aspects of irradiated teeth. A recent study reported that the rates of dental restoration failure are more significant in RMGIC and GIC than in CR, and therefore, the authors suggest the use of CR associated with fluoride gel compliance for restoring class V lesions after HNRT [35]. Furthermore, the mechanical behavior of composite resins and adhesive systems seem to be the best alternative to RC treatment [36].

The adhesive restorative treatment protocol may be divided into two steps. The first step is to expose the RC tissue, mainly when root decay occurs, and perform enamel bezel and cavity cleaning. Second, after preparing the teeth before receiving the restorative treatment, selective enamel conditioning with 37% phosphoric acid and dental conditioning with an adhesive system are performed following tooth restoration with resin composite and polishing with sanding disks. Cervical adaptation of the restoration and fully covered smooth vestibular surfaces are essential without the presence of enamel craze lines [5]. Regular dental follow-up should be performed every 3 months to reinforce dental education, perform the management of RC early lesions, and treat advanced cases [37].

Potential Future Development in RC Research

Further studies should consider assessing clinically validated methods to standardize RC diagnosis and treatment. A specific clinical classification system would help clinicians have better success rates when using adhesive restorative protocols and decrease treatment failures. Furthermore, protocols for management should be better described and evidence-based. Primary prevention strategies should focus on the weakening of the clustering of oral symptoms and be based on oral care improvement, dosimetric studies, microbiological surveillance, and fluoride supplementation. The early RC clinical signs screening supported by AI algorithms are promising tools to help clinicians toward secondary prevention and personalized treatment.

CONCLUSIONS

The lack of a validated clinical system for RC prediction and diagnosis, and asymptomatic early RC involvement contributes to late detection, foments inefficient preventive interventions, and ultimately limits the longevity of restorative adhesive protocols. Prevention and intervention must be comprehensive and include pre-RT treatment dental intervention and prevention, with ongoing expert care addressing all components of RC risk. Therefore, acknowledging RC risk predictors before and during HNRT is paramount when designing future clinical studies for head and neck cancer survivors. It is important to reflect on the fact that most of the 300 studies in this context have been focused on the pathogenesis of RC and conducted through pre-clinical analyses. It is time to focus on randomized clinical trials for a better understanding of the apparent asymptomatic clinical progression of CR, as well as the development of more effective methods of prevention and restorative treatment.

Meanwhile, daily fluoride supplementation, dietary counseling, oral hygiene support, and *ad infinitum* post-HNRT dental follow-up are highly recommended for the dental management of head and neck cancer survivors.

AUTHOR CONTRIBUTIONS

CP and AS-S wrote the manuscript. ML, MG, and CM reviewed the manuscript. AS-S, AR, and TB designed and contextualized the study idea and reviewed this paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Osteoradionecrosis of the jaw: A mini review

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Osteoradionecrosis (ORN) of the jaw is one of the most dreaded complications of head and neck radiation therapy. Despite the evolution of radiation treatment modalities, ORN continues to remain a therapeutic challenge and its etiopathogenesis still remains unclear. It is clinically characterized by exposed necrotic bone within the head and neck radiation field. Over the past years, several studies have reported on the definition, staging, incidence, etiology, and management of this oral complication. In this review, we summarize the literature on ORN and discuss our institutional experience and management strategies that aim to predict and mitigate risk for ORN.

KEYWORDS

osteoradionecrosis (ORN), head and neck cancer, osteoradionecrosis of jaw, intensity modulated radiation therapy (IMRT), oral complications of cancer therapy

Introduction

Radiation therapy (RT) plays a key role in the management of head and neck cancers resulting in improved tumor control and increased survival rates [1]. Despite these advances, patients treated with RT often develop radiation-associated toxicities such as osteoradionecrosis (ORN) [2, 3]. In this condition, bone within the radiation field becomes devitalized and exposed through the overlying skin or mucosa that persist as a non-healing area. The history of ORN dates back 100 years when it was first noted by Regaud in 1922 [4]. Although rare, ORN is one of the most dreaded complications of head and neck RT that can significantly impact quality of life [5, 6]. Review of the literature over the past 100 years showed improvement in the prevalence of ORN. This could be attributed to the technological advancements of radiation modalities, clinicians' awareness, patient education, improvement in recognizing and mitigating risk factors and cautious approach in the dental management post head and neck RT. In this review, we summarize the literature on ORN and discuss our institutional experience and management strategies that aim to predict and mitigate risk for ORN.

Methods

An electronic search of PubMed was performed using the keyword "osteoradionecrosis" to identify literature published in English between January 1922 and April 2022 which revealed 2740 publications. Following the search results, relevant publications that focused mainly on "osteoradionecrosis of the jaw" were

carefully reviewed, the most significant information was collected and compiled in this mini review.

Review of the condition

Diagnosis

The bone changes associated with head and neck RT was first described as "radiation osteitis" [7]. Since then, numerous terms and definitions have been used to describe ORN with subtle differences based on the clinical presentation and duration of condition [8, 9].

Based on the consensus, clinical diagnostic criteria of ORN are as follows [10–12]:

- The affected site is within the head and neck radiation field.
- Mucosal breakdown or failure to heal occurs, resulting in bone exposure.
- The overlying bone is "dead" or necrotic.
- The bone exposure persists for a minimum 3 months.
- There is an absence of recurrent tumor/metastases on the affected site.

Although these criteria are widely accepted for a clinical diagnosis, they fail to incorporate the radiographic evidence of ORN with intact mucosa [13, 14].

Staging

Likewise, various staging systems for ORN have been published for routine clinical practice and management. Marx's staging system is based on response to hyperbaric oxygen (HBO) therapy and the need for subsequent surgical intervention [10]. The other classifications were based on various criteria, including clinical–radiological findings, disease progression, degree of bone damage, duration of bone exposure, oro-cutaneous fistulae, pathological fracture, and management [9, 15]. A recent study has quantified ORN in terms of hard and soft tissue involvement [16]. Notani's classification is a simple system based on anatomical boundaries [17]:

Stage I ORN is confined to alveolar bone.

Stage II ORN is limited to the alveolar bone and/or above the level of the inferior alveolar canal. Stage III ORN is under the lower part of the inferior alveolar canal, with fistula or bone fracture.

A recent study has modified the Notani's ORN classification incorporating minor bony spicule measuring <20 mm^2 that is seen as a common outcome in clinical trials [18]. The authors believe that this modification might be most suitable for prospective interventional trials of ORN prevention or treatment. NCI Common Terminology Criteria for Adverse Events (CTCAE) also includes "osteonecrosis of mandible" as a musculoskeletal and connective tissue disorder and consider mainly its functional impact [19]. This staging system has been used in recent studies reporting ORN toxicity following proton radiation therapy [PRT] [20, 21]. A recent study has applied the American Academy of Maxillofacial Surgeons classification system, commonly used for medication-related osteonecrosis of the jaw, in analyzing the severity of ORN in head neck cancer patients [22].

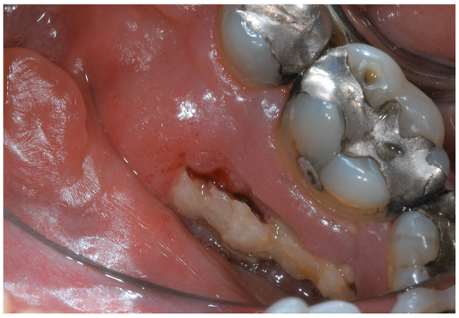

FIGURE 1
A 57-year-old male patient, diagnosed with HPV positive T2N2c squamous cell carcinoma of left base of the tongue and treated with definitive chemoradiation (6996cGy in 33 fractions), developed a spontaneous exposed bone measuring 1.5 × 0.5 cm in the lingual posterior mandible adjacent to right mandibular first and second molars, consistent with Notani Stage II ORN. The exposed bony edges were sharp causing irritation to adjacent soft tissues.

Signs and symptoms

Although ORN manifestation varies greatly, clinical sign typically includes an area of exposed bone area (Figure 1) or a fistula that probes to bone. Tooth mobility or spontaneous tooth exfoliation can also be an indication for ORN. Several cases of "radiographic" ORN with unexposed bone necrosis and intact mucosa have also been reported [14]. Radiographic signs can range from localized osteolytic areas, extensive osteolytic areas, sequestrum and mandibular fracture as seen on a panoramic radiograph [23]. ORN can present as radiolucent areas surrounding the extraction sockets that remain visible for more than 12 months [9]. Computed tomography scan can depict ORN lesions as osteolytic lesions or cortical erosions involving the buccal or lingual surface and often associated with bone fragmentation [23]. Early stages of ORN can be asymptomatic [8]. However, pain, with or without swelling, is a common symptom associated with ORN. Poor oral hygiene and food impaction within the exposed bone area may also be present [8, 12, 24]. Patients may present with sensory neurological symptoms such as dysesthesia, or anesthesia in the

distribution of the inferior alveolar nerve in the mandible in late stage ORN. As ORN progresses, patients may develop trismus, neuropathic pain, and other symptoms such as secondary infection resulting in chronic pus drainage, draining extra oral fistulae or even pathological jaw fracture [25].

Pathophysiology

ORN has a known predilection for the mandible over maxilla [26]. This vulnerability may be due to its relative hypovascular nature and proximity to the primary tumor causing inevitable radiation exposure within the radiation field. The posterior mandible is more commonly affected because of its high bone density resulting in an increased absorption of radiation dose. [27]. Multiple theories have been postulated regarding the etiopathogenesis of ORN, but the exact mechanism is complex and poorly understood [8]. Early studies showed evidence of bacteria in tissues affected by ORN as well as microscopic tissue changes [28]. This was popularized by Meyer who proposed the classic triad sequence of pathogenesis as "radiation, trauma, and infection" [29]. He believed that ORN resulted from secondary infection due to local injury to the devitalized bone resulting in "radiation induced osteomyelitis." This theory explained the role of antibiotic therapy in ORN management. Based on the evidence of ORN in the absence of trauma (extraction), Marx proposed a new theory that was attributed to the radiation-induced endarteritis resulting "hypoxia, hypovascularity, and hypocellularity" [10]. Driven by his theory that persistent hypoxia can cause a chronic non-healing wound, his hypothesis formed the cornerstone for the use of hyperbaric oxygen (HBO) in the treatment of ORN. A current theory proposes that ORN occurs by a "radiation-induced fibro atrophic mechanism" whereby the activation and dysregulation of fibroblastic activity leads to atrophic tissue within a previously irradiated area [30]. To reverse these changes, new therapeutic regimens have been developed wherein pentoxifylline and tocopherol (vitamin E) act synergistically as potent antifibrotic agents [31].

Prevalence

The prevalence of ORN varies widely in the literature ranging from 0.4 to 56% [9]. There is an approximately 20% decrease in the rate of ORN from earlier decades [32, 33] to 4–8% in modern era [34, 35]. This overall reduction of ORN can be attributed to the evolution in radiation modalities from the conventional/2D RT to 3-D conformal RT to intensity modulated radiation therapy (IMRT) [36, 37]. One study also reported lack of mandibular ORN in head neck cancer patients following IMRT with the use of a strict prophylactic dental care policy [38]. A retrospective study from our own institution reported an incidence of 4.3% over a ten-year period in 1023 patients oral and oropharyngeal cancers with IMRT [39]. Proton radiation therapy (PRT) allows further conformal treatment volumes and greater tissue-sparing capability in head and neck radiation due to its inert property of Bragg Peak [40]. This technique includes a smaller volume of the jaw that receives high irradiation doses thus potentially decreasing the likelihood of ORN [41]. Zhang et al. reported reduced incidence of ORN in oropharyngeal cancer patients: 2 vs 7.7% when treated with PRT as compared to IMRT [20].

Time lapse to ORN

ORN can occur at any time, even beyond 10 years following RT [42, 43]. A retrospective study reported that the median time interval between RT and development of ORN was 13 months (range, 2–122 months) [26]. However, it is most frequently noted (70–94%) in the first few years after completion of RT [42, 44]. The median latency period is usually reported as 12–24 months [39, 45]. Early onset ORN occurring within 24 months after RT is thought to be related to radiation doses higher than 60Gy; it can develop spontaneously or following dentoalveolar trauma. In contrast, late onset ORN is thought to arise from trauma in a chronically hypoxic tissue environment [42, 46]. A systematic review described increased risk of ORN following post-radiation extraction in the time period of 2–5 years after RT [47]. In a retrospective study of treated with IMRT in our institution, ORN developed earlier in patients with oropharyngeal cancer (median, 14.6 months) than those with oral cavity cancer (median, 36.1 months) [39].

Management

The management of patients with ORN varies considerably and depends on the severity of the complication [48]. Conservative approaches are generally reserved for asymptomatic or mildly symptomatic patients (Notani I or II) [49, 50]. This includes close observation, strict oral hygiene maintenance, saline irrigation and chlorhexidine mouth rinses, systemic antibiotic therapy for acute infections, anti-inflammatory and analgesics when necessary, avoidance of local irritants like tobacco and alcohol use, discontinuation of ill-fitting dentures. Simple surgical intervention involves smoothening of sharp bony edges to prevent traumatic ulcerations to adjacent soft tissues and gentle debridement of mobile bony sequestrum. Fixation plates and screws are removed if they appear to be a contributing factor. Studies have shown that early intervention with minor surgical procedures combined with pharmacological methods may improve the prognosis of ORN [51]. Surgical management is generally employed when conservative management is unsuccessful and there is progressive (Notani III) ORN resulting in pathological

fractures and draining fistulae [52]. Those with more advanced ORN may require extensive surgical resections such as segmental mandibulectomy and osteo cutaneous free-flap reconstruction. Although a variety of free flaps are available for microvascular reconstructive technique, the fibula remains the workhorse for reconstruction in mandibular ORN [53]. The literature on the use of HBO for prevention or management of ORN is controversial. Based on a systematic review, there was no conclusive evidence to support the routine use of HBO for the prevention or management of ORN. However, adjunctive HBO may be considered for use on an individual basis in patients who failed response to conservative management and subsequent surgical resection [54]. There is insufficient evidence to support the use of HBO prior to dentoalveolar procedures in order to prevent ORN [55]. Based on the understanding of pathogenesis of ORN as a "radiation-induced fibro atrophic process," a new therapeutic strategy with a combination of pentoxifylline (antifibrotic agent) and tocopherol (antioxidant) has shown promising results [56]. Although current literature supports the use of pentoxifylline in the treatment of ORN of the jaws, well-designed prospective studies are needed to further validate its true efficacy in the treatment of ORN [57].

Risk prediction and prevention strategies

Numerous factors associated with the risk of developing ORN have been well documented in the literature [58, 59]. These can be broadly categorized into tumor-related factors, treatment- related factors and patient-related factors. Tumor-related factors include primary tumor site, size, stage, and proximity of tumor to bone. Treatment-related factors include total RT dose, RT technique, volume of irradiated mandible, dose fractionation, concurrent chemotherapy, and re-irradiation. Patient-related factors include tobacco and alcohol use, oral hygiene, dental caries, periodontal disease, and dental extractions before or after RT [37, 60]. Spontaneous ORN can also occur at radiation doses above 70Gy without any preceding dental trauma [12, 39]. Exposure of salivary glands to RT can lead to decreased salivary flow, increases risk of radiation caries leading to pulpal disease, infection and need for dental extraction both of which can trigger ORN. Gomez et al. found that maximum mandibular dose of >70Gy and a mean mandibular dose of >40Gy were associated with increased subsequent dental events and extractions after IMRT [61]. Also, mean parotid dose of >26Gy was predictive of subsequent dental caries [61].

A study from our institution showed that tumor size may be an important predictor of mandibular dose [62]. Larger (T3-T4) tumors showed mean doses ≥60Gy across the entire mandible. In contrast, RT for smaller (T1-T2) tumors showed higher prescribed doses to the molar regions (when compared to the anterior and premolar regions) and to the ipsilateral sides (when compared to the contralateral sides) [62]. With large T3-T4 base of tongue disease, the entire mandible is potentially in the field of radiation, and all mandibular teeth, irrespective of the laterality of the tumor, require evaluation regarding their long-term prognosis. It is reported that mandibular V50 and V60 values were higher for patients who developed ORN following IMRT [36]. Another study demonstrated zero to negligible radiation dose to the contralateral mandible in patients treated with PRT compared to IMRT and suggested that using PRT could presumably result in lower risk of ORN [41].

In our institution, the main strategy in mitigating ORN risk focuses on patient related factors including dental extractions before and after RT. A recent study that aimed to investigate the incidence of ORN between patients who have dental extraction before or after RT showed no statistical difference between the two groups [63]. To prevent risk for ORN, it is generally recommended to remove dental foci of infection within the RT field before RT [26]. All patients receiving head and neck RT at our institution are referred to the Dental Service for pre-treatment oral and dental evaluation. The decision to perform pre-RT dental extractions is based on several factors. Knowledge of radiation dose, treatment modality, field of radiation, and tumor prognosis play an important role in the clinical decision-making. Consideration is given to the pre-existing dental status, and extraction is indicated when there is evidence of advanced caries with poor restorative prognosis, periodontal disease, and nonfunctional teeth within the radiation field. An atraumatic approach in the extraction procedure with primary closure at the time of extraction is applied for soft tissue integrity and minimizing postoperative complications (i.e., postoperative wound healing and ORN). Adequate time for healing of extraction sites before RT is considered essential. Following the consensus report from the National Cancer Institute (NCI), we recommend a healing time of 10 to 14 days between extractions and the commencement of head and neck RT [64]. The protocol for dentate patients undergoing head and neck RT or with a history of head and neck RT also includes a prescription of neutral sodium fluoride 1.1% with 5,000 parts per million (ppm) in the form of a dentifrice toothpaste [65].

The major risk of ORN has been associated with post-RT dental extraction [66]. Wound healing in the mandibular posterior arches is considered compromised when dental extractions are performed in the field of radiation doses above 60Gy. Because of IMRT's complex 3-dimensional dose delivery and tissue sparing favoring the major salivary glands, different dose gradients across the mandible are created. This makes it difficult to determine the dosimetric distribution to the jaws and thus, predict areas at risk for ORN. Dosimetric contouring provides an estimate of the prescribed radiation dose to specified regions of the jaws, thus allowing the clinician to make dental treatment recommendations based on predicted risk for ORN (Figure 2). At our institution, dosimetric analysis is performed for all patients by retrieving radiation treatment planning and

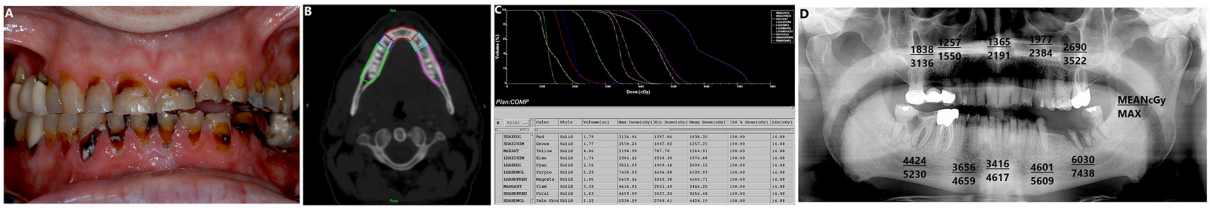

FIGURE 2
(A) A 55-year-old- male patient, diagnosed with HPV positive T2N2M1 squamous cell carcinoma of left palatine tonsil and treated with concurrent chemoradiation (6996cGy in 33 fractions), reported to our Dental Service for opinion and management of grossly decayed left mandibular posterior teeth. **(B)** CT slide with 5 different teeth regions contoured in the mandible. **(C)** Dose volume histogram depicting maximum and mean radiation dose to 10 different teeth region in the maxilla and mandible. **(D)** Mean and maximum dose to the different teeth regions are mapped on to the patient's panoramic radiograph. Teeth-bearing regions with prescribed dose = above 5000Gy are considered at increased risk for ORN. For example, the ipsilateral mandibular left molar region had prescribed mean and maximum doses of 6030cGy and 7438cGy, respectively. Thus, this region is believed to be at high risk for development of ORN. Our recommended treatment included endodontic therapy of tooth # 17 followed by crown amputation and maintenance of tooth #18 to allow self-exfoliation.

using calculation algorithms that incorporate tridimensional beam modeling. A dedicated dental oncologist, assisted by a medical physicist, reviews each patient's computerized treatment plans based on axial slices of computed tomography scans to calculate the cumulative dose for each group of radiated teeth. Using institutional radiation treatment planning software, the mandible in its entire height, from the alveolar crest to the inferior cortex, is manually contoured for the bone surrounding the five regions namely, right molars, left molars, right premolars, left premolars, and anterior teeth (canine to canine) for mandible and maxilla [62]. The teeth are evaluated on both the ipsilateral and contralateral sides of the primary tumor location. After selecting the five regions, the mean dose delivered to each group of teeth is determined by individually contouring teeth-bearing regions on the treatment planning systems and cumulative doses volume histograms are produced for each region. The mean and maximum point doses for each defined region are then calculated. Tsai et al. demonstrated prediction models that could also be used to estimate the maximum radiation dose to the different teeth region following RT in tonsillar cancer patients and suggested that similar methodologies can be used to generate nomograms for different disease subsites [67].

Conclusion

Despite reduced prevalence due to advances in head and neck radiation treatment modalities, ORN remains a significant oral complication of head and neck RT. Future research directions include multi-institutional studies with large sample sizes and randomized controlled trials focused on the management of established cases. Management of ORN should focus on prevention or risk mitigation. Unfortunately, standardized preventive protocols, which may be the most effective way in reducing the risk for ORN, are lacking in the literature. In the meantime, multidisciplinary team communications, carefully planned dentoalveolar procedures pre- and post-radiation therapy and a meticulous survivorship program can reduce risk for ORN and maintain and improve quality of life in head and neck cancer patients.

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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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Immune checkpoint inhibitors in cancer therapy: Review of orofacial adverse events and role of the oral healthcare provider

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Immune checkpoint inhibitors (ICIs) are a revolutionary class of antineoplastic therapy that restore anti-tumor immunity. Consequences of this enhanced immune response include a multitude of immune related adverse events (irAEs) that can affect any body system, including the mouth. Orofacial irAEs reproduce features of numerous immune-mediated conditions, including oral lichen planus, mucous membrane pemphigoid, and Sjögren syndrome, among others. The aim of this review is to summarize known orofacial irAEs and to familiarize oral healthcare providers with how to identify and manage these toxicities as part of the care team for patients treated with ICIs.

KEYWORDS

cancer, immunotherapy, oral medicine, oral pathology, toxicity

Introduction

Cytotoxic T cell lymphocyte-associated antigen (CTLA-4) and programmed cell death 1 (PD-1) and its ligand, programmed cell death 1 ligand (PD-L1), represent immune checkpoint pathways that downregulate T cell activation to promote peripheral tolerance. These pathways can be exploited by tumor cells to promote immune evasion [1]. Immune checkpoint inhibitors (ICIs) block these receptor-ligand relationships, thereby restoring and activating anti-tumor immunity [2]. ICIs have dramatically improved outcomes in an extensive and growing list of solid (e.g., melanoma, lung, head and neck, colorectal) and hematologic (e.g., Hodgkin and non-Hodgkin lymphoma, multiple myeloma) malignancies, both in metastatic disease and, increasingly, in earlier stages and (neo)adjuvant settings [3, 4]. There are currently eight Food and

Drug Administration (FDA)-approved agents targeting CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab, dostarlimab), and PD-L1 (atezolizumab, durvalumab, avelumab) [4, 5].

ICIs modulate endogenous regulatory immune mechanisms to enhance immune system activation and mount a successful immune response against tumor cells [1]. However, this activation occurs broadly, is non-specific, and can lead to a wide variety of immune-related adverse events (irAEs) [6, 7]. These irAEs can affect any body system at any time during the course of or following treatment, though they most commonly present within the first months of therapy [3, 8]. The skin tends to be the earliest (i.e., between 2 and 12 weeks after initiating treatment) and the most frequently affected site [9]. These events are not uncommon: 60% of patients treated with an anti-CTLA-4 antibody, nearly 30% of patients treated with an anti-PD-1 or anti-PD-L1 antibody, and as many as 90% treated with a combination of a CTLA-4 and PD-1 or PD-L1 inhibitor will experience one or more irAEs [8]. IrAEs can be acute and reversible, but may also be chronic and/or permanent toxicities (i.e., endocrine and rheumatologic irAEs) in as many as 43% of patients [4, 10]. Severity of irAEs can vary and there are a number of clinical grading systems that have been proposed; the most ubiquitous in the literature is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5—a five-point scale from grade 1 (mild) to grade 5 (death) [11]. An objective and widely adopted grading system is a crucial tool to inform management of ICI therapy. As a general rule, ICIs are temporarily held in the setting of a grade 3 (severe) irAE and permanently discontinued for any grade 4 (life-threatening) irAE [12]. Corticosteroids are a mainstay of treatment for irAEs, though steroid-sparing, reaction-specific regimens (e.g., mycophenolate mofetil, infliximab, hydroxychloroquine) are being increasingly utilized [3, 6, 12]. While irAEs can be associated with significant morbidity and even mortality, there is emerging evidence that they are a positive predictor of clinical outcomes [13].

Oral mucosal and salivary gland irAEs have been inconsistently reported and classified, so the prevalence is not clearly defined, though the incidence may be as high as seven percent [14, 15]. They can occur with or without cutaneous or systemic manifestations [9]. This review summarizes current knowledge on orofacial irAEs and suggests a pragmatic approach to their identification and management by the oral healthcare provider (OHP).

History and examination for the oral healthcare provider

For cancer patients planned to initiate immunotherapy, OHPs should be aware of any existing immune-mediated conditions. ICI therapy may exacerbate pre-existing immune-mediated conditions, and it is important to be able to distinguish a *de novo* irAE from an exacerbation of an underlying disease process [1]. Patients should be made aware of this risk and be encouraged to notify their care team about worsening or new symptoms. A comprehensive oncologic history that includes any past or concurrent treatments should be obtained, as ICI therapy may be given in combination with cytotoxic chemotherapy, radiation, other targeted therapies, or even supportive care measures that can introduce additional risk factors/concomitant side effects (e.g., bone marrow suppression, osteonecrosis of the jaw) [3].

Workup of a patient with a suspected oral irAE should begin with a thorough medical history and history of present illness (Figure 1). Inquire about the onset (sudden or gradual), duration (days, weeks, or months), nature (pain, sensitivity, difficulty eating/swallowing, etc.) and severity of symptoms (visual analog scale (VAS) pain/sensitivity score), sites affected (including extraoral sites), and any other irAEs they have experienced [16]. A review of systems (ROS) should also be performed as this may identify other extra-oral irAEs. Any positive findings, whether identified by patient report, ROS, or physical examination (for cutaneous lesions in particular) should be communicated to the patient and their oncologist.

When conducting a head and neck intra-oral and extra-oral examination in this patient population, general principles apply [17]. Each site should be examined methodically and an attempt should be made to assess salivary gland function by expressing saliva from the major salivary gland ducts. All findings should be documented and thoroughly described, including location, number, size (with measurements if possible), color, and texture of any mucosal abnormality (including that of saliva). Clinical photographs can be a helpful tool to monitor oral mucosal lesion progression (or resolution) and to communicate with other members of the patient's care team.

Oral mucosal irAEs

Oral mucosal irAEs typically mimic or recapitulate the pathogenesis and clinical features of a range of well-defined immune-mediated mucocutaneous disorders, including oral lichen planus (OLP), mucous membrane pemphigoid (MMP)/bullous pemphigoid (BP), erythema multiforme (EM), and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (Figure 2) [3, 16, 18]. These reactions may also present with overlapping features of more than one condition [16].

OLP-like irAEs present with white striations, erythema, and/or ulcerations of the oral mucosa, particularly the ventral tongue and buccal mucosa, ranging from asymptomatic to severely painful [19, 20]. Cutaneous LP-like irAEs are one of the most common dermatologic irAEs, present in between 0.5 and 6% of patients, so many patients with oral lesions

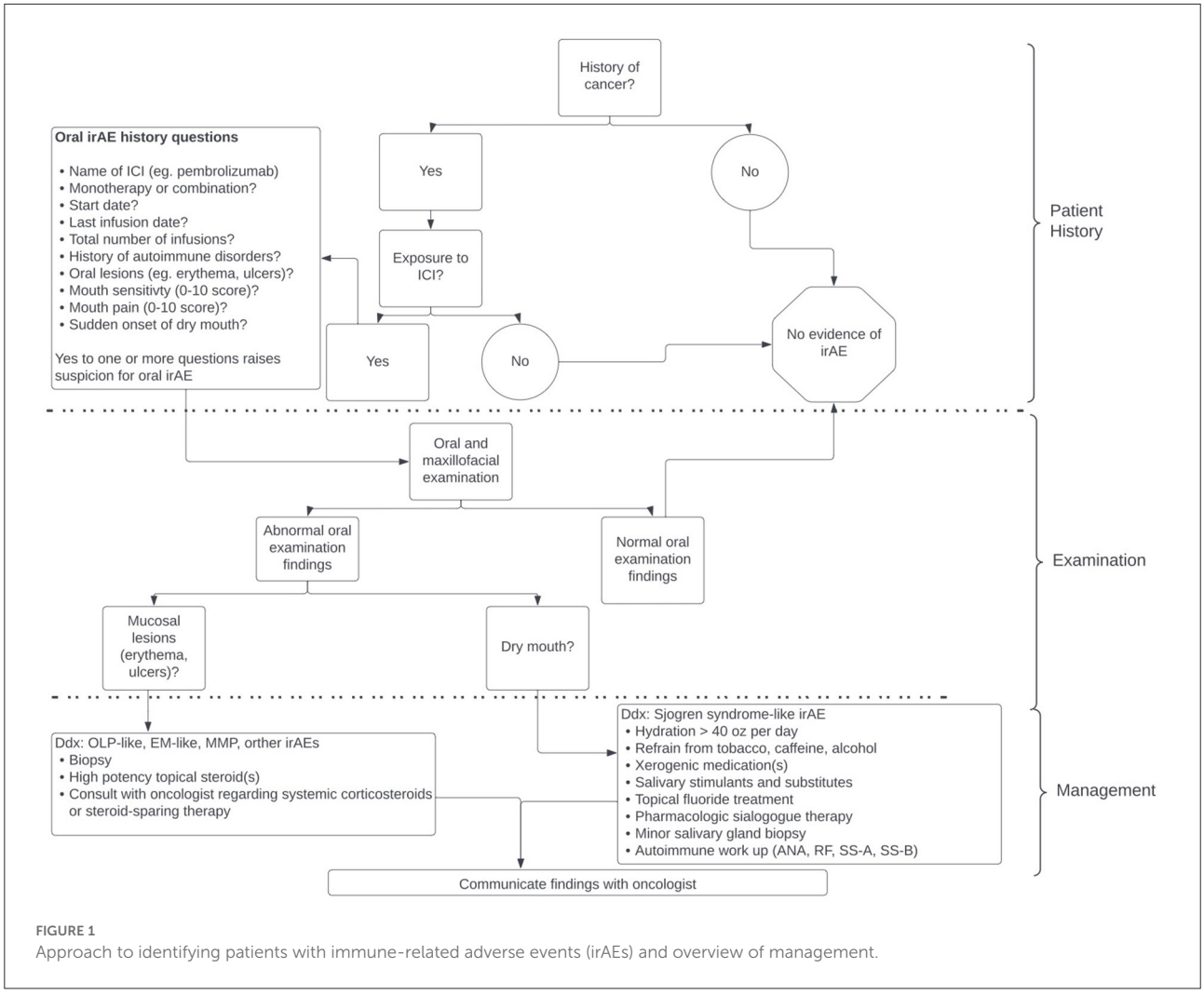

FIGURE 1
Approach to identifying patients with immune-related adverse events (irAEs) and overview of management.

will also have skin involvement [9]. Autoimmune cutaneous blistering disorders are also common—affecting 1% of patients treated with ICIs [21]. BP only rarely includes oral lesions, whereas MMP often exclusively affects the oral mucosa, presenting with desquamative gingivitis, erosions, ulcers, and/or intact bullae [21–24]. EM-like irAEs typically present with targetoid skin lesions and, intraorally, multiple irregularly shaped erosions and ulcers with hemorrhagic crusting of the lips; cases involving exclusively the oral mucosa, while controversial, have also been described [25–27]. SJS and TEN-like irAEs represent severe and, in the case of TEN especially, life-threatening mucocutaneous reactions with oral lesions resembling that of EM, including multiple, large, irregularly-shaped, ulcerations/erosions and hemorrhagic crusting of the lips [18, 28]. There have additionally been cases reported of systemic lupus erythematous and scleroderma with oral involvement, as well acute oral GVHD reactivation and linear IgA disease [18, 29–31]. These irAEs are rare, underrepresented, and/or poorly characterized, underscoring the fact this is an evolving area of study.

Diagnosis of oral mucosal irAEs can be confirmed based on histopathology and/or immunofluorescent studies, though in some cases, clinical diagnosis may be sufficient. Biopsies should ideally be obtained prior to initiating treatment of the irAE. If a vesiculobullous condition is suspected, specimens should be submitted for both histopathologic analysis and direct immunofluorescence (DIF). In the appropriate clinical context, indirect immunofluorescence (IIF) and/or enzyme-linked immunosorbent assay (ELISA) can also be considered.

Histopathologic features of oral mucosal irAEs, much like the clinical presentation, may mimic the condition or can have absent, overlapping, or non-specific findings [20, 32]. OLP-like irAEs are characterized by interface mucositis and may exhibit a dense lymphocytic band, basal vacuolar changes, spongiosis, and/or subepithelial clefting [20, 32]. On DIF, a non-specific patchy deposition of fibrinogen will be

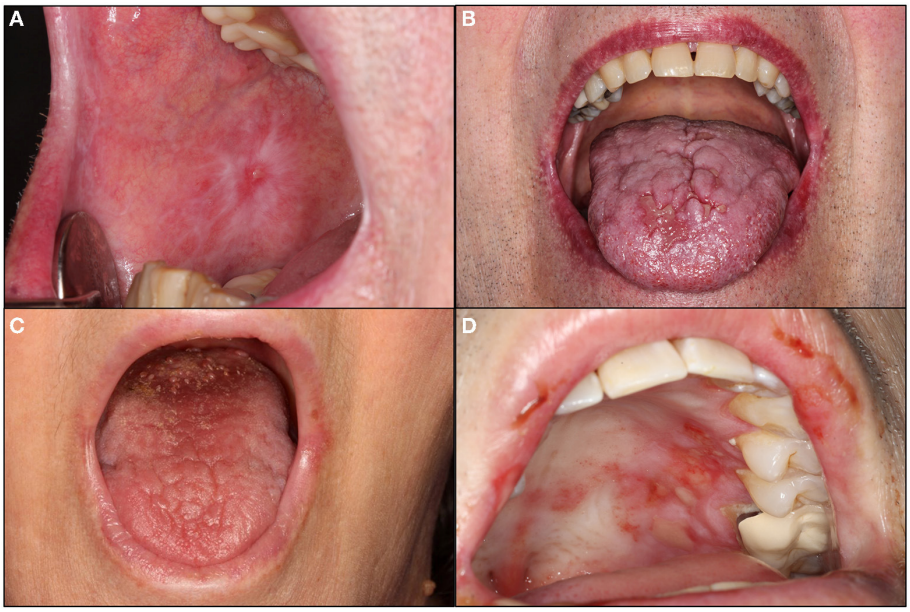

FIGURE 2
Oral mucosal and salivary immune related adverse events (irAEs). **(A,B)** demonstrate oral lichen planus-like irAEs characterized by white striations of the right buccal mucosa with a central pinpoint ulceration and surrounding erythema **(A)** and generalized erythema of the upper and lower lip vermilion with atrophy, white changes, and coalescing ulceration of the midline anterior dorsal tongue with surrounding erythema (HSV-negative; **B**). **(C)** demonstrates a Sjögren syndrome-like irAE with desiccated oral mucosa and loss of filiform papillae of the dorsal tongue. **(D)** demonstrates a mucous membrane pemphigoid irAE characterized by scattered ulcerations of the hard palatal mucosa and upper lip mucosa with significant surrounding erythema (HSV-negative).

observed at the basement membrane zone without specific reactivity to immunoglobulins [20]. ELISA is negative to antidesmoglein-1 (Dsg-1), antidesmogelin-3 (Dsg3), and anti-BP180 (BP180) antibodies [33]. There are no published oral mucosal histopathology findings in BP irAEs, but skin immunofluorescence studies reveal linear deposition of IgG and C3 at the dermo-epidermal junction and positive serologic titers to BP180 [21, 34]. Features of MMP include subepithelial clefting with preservation of the basal layer of epithelium and a mixed perivascular inflammatory infiltrate on histopathology and linear deposits reactive to IgG, IgA, and C3 on DIF [23, 35]. Approximately half of MMP irAE cases are positive for BP180 [23, 35]. Histopathologic and immunofluorescent findings in EM-like irAEs are non-specific and include a mixed inflammatory infiltrate and no specific reactivity [36]. In such cases, the absence of findings is itself revealing. Oral lesions of SJS and TEN will similarly reveal non-specific ulceration and inflammation [37]. Among any of these conditions, overlapping histopathologic features are possible.

We have previously published suggested grading criteria based upon symptom severity and impact on oral alimentation and accompanying management guidelines for oral mucosal and salivary irAEs [16]. The grading criteria for oral mucosal irAEs draw from several established guidelines for irAEs [i.e., CTCAE, American Society of Clinical Oncology (ASCO), National comprehensive Cancer Network (NCCN), and Society for Immunotherapy of Cancer (SITC)] and range from grade 1 (asymptomatic or mildly symptomatic) to grade 4 (severely painful oral lesions making oral alimentation impossible). In line with these established guidelines, we generally recommend that systemic steroids be considered for any grade $\geq$2 irAE and the ICI be temporarily held for any grade $\geq$3 toxicity with consideration of permanent discontinuation for any grade 4 toxicity.

Integral to the management approach of oral mucosal irAEs is early and aggressive intervention with high-potency topical steroids [15]. Solution formulations work well for multifocal and/or hard to reach lesions, and gels can be applied to focal lesions with gauze or a cotton tip applicator. Adequate contact time is critical to ensure maximum efficacy (e.g., hold solution or leave gauze in place for 5 min). If lesions are severe at presentation, fail to respond to, or progress while using topical steroids, systemic treatment is indicated, generally with oral prednisone at a dose of 1 mg/kg followed by a slow taper to avoid flares [6]. The plan to initiate corticosteroids should be coordinated with the patient's oncologist, who may make the decision to hold ICI therapy until lesions improve or resolve. Steroid-sparing immunosuppressive agents can also be considered, such as doxycycline, mycophenolate mofetil, acitretin, infliximab, dupilumab, or IVIG [6]. EM-like

oral mucosal manifestations may be managed with topical corticosteroids (plus or minus systemic prednisone), whereas mucocutaneous manifestations of SJS TEN-like irAEs require aggressive, multidisciplinary inpatient management [6]. If the ICI is rechallenged or another is initiated, patients should be followed closely by their oral healthcare provider to identify recurrence, flares, or new irAEs.

Salivary gland irAEs

IrAEs affecting the salivary glands occur, as with other irAEs, along a spectrum of severity and are generally referred to as sicca syndrome or Sjögren syndrome (SS)-like, reflecting the largely shared symptoms, clinical features, and treatment approaches to these entities (Figure 2) [38, 39]. While clinically similar to Sjögren-syndrome, there is some histopathologic evidence that SS-like irAEs may be mediated primarily through autoreactive T cells rather than the B cells classic of SS [40]. There are, however, cases that meet the diagnostic criteria for SS, suggesting they are clinically indistinguishable from SS [38].

Xerostomia is reported by 0.4–7% of patients treated with ICIs, though some of these may be attributable to other causes (e.g., polypharmacy, dehydration) [14, 38]. Patients with a true salivary irAE typically present with acute onset of severe dry mouth and hyposalivation, with or without dry eyes [38, 39]. A thorough diagnostic workup may include measurement of whole unstimulated salivary flow rate (WUSF), minor salivary gland biopsy (i.e., from the labial mucosa), and serology (ANA, RF, anti-Ro, anti-La). That said, clinical judgement should be employed to weigh the utility of such tests. For instance, clinical examination may be sufficient to assess for hyposalivation based on any of the following: visibly desiccated mucosa, lack of floor of mouth pooling, inability to express saliva from the parotid or submandibular gland ducts, mirror or glove sticking to the mucosa, or qualitative changes to the saliva (i.e., frothy, sticky, or ropey). In this patient population, serology is positive in only a minority of cases [38, 39]. Similarly, histopathology of minor salivary gland biopsies in SS-like irAEs variably demonstrate the focal sialadenitis characteristic of SS; half of cases demonstrate non-specific chronic sialadenitis with a focus score of zero [38, 39].

As with oral mucosal irAEs, we have previously proposed a set of grading criteria and management guidelines for salivary irAEs informed by CTCAE, European League Against Rheumatism (EULAR) guidelines for the management of SS, and the guidelines published by Klein et al. [16] and Warner et al. [39]. In this case, the grading criteria range from grade 1, characterized by xerostomia without hyposalivation or impact on diet, to grade 3, which presents with hyposalivation so severe as to prevent adequate oral alimentation and/or systemic features of SS that impact the patient's ability to perform activities of daily living (ADLs). In a patient with a history of exposure to ICIs with a complaint of dry mouth, it is important to recognize other common etiologies of xerostomia/hyposalivation including dehydration, polypharmacy, and anxiety. Regardless of grade, symptomatic management is a cornerstone, including over the counter mouth moisturizers and saliva substitutes as well as prescription sialagogues (e.g., pilocarpine or cevimeline). Adequate hydration and avoidance of caffeine and smoking should also be encouraged. Once there is evidence of hyposalivation, topical fluoride supplementation should be prescribed to prevent caries [41]. If there is impact on diet and/or systemic features of SS, this should be communicated to the patient's oncologist who may elect to hold the ICI and/or involve a rheumatologist. Systemic treatment options for grades 2 and 3 include prednisone, hydroxychloroquine, or other disease modifying antirheumatic drugs (DMARDs) [3, 39].

Other orofacial irAEs

There have been at least four reported cases of medication related osteonecrosis of the jaw (MRONJ) related to ICIs in patients with no prior or concurrent exposure to antiresorptive or anti-VEGF therapies [42–45]. Three cases occurred spontaneously, and one occurred following a dental extraction. All presented with pain (of varying degrees) and local swelling, with a sinus tract, exposed bone, or non-healing extraction site observed on initial examination [42–44]. Ultimately, all cases exhibited clinically exposed necrotic bone. Radiographic (e.g., panoramic radiograph or computed tomography) findings were variable among cases and included a moth-eaten trabecular pattern with bilateral mandibular fractures, maxillary sinusitis with osteolysis, and a non-healing extraction site [42, 44, 45]. Antibiotics (e.g., amoxicillin-clavulanate or amoxicillin/metronidazole) were prescribed in all four cases, and chlorhexidine rinses in three cases. Sequestrectomy was performed in three cases, followed by complete re-epithelization in two cases [43, 44]. For the case complicated by bilateral mandibular fractures, a total mandibulectomy with fibula reconstruction was performed; histopathology confirmed necrosis of the trabecular and cortical bone with fibrosis of the marrow space [42]. OHPs should be alert to the possibility of osteonecrosis as an irAE secondary to ICI therapy in addition to better known culprit medications (e.g., bisphosphonates, denosumab).

Dysgeusia has been reported as an irAE in 16 randomized controlled trials, with a pooled incidence of 4.9% [46]. A recent single center retrospective review estimated the incidence to be 3.6% [14]. Further studies are needed to characterize the features, clinical course, and management approach. OHPs should be aware of this as a possible explanation for taste changes in patients who have been treated with ICIs.

Conclusion

ICIs have quickly become a mainstay of cancer therapy [3]. Thus, it is important for practitioners of all disciplines to recognize both their therapeutic mechanisms and adverse events (irAEs), which are distinct from conventional cytotoxic chemotherapy. OHPs can provide three key roles for patients who are initiating, actively being treated with, or who have been on an ICI: [1] identification of and supportive care for orofacial irAEs; [2] communication of orofacial and/or pertinent positive systemic findings to the oncologist; [3] continued routine dental treatment with emphasis on the maintenance of oral hygiene practices. With attention to each of these facets, OHPs can play a critical supportive role in the multidisciplinary oncology team for patients treated with ICIs.

Author contributions

BK, MS, SF, and NT contributed to conceptualization. BK and MS contributed to writing (original draft and editing). AV, FA, PV, SS, SF, and NT contributed to reviewing and editing. 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.

Publisher's note

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Precision medicine for risk prediction of oral complications of cancer therapy–The example of oral mucositis in patients receiving radiation therapy for cancers of the head and neck

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Oral complications of cancer therapy are common, markedly symptomatic, negatively impact patients' quality of life, and add significantly to the cost of care. Patients' risk of treatment-related toxicities is not uniform; most patients suffer at least one side effect, while others tolerate treatment without any. Understanding those factors which impact risk provides opportunities to customize cancer treatment plans to optimize tumor kill and minimize regimen-related toxicities. Oral mucositis (OM) is an iconic example of a clinically significant and common complication of head and neck radiotherapy. Individuals' OM risk is governed by the cumulative impact of factors related to treatment, the tumor, and the patient. In addition to OM risk prediction, a second opportunity to apply precision medicine will evolve as viable treatment options become available. Patients vary widely in how well or poorly they respond to specific treatments. What works well in one individual, might fail in another. Prospective determination of the likelihood of a patient's response or non-response is based on a range of biological interactions. Coupled with risk determination, the application of precision medicine will allow caregivers, patients, and payers to integrate risk/benefit to optimize the probability that the best treatment is be given to the most appropriate patients.

KEYWORDS

precision medicine, oral mucositis, radiation, head and neck cancer, treatment complications

Introduction

Radiation therapy is a mainstay in the management and treatment of cancers of the mouth and oropharynx and may be used as definitive treatment, following induction chemotherapy, or after surgical resection. Optimally, radiation is administered with concomitant radiosensitizing chemotherapy. Based on current guidelines, cisplatin is the agent of choice. A typical regimen consists of daily (weekdays) fractions of 2 Gy for a total dose of 70 Gy with cisplatin infused either weekly (40 mg/m^2) or tri-weekly (100 mg/m^2) [1].

Almost all patients treated with standard regimens of chemoradiation (CRT) for oral or oropharyngeal cancers develop some level of tissue damage in the form of oral mucositis (OM) [2]. The clinical presentation of OM ranges from mild erythema and atrophy to deep, confluent, irregular full-thickness ulcerations impacting the movable oral mucosa. The symptoms, systemic impact and disease burden are proportional to the extent and severity of lesions [3]. While mild manifestations may result in soreness like a food burn, more extensive mucositis is excruciatingly painful and of such intensity that it is refractory to opioids and functionally compromising. Secondary bacterial colonization of ulcerated areas may be associated episodes of bacteremia. In addition, severe mucositis (SOM; defined as ulcerations extensive enough to limit diet to non-solids; WHO grades 3 or 4) may cause treatment breaks which impact negatively tumor response [4]. Patients with SOM visit emergency rooms more often, have more unplanned office visits, are hospitalized more frequently, and are more reliant on parenteral nutrition (gastrostomy feeding) than are patients who have little or no mucositis [5, 6]. It is not surprising that the incremental cost of SOM is over $30,000 (US) [7].

Opportunities for precision medicine

The application of precision to cancer regimen-related toxicities, including OM, presents two significant opportunities: first, the determination of mucositis risk, and second, assessment of an individual's likelihood of responding to a specific preventive or treatment intervention. Ideally, the probability of both would be determined prior to the initiation of cancer therapy and guide clinicians' and patients' decision-making.

It is clear that there is a risk spectrum for CRT-associated OM. While the majority of patients suffer some level of mucosal damage, a very few complete treatments free of the condition. More commonly are a group of patients (about 30–35%) who develop mild forms of the condition, and a reciprocal cohort (roughly 20%) who manifest the most severe manifestations of OM [8]. Knowledge of a patient's OM risk could be of value in customizing a treatment plan which optimizes tumor control, but limits side effects.

The second opportunity for precision relates to the prediction of who will or who will not respond to a particular treatment. The success of current population-based clinical trials is determined by results associated with the whole study population, even though we know that patients respond to therapies in non-equivalent ways. The dependence of such bell-shaped curve data ignores those patients at either end – those who are hyper-responders or those who do not respond at all. Being able to prospectively identify into which category a particular patient falls informs providers as to dosing decisions or whether to even expose the patient to the proposed treatment [9]. For example, an analgesic at one dose might be very effective in one individual and useless in another. While one patient might benefit from palifermin or another from photobiomodulation, others may not benefit at all. Our ability to differentiate responders from non-responders not only optimizes outcomes for patients, but it saves costs associated with the treatment of non-responders. Treatment should not be a "one size, fits all" proposition. And this approach is true for all forms of treatment – drugs, biologicals, and devices.

Factors impacting risk definition and outcome assessment

Defining mucositis as a phenotype

Before trying to understand factors, which contribute to OM risk, it seems critical establish a "gold standard" that defines OM severity. While a patient might be considered to be at risk of SOM when evaluated with one scale, the same risk factor could seem insignificant if SOM is defined by different criteria. Likewise, treatment success defined by one scale might not be observed using another.

Scoring scales for mucositis range from some that are heavily anchored on clinical findings (erythema, atrophy, ulceration, bleeding) to others which categorize severity purely by function (ability to eat a normal diet, soft solids, etc.), or patient-reported symptom-based endpoints [10]. While most studies are interested in "severe" mucositis, this definition is not uniform. For example, WHO scale grades of 3 or 4 (Table 1) are typically defined as severe and mandate the presence of mucosal ulceration, the extent of which is enough to cause the patient to modify the diet to liquids or nothing by mouth. The newest version of the NCI-CTC does not require clinical assessment and relies symptoms and diet, whereas older CTC versions were dependent on clinical descriptors of ulcerations. Even more complicating are those studies, usually retrospective, in which OM severity is based on an interpretation of clinical notes [2].

The lack of a clinically relevant standardized definition of OM also hinders the interpretation of surrogate measures of mucositis such as biomarkers since their accuracy, specificity and sensitivity are measured against standard scale outcomes.

TABLE 1 World Health Organization Scale (WHO) for scoring oral mucositis.

Grade	Description
0	None
1	Erythema and oral soreness
2	Oral ulceration; solid diet tolerated
3	Oral ulceration; liquid diet only
4	Oral ulceration; oral alimentation impossible

The WHO mucositis scoring scale has been unchanged since its introduction more than 30 years ago and has served a the basis for efficacy definitions for many interventional trials. It assesses OM severity based on a combination of symptoms, clinical findings, and patient functionality (diet modifications based on oral symptoms) [11].

Fortunately, while there is not complete congruity in OM scoring, the three most used scales (WHO, NCI-CTC, RTOG) are reasonably consistent in identifying SOM [11].

Aside from scoring scales that is selected, a clinical meaningful definition of what constitutes risk is essential. The trajectory of OM over the course of CRT is remarkably consistent and exposes patients to 3–5 weeks of SOM (weeks five until 2–3 weeks post radiation) [12, 13]. Should patients who develop 2–3 days of SOM be considered to be at the same risk as who develop 4 weeks of the condition? Is severe mucositis incidence (a binary, yes/no endpoint) as important in defining risk as duration? Binary endpoints like incidence are easy to interpret but lack the same consideration of clinical impactfulness as does SOM duration. For example, while a patient with 7 days of SOM might require G-tube feeding or hospitalization for hydration and pain management, it is unlikely that a single day of SOM would have similar consequences.

Factors affecting mucositis risk

Overview

OM risk prediction has long been of interest. In general, risk factors can be grouped into three categories: (1) Those associated with treatment, (2) Those associated with the patient, and (3) Those associated with the tumor [14].

Treatment-associated risk influencers include radiation intensity and field(s) of exposure, inclusion of concomitant chemotherapy and agent selection, and treatment scheduling. Until the biological consequences of CRT and its impact on OM pathogenesis were described risk was almost exclusively based on factors impacting radiation intensity on the oral mucosa. Patient-related variables evolved with more knowledge about radiobiology and the complex biological cascade that defines the progression of mucositis and include genomics, metabolomics, epigenetics, and microbiomics. Finally, the observation that tumor's biological activity and crosstalk with normal tissue influences toxicity risk has been recently noted.

Conceptually, studies for which oral mucositis risk assessment was the primary outcome have only focused on one element at a time – radiation dose, chemotherapy agent and schedule, genomics, etc. Given OM's biological complexity, this approach is naïve as it assumes a linear and causal relationship between a specific risk element and the development of OM, while largely ignoring the dynamics and interaction of the multiple facets which contribute to risk. Indeed, it is possible that in the case of risk determination, 1 + 1 does not equal 2, but might, if one element catalyzes, accelerates, or promotes another, equal 3 or more. A reductionist approach to risk analysis may provide hints, but it is unlikely to describe the consolidated impact of multiple factors [15].

Treatment-related factors which might impact mucositis risk

Radiation

The stomatotoxic effects of radiation have been extensively described and are associated with the cumulative dose, daily fraction size and schedule, and field [16]. While the administration of concomitant chemotherapy enhances the tumoricidal effect of radiation [17], it also increases OM risk by a factor >3 [18] and hastens it onset [19].

Intensity modulated radiation therapy (IMRT) is currently preferred as it delivers more tumor-focused radiation thereby effectively reducing the level of cumulative radiation delivered to normal mucosal tissue when delivered in daily 2 Gy fractions. Since tumor response is dependent on both cumulative radiation dose and the time over which it is delivered, attempts at using higher daily radiation doses (daily fractions up to 3.5 Gy) in accelerated fractionation regimens have been suggested [20, 21].

While reported survival impacts vary, the stomatotoxicity of these regimens was significant with SOM of such severity as to be the major reason from breaks in treatment and protraction of overall treatment time [22].

In addition to factors associated with radiation dose, field and schedule, timing of radiation administration has been shown to impact mucositis risk as patients treated early in the day are less likely to develop SOM than patients radiated later [23, 24].

Concomitant chemotherapy

As noted, the addition of chemotherapy to a standard radiation regimen favorably affects tumor response, but at an expense of added toxicity, including mucositis. While a range of drugs has been used in this role, cisplatin is the gold standard. The original dosing schedule for cisplatin was 100 mg/m^2 infused on days 1, 21, and 42 of radiation (q3weeks). In response to a challenging systemic toxicity profile, a more conservative scheme of 40 mg/m^2 weekly evolved. While controversy exists

as to the superiority of one regimen vs. the other relative to tumor management, the weekly regimen is more popular in the United States, especially among patients being treated for oropharyngeal cancers. While some have reported that mucositis (all grades qw 61.2 vs. q3w 87.6%; severe qw 12.1 vs. q3w 34%) was more common and severe with high dose cisplatin [25]. In contrast, no differences in either incidence or intensity of mucositis have been reported in other trials in which the tumor impact of the two regimens was evaluated for both oral/oropharyngeal cancers [26–28]. The results of a recently reported Phase 2 interventional trial in which trained evaluators scored mucositis throughout treatment agrees with that conclusion [8].

Since cisplatin cisplatin may not be tolerated by all patients, radiation plus carboplatin, either as monotherapy or with another agent such as 5-fluorouracil, is an alternative. Neither the rate nor severity of mucositis is significantly different than that observed with cisplatin [29, 30].

While of questionable impact on tumor response, the inclusion of EGFR inhibitor as a component of standard cisplatin concomitant chemotherapy appears to increase the risk of oral mucositis [31].

Patient-related factors which impact mucositis risk

Patient-related variables dominate OM risk and while multiple factors contribute to risk, the extent to which each factor affects an individual's risk is not the same from patient to patient. Secondly, while the determination of a patient's OM risk represents the collective impact of multiple factors, it is probable that there is biological crosstalk that amplifies or retards the influence of each.

A relationship between past or current tobacco uses on mucositis risk is unclear. Reports of tobacco smoking having no effect on the rate of acute radiation-associated toxicities including mucositis [32] are contradicted by reports that tobacco use is protective of oral mucositis [33, 34] or that smoking adds the risk of mucositis [35, 36].

Sex has been increasingly studied as impacting regimen-related toxicity risk, particularly amongst patients being treated with chemotherapy. For the most part, females appear to be at higher risk than males [37]. Little data exist relative to sex being a risk factor for mucositis in the head and neck cancer population, and to date, conclusions regarding gender are inconsistent with studies suggesting that sex does not significantly increase risk [38], or that males are more likely to be affected [39].

In the case of HNC patients, the events associated with continuous exposure to fractionated doses of radiation have revealed a repeating biological cascade the is initiated with the production of reactive oxygen species and the activation of the innate immune system, is followed by the activation of transcriptions factors, the expression of multiple genes pathways, and the release of mediators that culminates in apoptosis and necrosis of basal epithelial stem cells, atrophy and ulceration. The obvious opportunities for genes to control and influence of these events have led to a range of candidate gene and mutation studies and genome-wide association studies which have attempted to identify genome-based OM risk factors. With very few exceptions, these studies have used peripheral blood monocytes as sources for RNA, and both blood and saliva for DNA of germline origin. The advantages and shortcomings of these has been previously reviewed [40].

In general, three classes of genes have emerged as being particularly associated with mucositis risk, those associated with oxidative stress [41], inflammation [42, 43], those associated with telomere function regulation and its downstream consequences [44], and DNA repair [45].

While somatic mutations have been studied with respect to tumor behavior, the contribution of a tumor's genome to patient toxicity risk has been overlooked until recently. It now appears that both germline and somatic genomic sources contribute to OM. Sumner et al. reported the association of radiation-induced toxicities, including mucositis, and gene alternations expressed in tumor specimens from thirty-seven patients with HNC. More studies are needed to assess how both gene sets interact to affect risk, particularly given the heterogeneity of somatic genes from tumor to tumor [46].

While there seems little doubt that genomics plays a significant role in risk determination, three important considerations remain: (1) The impact of genes on risk is likely the consequence of collective and collaborative activity between and amongst genes so consequently, the risk impact represents the consequences of a collective effect of multiple genes. (2) There is an absence of large-scale prospective trials to confirm the predictive accuracy of proposed risk genes. (3) The global somatic and germ line gene expression impact and their relationship to each other is still lacking.

In addition to genomics influences on risk, metabolomics, epigenomics and proteomics are important, but have yet to be comprehensively studied.

Non-genomic peripheral blood markers

High pre-treatment neutrophil/lymphocyte ratios (NLR) (>5) prior to radiation have been proposed as a predictive factor for acute OM [47] as indicators of an inflammatory state. However, others have found NLR as predictive of late-onset OM [48] or not predictive of OM at all [49].

The microbiome

Bacterial colonization of OM ulcerations prolongs lesion resolution by provoking the inflammatory response [50]. Speciation studies have suggested that a range of dysbiotic changes impact the progression and severity of mucositis [51], and that individual variations in the microbiome composition may be associated with variations in OM trajectory. Similar

patient-specific dysbiosis has been proposed relative to the susceptibility and course of other diseases. It will be critical to assess the microbiome's impact in the context of multivariate analyses (i.e., neutropenia, sampled site, salivary changes, etc.).

More speculative are studies suggesting that bacteria may play an etiologic role in the development of radiation-induced mucositis [52]. These too often fail to account for other local, systemic, and treatment changes with which HNC patients are impacted. The failure of prophylactic antimicrobial strategies in mitigating or attenuating OM further confuses conclusions relative to the importance of the microbiome as an initiator of OM [53].

Implications of risk determinants on practice and clinical trials

The complexities of OM pathogenesis and their integration with risk determinants present both opportunities for research and challenges in clinical trial design of interventional agents. Given the range of treatment, tumor, and patient-related variables that impact risk and the uncertainty of the weight of each, trying to assure an even playing field for clinical study populations is a high bar. The interactions between risk factors are not two dimensional, but rather a dynamic multiplex problem in which the impact of specific OM risk factors changes over the course of treatment. For example, not only do patient genes interact with each other, but the genome also affects patients' responses to the microbiome, and that response might be more robust at high cumulative doses of radiation then early in the course of therapy. Analyses of these interactions represents a rich opportunity for research to create a hierarchical risk algorithm for OM in which all risk factors are integrated over time.

In the meantime, real world considerations require the assessment of investigational agents in study populations that are not only large enough to evaluate efficacy outcomes taken together, but also sufficient to stratify data to determine the best target population for intervention. For example, a drug which fails to show activity in an "all-comers" study (all HNC diagnoses), might be efficacious for patients with HPV+ cancers, but not HPV- cancers for radiation doses up to 60 Gy. Importantly, given the multifactorial nature of risk factors and those influencing OM trajectory, small study data risks leading to erroneous, misleading, or marginally broadly applicable conclusions.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

Author SS was employed by Biomodels, LLC and Primary Endpoint Solutions, LLC. Both companies assist industry, government and academics to study and enable drugs, biologicals and devices to treat patients for a variety of indications including cancer and the side effects and toxicities of its treatment. SS does not have equity in any of the companies with which he works.

Publisher's note

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Taste and smell disturbances in patients with chronic oral graft vs. host disease: An observational study

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Background: A common complication of allogeneic hematopoietic stem cell transplantation (alloHSCT) is chronic oral graft vs. host disease (cGvHD). Oral cGvHD may present as mucosal lesions, salivary gland dysfunction, and trismus. Moreover, taste and smell ability may be affected, but the prevalence, nature and severity of altered taste and smell function, and their impact on quality of life (QoL) are understudied.

Aim: To identify the prevalence, nature, and severity of taste and smell disturbances, their impact on QoL and to assess whether altered taste/smell ability is associated with oral mucosal cGvHD or hyposalivation.

Materials and methods: AlloHSCT recipients at least 100 days post-HSCT and referred for oral cGvHD-related oral complaints were eligible for participation in this cross-sectional study. Manifestations of oral mucosal cGvHD were scored, the (un)stimulated salivary flow was measured, and objective taste and smell ability was evaluated. Subjective taste and smell alterations, and overall and oral health (OH)-related QoL were assessed.

Results: In total, 45 patients were included, of which objective reduced taste ability (hypogeusia) was identified in 68.9%; 28.9% had reduced smell ability and 11.1% had complete loss of smell. Nevertheless, only 31.1% of patients reported severe taste alterations and 22% reported moderate taste alterations indicating that not all the patients were aware of their altered taste sense. Taste/smell disturbances were not related to oral mucosal cGvHD or hyposalivation. Most alloHSCT recipients reported a decreased OH-related QoL. However, a relation between taste/smell ability and global or OH-related QoL could not be identified.

Conclusion: Taste and smell disturbances are prevalent among alloHSCT recipients. Most patients reported a decreased OH-related QoL, but the specific impact of taste and smell disturbances remains to be elucidated.

KEYWORDS

hyposalivation, hypogeusia, quality of life, allogeneic hematopoietic stem cell transplantation (alloHSCT), chronic oral graft-vs.-host disease, taste and smell disturbances

Introduction

Chronic graft vs. host disease (cGvHD) is a common complication of allogeneic hematopoietic stem cell transplantation (alloHSCT) [1, 2]. Patients receive stem cells collected from peripheral blood, bone marrow, or umbilical cord blood from a related or unrelated donor. Immune cells derived from these donor stem cells (the graft) eradicate malignant cells in hematological malignancies, but may also interact with normal host cells. This allo-immune response can affect various organs, usually targeting the skin, eyes, mouth, gastrointestinal tract, liver, lungs, musculoskeletal and genitourinary system, resulting in cGvHD, that may be associated with pain, severe impaired function and poor quality of life (QoL) [1, 2].

The oral cavity is estimated to be involved in 45–83% of patients with cGvHD [1]. Oral cGvHD can develop at any oral or orofacial site and may present as mucosal lichenoid hyperkeratotic changes, ulcerations, redness, sensitivity/pain, mucoceles, salivary gland dysfunction, reduced mouth opening, and taste impairment (dysgeusia or hypogeusia) [1–6].

Human flavor perception is a complex entity that interacts with taste, smell, somatosensory signals (texture and temperature), and psychological elements [7]. Taste buds can distinguish five basic tastes: sweet and umami serve intake of high calorie food and pleasure of eating, bitter warns for unbecoming ingredients, and salt and sour are integrated in the homeostasis of the ionic and osmotic regulation [8]. Studies on altered taste function in the alloHSCT recipients reported a persistent, selective alteration in umami, salty and sweet taste by 47% of patients even years after transplant [4, 9].

Receptors of the olfactory nerve (cranial nerve I) are clustered in the small area in the back of the nasal cavity, facilitating the detection of/and response to odor molecules provided by chewing and swallowing. A heightened sensitivity to odors or a complete loss of smell can hinder nutritional intake by reducing the ability to taste and enjoy eating and drinking [10].

In addition to a reduced or a complete loss of smell, multiple factors could contribute to the development of taste alterations in alloHSCT recipients such as conditioning regimen-related toxicity, damage to taste buds by oral cGvHD-induced inflammation, neurotoxicity involving the cranial nerves VII, XI, and X, modifications of the oral microbiota, infections including dental diseases, poor oral hygiene, medication use, reduced salivary flow, and increased anxiety [11, 12].

Although there is some evidence suggesting taste and smell changes in alloHSCT recipients, the prevalence, and severity of these changes and their relation with oral cGvHD are largely understudied. In addition, impaired taste and smell function may lead to malnutrition and provoke feelings of disappointment and sadness that may have a significant negative impact on patient's global and oral health-related QoL (OH–QoL) [13, 14]. Therefore, the aim of this study is to identify the prevalence, nature, and severity of taste, and smell disturbances in patients visiting our oral GvHD clinic and to examine whether taste and smell disturbances are related to the presence and severity of oral mucosal cGvHD, hyposalivation and global, and OH-QoL.

Materials and methods

This cross-sectional study was conducted at the Department Oral and Maxillofacial Surgery of the Amsterdam University Medical Center, location AMC between February 2019 and December 2020. The study has been approved by the Institutional Medical Ethics Committee (NL69437.018.19). Written informed consent was received from all the participants. All patient data were anonymized before processing and stored in a secured database (Castor EDC, Amsterdam, The Netherlands).

Eligibility criteria

Patients who received an alloHSCT for a hematological malignancy at least 100 days ago and were referred because of oral cGvHD-related complaints were eligible for inclusion. In addition, patients had to have either manifestations of oral cGvHD or a history of cGvHD-related oral manifestations. Patients were excluded if they were current smokers, had pre-existing autoimmune disorders (Sjögren syndrome or lichenoid granulomatous disorders), neurodegenerative comorbidity (Parkinson's disease or Alzheimer's disease) or uncontrolled diabetes mellitus.

Oral examination

The oral cavity was examined clinically in order to verify the presence or absence of oral manifestations of cGvHD. All the oral examinations were performed by an experienced dentist specialized in diagnosing and managing oral complications in patients with cancer (JR–D). Mucosal changes were scored using the NIH oral cGvHD Activity Assessment Tool. This scoring system takes into account the severity and extent of erythema, lichenoid hyperkeratotic changes, ulcerations, and mucoceles with a total score ranging from 0 to 15 points [15]. Patients with scores of 0–2 were considered as having no oral cGvHD, whereas scores of 3–15 were considered indicative for the presence of oral cGvHD [16].

Questionnaires

Questionnaires assessing the gustatory sense and patient-reported oral GvHD (NIH), the quality of life (EORTC QLQ–C30), oral health-related quality of life (EORTC QLQ–OH15 and OHIP-14) were used.

Taste and smell addendum of the EORTC QLQ–C30 is designed to detect patient-reported changes of the sensitivity and the specificity of smell and taste, specifically with respect to the basic tastes of salt, sweet, sour, and bitter [17]. The items were rated on a 4-point Likert-scale: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much).

The NIH questionnaire records self-reported severity of oral cGvHD symptoms: dryness, pain, and sensitivity of the oral cavity at the worst moment over the past 7 days [15, 18]. These items are scored using a 11-point Likert-scale ranging from 0 (not existing) to 10 (the worst imaginable).

The EORTC QLQ–C30 is a validated global QoL questionnaire designed to be self-administered by patients with cancer [19]. The QLQ–C30 consists of multiple subscales: functional scales, symptom scales, and subscales addressing various symptoms (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact). All the items are scored using a 4-point Likert scale: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much). Global health status subscale is scored using a 7-point Likert scale, 1 ("very poor") to 7 ("excellent") [20].

The EORTC QLQ–OH15 is an addition to the EORTC QLQ–C30 that relates oral problems to OH-related QoL in patients with cancer [21]. The items were categorized in 6 subscales: OH–QoL score (8 items), information scale (2 items), scale regarding dentures (2 items), and three single items (sticky saliva/mouth soreness/sensitivity to food/drink). All the items are graded using a 4-point Likert scale: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much). The minimum score on this questionnaire (excluding the information on denture related questions) is: 11, the maximum score is 44. A higher score indicates a reduced oral health-related quality of life.

The Oral Health Impact Profile (OHIP-14) indicates the social impact of OH-related QoL over the past 30 days [22]. The items of the OHIP are divided into seven dimensions: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicaps. All the items are evaluated using a 5-point Likert scale: 1 (never), 2 (hardly ever), 3 (occasionally), 4 (fairly often), to 5 (very often). The minimum score of this questionnaire is: 14, and the maximum score is 70. A higher score indicates a reduced OH-related QoL.

Sialometry

Whole (un-)stimulated salivary flow rates and the salivary pH-values were assessed. Before the saliva measurements, the participants were requested to refrain from eating, drinking (other than water), and any oral hygiene practices for at least 30 min. Measurements were performed between 9:30 and 11:30 am. The procedure consisted of expectoration of all produced (un-)stimulated saliva, continuously for 5 min, into a pre-weighted plastic tube. During the stimulated salivary flow test, patients received a tasteless paraffine chewing gum to stimulate the salivary glands. Patients were asked not to talk and to swallow during the collection of both samples [23]. Salivary flow rates were determined in grams per minute (g/min). Severe hyposalivation was identified when the unstimulated salivary flow rate was below 0.1 g/min and/or the stimulated salivary flow rate was below 0.5 g/min [24].

Taste evaluation

The Burghart taste strips test (Medisense, Burghart Messtechnik, Wedel, Germany) evaluated the taste sensitivity of the oral cavity as a whole. The 16 taste strips are impregnated with four different flavors in different concentrations: sweet (0.05, 0.1, 0.2, or 0.4 g/ml sucrose), salty (0.016, 0.04, 0.1, or 0.25 g/ml sodium chloride), sour (0.05, 0.09, 0.165, or 0.3 g/ml citric acid) or bitter (0.0004, 0.0009, 0.0024, and 0.006 g/ml quinine hydrochloride). All the strips were offered in a fixed order to every patient, according to the protocol. The patients were asked to place the strip on the tongue and to close the mouth and choose one of the four answer options (sweet, sour, bitter, and salt). If they did not taste anything, flavorless was reported. Hypogeusia was identified if the overall score was lower than 9 (out of 16) [25].

Smell evaluation

For testing the olfactory performance of the patients, the validated smell test Sniffin' Sticks (Burghart Messtechnik, Wedel, Germany) was used [26]. This diagnostic screening test

allows for differentiating the inability in the detection of odors (anosmia) and a reduced ability to detect odors (hyposmia) from a common smell sense (normosmia). Odor pens containing 12 different all-day aromas were used, for example, lemon, coffee, and leather. Patients were asked to place the pen straight under their nose (at a distance of 2 cm) for 3–4 s. They were offered a card with four answers and had to pick the answer which described the presented odorant the best. Anosmia was identified if the overall score was below 6 (out of 12) and hyposmia if the score was between 6 and 9 (out of 12).

Statistical analysis

Relations between oral GvHD, taste and smell disorders, salivary flow and QoL were calculated using Fisher–Freeman–Halton exact test, the Mann–Whitney *U*-test and the Kruskal–Wallis test. The IBM SPSS Statistics software package (IBM SPSS Statistics version 27, IBM, Armonk, NY) was used to perform all the data analyses. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

In total, 45 recipients treated with allogeneic HSCT (44.4% women: 55.6% men) were enrolled in this study (Table 1). The mean age of the participants was 53 years (±14.7), the most commonly encountered diagnosis was acute myeloid leukemia (30.8%). Patients received an alloHSCT at least 100 days ago. One patient was transplanted more than 10 years ago, but most patients received an alloHSCT between 1 and 3 years ago. Conditioning regimens and other medications were tailored to the diagnosis and specific patients' needs. At the time of their assessment in this study, patients used on average 11.5 (±5.5) different medications, namely, antiviral, antifungal, antibacterial, and immune suppressant medications. All patients used at least one drug that potentially could have affected their taste [27, 28].

TABLE 1 Patient and treatment characteristics.

Variables	*n* (%), Mean ± SD
Age (years)	53.27 ± 14.727
Gender	
Female	20 (44.4%)
Male	25 (55.6%)
Diagnosis	
Acute myeloid leukemia	14 (30.8%)
Myelodysplastic syndrome	7 (15.4%)
Angioimmunoblastic T-cell lymphoma	3 (6.6%)
Mantle cell lymphoma	3 (6.6%)
Acute lymphocytic leukemia	2 (4.4%)
Chronic lymphocytic leukemia	2 (4.4%)
Sickle cell anemia	2 (4.4%)
Multiple myeloma	2 (4.4%)
Non hodgkin lymphoma	2 (4.4%)
Other	8 (17.6%)
Conditioning regimen	
Myeloablative	11 (24.4%)
Non-myeloablative	14 (31.1%)
Reduced intensity	20 (44.4%)
Time since transplantation (years)	
<1	12 (26.7%)
1–3	19 (42.2%)
3–5	8 (17.8%)
>5	6 (13.3%)
Stem cell source	
Peripheral progenitor cell	34 (75.6%)
Bone marrow	11 (24.4%)
Number of medications taken that could potentially affect taste	11.5 (± 5.5)

TABLE 2 Presence and severity of oral mucosal cGvHD scored by the Oral cGvHD Activity Assessment Tool [15].

	Not present	Mild	Moderate	Severe
Erythema	29 (64.4%)	10 (22.2%)	1 (2.2%)	5 (11.1%)
Lichenoid	27 (60.0%)	7 (15.6%)	6 (13.3%)	5 (11.1%)
Ulcers	40 (88.9%)		4 (8.9%)	1 (2.2%)
Mucoceles	39 (86.7%)	3 (6.7%)	3 (6.7%)	0

Oral cGvHD

All the patients had either manifestations of oral cGvHD at the time of assessment in this study or had a recent history of oral cGvHD manifestations diagnosed and treated in our clinic. At the oral examination performed for this study, 24 patients (53.3%) had manifestations of oral mucosal cGvHD. Lichenoid changes (40%) and erythema (36%) were most commonly present and their extent/severity scored highest at the NIH Activity Assessment scoring instrument in Oral cGvHD Activity Assessment Tool. Ulcerations (11%) and mucoceles (13%) manifested less frequently and were mild-to-moderate in the most patients (Table 2). None of the patients had manifestations of mucosal infections.

With respect to self-reported severity of oral cGvHD symptoms over the last 7 days, patients reported the highest scores concerning oral dryness (5.4 ± 2.9), followed by sensitivity of the oral mucosa during food and drink consumption (4.0 ± 3.1) and oral pain (2.5 ± 3.0). Patients with objectively assessed oral manifestations of mucosal cGvHD

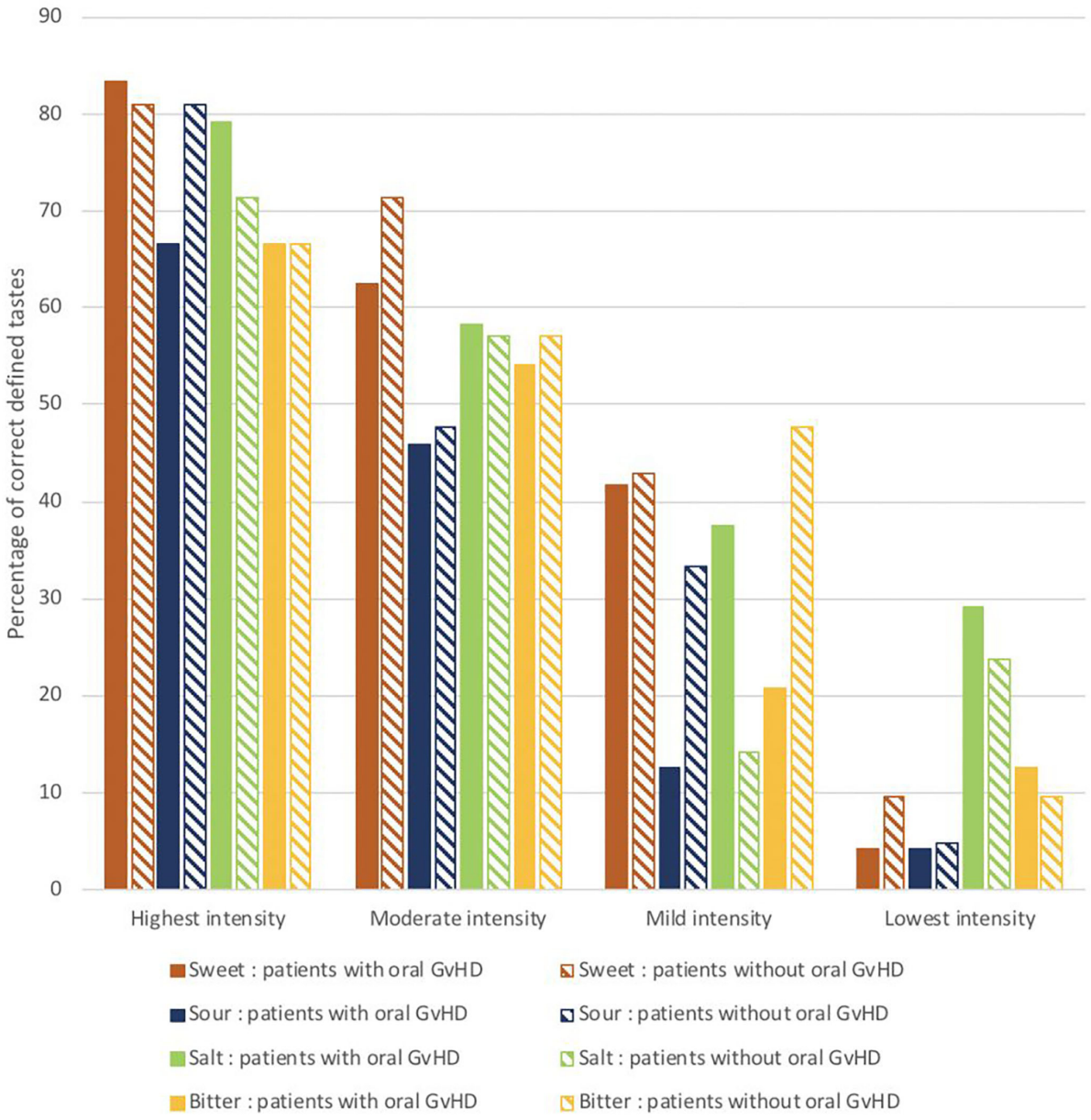

FIGURE 1
The percentages of correctly identified tastes at different test concentrations in the clinical taste evaluation test conducted in patients with oral mucosal cGVHD vs. those without oral mucosal cGVHD ($N = 45$).

experienced more oral pain (3.7± 3.1) compared with patients in which oral manifestations of mucosal cGvHD were not observable at the time of the study assessment (1.2 ± 2.1) (Mann–Whitney U-test, $p = 0.004$). Patients with oral mucosal cGvHD manifestations (4.9 ± 2.9) also noticed more oral sensitivity compared with patients without oral manifestations (2.9 ± 3.1) (Mann–Whitney U-test, $p = 0.012$). There was no difference in the reported oral dryness between patients with and without oral mucosal cGvHD (Mann–Whitney U-test, $p > 0.05$).

Taste

A reduced ability to taste (hypogeusia) was assessed in the majority of patients (68.9%). Although most patients were able to detect all the four tastes: sweet, salt, bitter, and sour at the highest test intensity, their ability to detect tastes decreased with the reduction of the concentration on the test strips (Figure 1). In none of the patients taste ability was completely absent (ageusia).

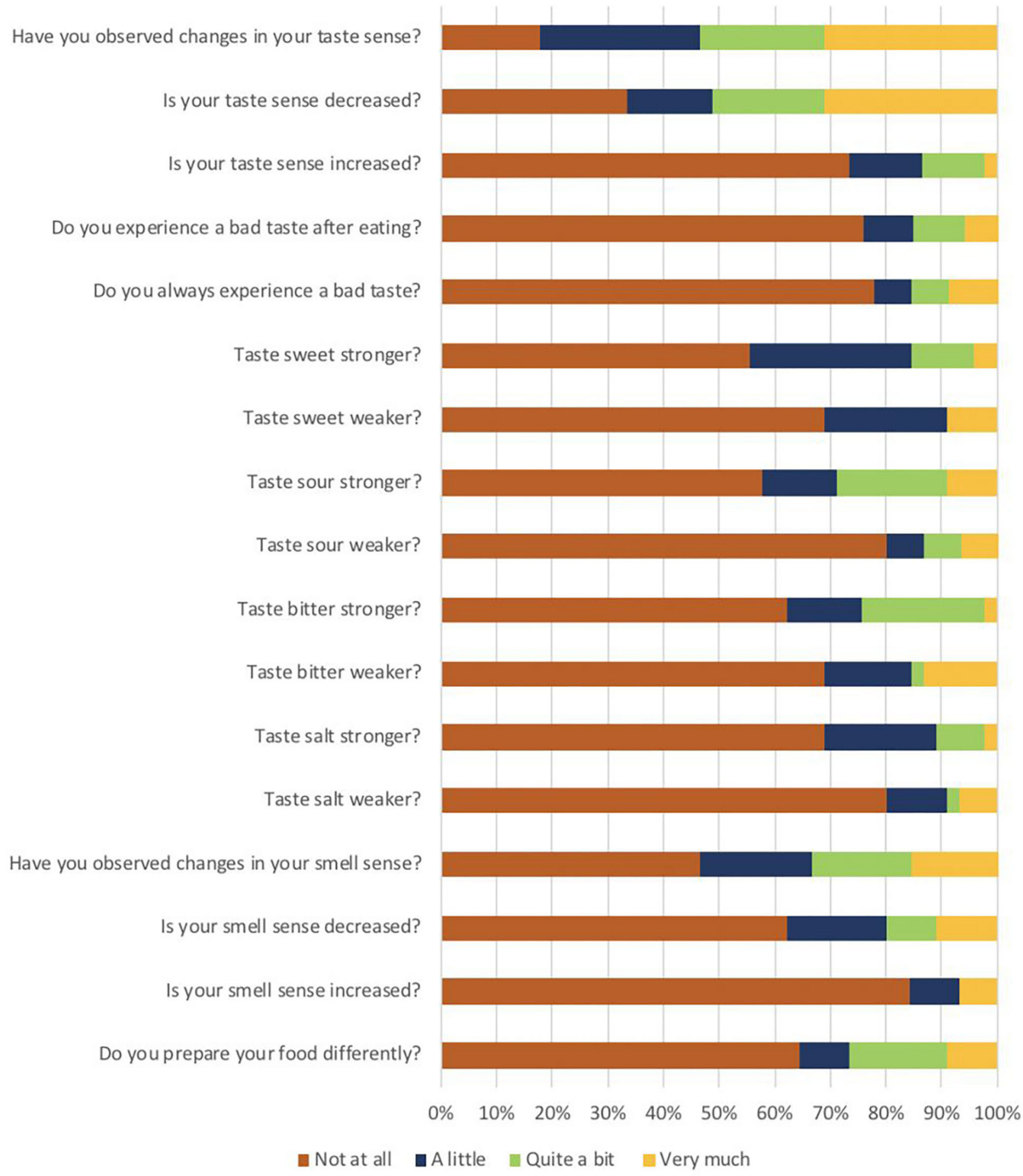

FIGURE 2
Distribution of the responses to the taste and smell addendum of the EORTC QLQ–C30 ($N = 45$).

From all the patients, 31.1% reported severe taste alterations and 22% experienced taste alterations "quite a bit", this was most often a decrease in taste sensitivity. An increased taste sensitivity was reported by 13.3% of patients. Bitter and sour were reported as being more intensively experienced by 24–29% of patients (Figure 2).

As suggested by the discrepancy in objective and patient-reported taste outcomes, patients with hypogeusia were not

TABLE 3 Distribution of oral mucosal cGvHD and hypogeusia (objective-reduced smell ability).

		Hypogeusia	Normogeusia	Total	Fisher's exact test (2-sides)	*P*-value
GvHD	**Present**	19	5	24		
	Not present	12	9	21	0.196	0.111
	Total	31	14	45		

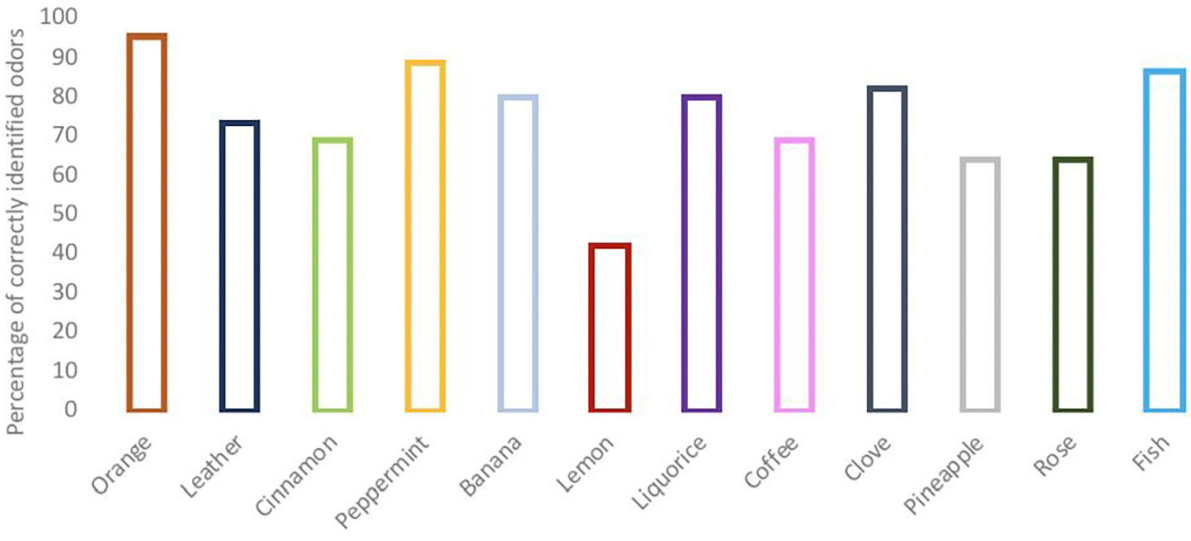

FIGURE 3
Outcomes of the clinical smell evaluation test.

always aware of their altered taste sense. Not all noticed reduced taste sense.

There was no significant difference in ability to taste when comparing patients with and without oral mucosal cGvHD (Table 3, Fisher–Freeman–Halton exact test, $p > 0.05$).

Smell

Smell disturbances were found in 18 patients (40%); of which 28.9% had a reduced ability (hyposmia) and 11.1% had a complete inability (anosmia) to detect the odors tested. The most commonly correct identified odor was orange, followed by peppermint. Lemon odor was the least often identified correctly (Figure 3).

In total, 15.6% of patients reported having "very much" smell alterations. In total, 17.8% experienced that the smell has changed "quite a bit" and 20% experienced "a bit". Part of the patients (11.1%) reported a severe overall reduction in their smell sensitivity, whereas 6.7% experienced that their ability to smell had increased "very much" (Figure 2).

Most patients with objectively assessed anosmia or hyposmia also reported a disturbance in their sense of smell. They experienced a reduced sensitivity of their smell sense (Fisher–Freeman–Halton exact test, $p = 0.002$) or an alteration in smell perception more often, compared with patients with a normal smell sense (Fisher–Freeman–Halton exact test, $p = 0.026$). There was no difference in smell sense between patients with or without manifestations of oral mucosal GvHD (Table 4, Fisher–Freeman–Halton exact test, $p > 0.05$).

Sialometry and xerostomia

About 85% of patients had a normal level of (un)stimulated salivary flow. The pH of the (un-) stimulated saliva was on average slightly below the normal values (Table 5). The sensation of oral dryness (xerostomia) was reported by 75.6% of patients (EORTC QLQ–OH15), of which 15.6% reported "a bit" oral dryness, 33.3% reported "quite a bit", and 26.7% reported "very much" oral dryness. There was no significant association between categories of (un)stimulated salivary flow and taste

TABLE 4 Relation between oral mucosal cGvHD and smell sense.

		Anosmia	Hyposmia	Normosmia	Total	Fisher-Freeman-Halton exact test	*P*-value
GvHD	**Present**	2	8	11	21		
	Not present	3	5	16	24	1.668	0.463
	Total	5	13	27	45		

TABLE 5 Salivary flow classification.

	Stimulated			Unstimulated		
	N (%)	Mean ± SD	Ref. Value	N (%)	Mean ± SD	Ref. Value
Hyposalivation	7 (15.6%)		**<0.5 ml/min**	6 (13.3%)		**<0.1 ml/min**
Normal	38 (84.4%)		**>0.5 ml/min**	39 (86.7%)		**>0.1 ml/min**
pH		6.9 ± 0.5	**7.0–8.0 pH**		6.2 ± 0.3	**6.8–7.5 pH**

TABLE 6 Distribution of taste and smell disorders and salivary flow.

	Hyposalivation	Normal salivary flow	Total	Fisher-Freeman-Halton exact test	*P*-value
Unstimulated					
Hypogeusia	6	25	31	-	0.156
Normogeusia	0	14	14		
Total	6	23	45		
Anosmia	1	4	5	0.908	0.832
Hyposmia	1	12	13		
Normosmia	4	23	27		
Total	6	39	45		
Stimulated					
Hypogeusia	5	26	31	–	1.000
Normogeusia	2	12	14		
Total	7	38	45		
Anosmia	2	3	5	2.701	0.307
Hyposmia	1	12	13		
Normosmia	4	23	27		
Total	7	38	45		

and smell disorders (Table 6, Fisher–Freeman–Halton exact test, $p > 0.05$).

Quality of life

In general, patients were moderately positive about their overall QoL at least 100 days after transplantation (EORTC QLQ–C30: 67.2 ± 24.6). However, on average patients reported a decreased OH-related QoL of 24.0 ± 16.0 (EORTC OH-15). Most reported problems included soreness in their mouth, sores in the corners of their mouth, a dry mouth, sensitivity to food and drink, taste alterations, and problems eating solid foods (Table 7). There were no differences in OH-related QoL between patients with and without taste disorders, smell disorders, or manifestations of oral mucosal cGvHD ($p > 0.05$).

The complaint most often reported by using the OHIP-14 questionnaire was oral pain (Table 7). Social disability assessed by the OHIP-14 was significantly more often reported by the patients with oral mucosal GvHD compared with those without these manifestations (Mann–Whitney *U*-test, $p = 0.030$).

TABLE 7 Differences between (oral health related) quality of life (sub)scales and taste/smell.

	Subscales	Taste					Smell					cGvHD			
		Overall	Hypogeusia	Normogeusia			Anosmia	Hyposmia	Normosmia			Not present	Present		
		Mean ± SD	Mean ± SD	Mean ± SD	Coefficient[a]	p-value	Mean ± SD	Mean ± SD	Mean ± SD	Coefficient[b]	p-value	Mean ± SD	Mean ± SD	Coefficient[a]	p-value
EORTC QLQ-C30	Global health status/QoL[c]	67.2 ±24.6	69.6 ± 26.0	61.9 ± 21.1	163.0	0.186	63.3 ± 32.6	70.5 ± 16.5	66.4 ± 27.0	0.066	0.969	71.8 ± 20.7	63.2 ± 27.5	210.0	0.342
EORTC QLQ-OH15	Oral health-QoL[c]	24.0 ± 16.0	25.7 ± 16.7	20.2 ± 14.2	180.5	0.377	25.8 ± 18.0	21.5 ± 10.7	24.8 ± 18.1	0.237	0.888	19.6 ± 14.6	27.8 ± 16.6	182.0	0.112
	Sticky saliva[d]	22.2 ±33.3	23.7 ± 36.7	19.0 ± 25.2	215.0	0.948	20.0 ± 44.7	18.0 ± 25.9	24.7 ± 35.3	0.440	0.802	22.2 ± 33.9	22.2 ± 33.6	251.5	0.997
	Sensitivity to food and drink[d]	40.7 ±33.2	45.2 ± 35.0	31.0 ± 27.6	168.5	0.235	46.7 ± 44.7	38.5 ± 32.9	40.7 ± 32.5	0.174	0.917	41.3 ± 37.9	40.3 ± 29.5	249.0	0.943
	Sore mouth[d]	48.1 ±37.9	49.5 ± 40.3	45.2 ± 33.6	207.0	0.806	46.7 ± 50.6	43.6 ± 37.0	50.6 ± 37.4	0.339	0.884	47.6 ± 42.9	48.6 ± 34.0	242.5	0.822
OHIP-14	Functional limitations[d]	4.2 ± 2.3	4.4 ± 2.3	3.6 ± 2.2	178.0	0.329	5.6 ± 3.6	3.5 ± 2.0	4.3 ± 2.0	2.417	0.308	3.7 ± 2.5	4.6 ± 2.0	179.0	0.086
	Physical pain[d]	5.0 ± 2.5	5.1 ± 2.4	4.8 ± 2.6	200.0	0.681	6.0 ± 2.7	5.5 ± 2.8	4.6 ± 2.3	1.954	0.387	4.2 ± 2.0	5.7 ± 2.7	173.0	0.069
	Psychological discomfort[d]	3.1 ± 1.8	3.4 ± 2.1	2.6 ± 1.1	181.5	0.326	3.2 ± 1.8	3.2 ± 1.8	3.1 ± 1.9	0.049	0.972	2.7 ± 1.2	3.5 ± 2.2	207.0	0.249
	Physical disability[d]	4.3 ± 2.4	4.4 ± 2.6	4.1 ± 2.1	209.0	0.848	5.2 ± 3.0	4.8 ± 2.5	3.9 ± 2.3	1.842	0.408	4.1 ± 2.6	4.5 ± 2.3	215.0	0.390
	Psychological disability[d]	2.8 ± 1.2	2.9 ± 1.4	2.6 ± 0.9	197.0	0.600	2.4 ± 0.9	2.8 ± 1.1	2.9 ± 1.3	0.787	0.690	2.6 ± 1.2	3.0 ± 1.3	207.5	0.255
	Social disability[d]	2.8 ± 1.3	2.9 ± 1.5	2.6 ± 0.9	209.5	0.824	2.8 ± 1.8	2.9 ± 1.3	2.8 ± 1.4	0.589	0.767	2.4 ± 0.9	3.3 ± 1.6	170.5	0.030*
	Handicap[d]	2.9 ± 1.5	3.0 ± 1.6	2.8 ± 1.2	208.0	0.818	3.8 ± 3.0	3.2 ± 1.3	2.6 ± 1.1	1.882	0.394	2.6 ± 1.1	3.3 ± 1.7	189.5	0.106

[a]Mann-Whitney U-test.
[b]Kruskal-Wallis H-test.
*p-value is significant <0.05 level (2-tailed).
[c]higher scores (EORTC: max. 100, OHIP: max. 10) denote an improved QoL (lower symptom burden).
[d]higher scores (EORTC: max. 100, OHIP: max. 10) denote an impairment in QoL (higher symptom burden).

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Discussion

The purpose of this study was to identify the prevalence, nature, severity of taste, and smell disturbances in patients with oral cGvHD and to examine whether taste and smell disturbances are related to manifestations of oral mucosal cGvHD, salivary flow, and global or OH-related QoL.

Reduced ability to taste was identified in 68.9% of patients, although not all the patients reported having reduced taste. Reduced smell ability was less common, 40% of patients had hyposmia (28.9%) or anosmia (11.1%). Most of the patients with hyposomia/anosmia also reported having disturbed smell. The presence of taste and smell disturbances were equally divided between patients with and without manifestations of oral mucosal cGvHD, which is in accordance with the findings of others [4]. Also, no significant association could be identified between taste sense and salivary flow. Taste and smell disturbances seemed not to have a significant negative impact on patients' overall and OH-related QoL.

The prevalence of objectively assessed hypogeusia to perceive basic flavors in this study (68.9%) is in line with the 66.6% prevalence reported by Ferreira and coworkers during the neutropenic phase after HSCT [29]. Our study, in which participants were evaluated at least 100 days post-transplant, suggests that patients may suffer from hypogeusia far beyond the neutropenic phase. Patient-reported taste disturbances may fade away within 3 years after HSCT [4, 9]. Patients in this cross-sectional study experienced taste problems from 3 months up to over 10 years after transplantation. Interestingly, some patients with an objective reduced taste ability were not aware of their reduced taste, indicating that they may have adapted to having reduced taste.

Taste and smell receptor cells have a short lifespan from 7 up to 10 days, making them vulnerable to the toxic effects of the conditioning regimen consisting of chemotherapy and/or radiotherapy [30, 31]. Radiation-related taste disturbances because of the altering the taste pores structure or thinning the papilla epithelium have not been reported for doses under 20 Gy administered to the head and neck region. Patients in this study received a total body irradiation dose of 10 Gy at maximum. Therefore, the effect of radiation therapy to taste and smell disturbances in our study was likely negligible.

It is interesting to note that one of the best preserved tastes in this study was the bitter taste, which is believed to evolve for early detection of potentially poisoning substances [32]. Antineoplastic drugs, such as cyclophosphamide, could play a role by disrupting taste sensation conduction resulting in specific taste sensations without stimulating the taste receptors or requiring the presence of the corresponding flavor molecules [31, 33]. Also, commonly used medications, such as antimicrobials, corticosteroids, and psychoactive drugs, could adversely influence the sense of taste and smell, either by altering ability to taste and smell, or by producing perceptual distortions, or phantom sensations because of the neurotoxity [34]. The diversity and amount of drugs used by our patients (over a 100 types) used made it impossible to determine their impact on taste and smell.

All patients included in this study had oral manifestations of mucosal cGvHD at the time of evaluation or a history of recently having such manifestations diagnosed in our oral GvHD clinic. Oral mucosal manifestations of cGvHD may vary significantly over time (even over several weeks) as a result of multiple factors, namely, therapy-related factors (i.e., immunosuppressive, other medications) and patient-related factors (i.e., infections, stress/anxiety that may trigger GvHD, adherence to therapy). Oral mucosal cGHVD manifestations were mostly mild-to-moderate in nature. As observed by us and others, patients may still report multiple oral cGvHD-related complaints in the absence of visible manifestations [35, 36]. According to Sato and coworkers, patient-reported oral cGvHD is a significant predictive factor for taste disorders in alloHSCT recipients 3 months or more post-transplant [9].

The salivary glands may also be affected by cGvHD, resulting in hyposalivation. Changes in biochemical and immunological salivary components are associated with the reduced salivary function after alloHSCT, which may reduce the ability to taste and oral/mucosal health [37]. We did not find taste/smell disturbances to be related to hyposalivation, but prospective studies with larger numbers of patients are needed.

Scordo et al. reviewed studies directed to taste alterations following HSCT and presented potential pathobiological mechanisms [38]. Although cells and tissues crucial for taste and smell perception may be damaged by the GvHD-associated inflammation, there is no clear understanding yet of how cGvHD may be linked to taste and smell dysfunction. To shed more light on the etiology and pathobiology of taste and smell alterations, a holistic approach aiming at identifying potential cellular targets and shared mechanisms affecting multiple organs and sites of patients with cGvHD, namely, the oral and nasal epithelium, lungs, kidneys, and liver may be helpful. Moreover, recent studies on COVID-19-related dysgeusia and anosmia may also provide clues for a better mechanistic understanding. Interestingly, the renin–angiotensin system has been proposed to be a key player in the taste sensitivity modulation, warranting further investigation [39].

Dominant drivers in patients' food choice are taste and smell. However, eating is more than just the ingestion of food. Eating has an important role in cultural and social identity, religion, and family memories. As a consequence, taste/smell disorders could not only lead to malnutrition and weight loss, but also impair social interactions resulting in reduced QoL [6]. This study identified a decreased oral health related quality of life. However, we could not identify a significant difference between patients with and without taste and smell disorders using the EORTC-15 and OHIP-14. In general, patients with GvHD in this study were able to adjust their lifestyle to the limitations

of their current health state and appreciate their new life after transplantation. However, they reported a negative impact of oral cGvHD on their social life. In this study, the focus was on oral cGvHD, not taking into account GvHD at other body sites or any comorbidities which may have negatively influenced overall QoL.

At present, available supportive care interventions to ameliorate taste disturbances are scarce and there is only limited evidence for their efficacy. Interventions include dietary counseling, amifostine, zinc supplementation, and photobiomodulation [31, 40, 41]. Thus, developing effective approaches for the prevention and treatment of these problems is an urgent clinical need.

Taken together, our results indicate a high prevalence of hypogeusia, whereas smell disturbances were less common but still represent a significant clinical problem. Future work is necessary to better understand the prevalence and pathogenesis of taste and smell disturbances, and their impact on patients' physical and mental well-being. Longitudinal studies are required in which significant numbers of patients stratified for age and gender, oral hygiene and disease, cancer diagnosis, cancer treatment before conditioning therapy, stem cell source, presence of any oral, or non-oral cGVHD are followed before and long term after transplant to evaluate patterns of taste and smell disturbances and potential risk factors. As the ability to taste umami was reported to be reduced, testing should include umami [9]. Structurally evaluating taste and smell ability could contribute to gaining awareness of this problem among clinicians and draw more attention toward the need of developing efficacious supportive care options tailored to the specific needs of the patients.

Conclusion

Taste and smell disturbances are prevalent among the alloHSCT recipients even a considerable time post-transplant. Most patients reported a decreased OH-related QoL, but specific impact of taste and smell disturbances remains to be elucidated.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by NL69437.018.19. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MB contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, and drafted the manuscript. JR-D contributed to conception, data acquisition and critically revised the manuscript. MH contributed to conception, design and critically revised the manuscript. FR contributed to conception, data interpretation and critically revised the manuscript. AL contributed to conception, design, contributed to analysis and data interpretation, drafted and critically revised the manuscript. 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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Transfer learning approach based on computed tomography images for predicting late xerostomia after radiotherapy in patients with oropharyngeal cancer

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Background and purpose: Although the latest breakthroughs in radiotherapy (RT) techniques have led to a decrease in adverse event rates, these techniques are still associated with substantial toxicity, including xerostomia. Imaging biomarkers could be useful to predict the toxicity risk related to each individual patient. Our preliminary work aims to develop a radiomic-based support tool exploiting pre-treatment CT images to predict late xerostomia risk in 3 months after RT in patients with oropharyngeal cancer (OPC).

Materials and methods: We performed a multicenter data collection. We enrolled 61 patients referred to three care centers in Apulia, Italy, out of which 22 patients experienced at least mild xerostomia 3 months after the end of the RT cycle. Pre-treatment CT images, clinical and dose features, and alcohol-smoking habits were collected. We proposed a transfer learning approach to extract quantitative imaging features from CT images by means of a pre-trained convolutional neural network (CNN) architecture. An optimal feature subset was then identified to train an SVM classifier. To evaluate the robustness of the proposed model with respect to different manual contouring practices on CTs, we repeated the same image analysis pipeline on "fake" parotid contours.

Results: The best performances were achieved by the model exploiting the radiomic features alone. On the independent test, the model reached median AUC, accuracy, sensitivity, and specificity values of 81.17, 83.33, 71.43, and 90.91%, respectively. The model was robust with respect to diverse manual parotid contouring procedures.

Conclusion: Radiomic analysis could help to develop a valid support tool for clinicians in planning radiotherapy treatment, by providing a risk score of the toxicity development for each individual patient, thus improving the quality of life of the same patient, without compromising patient care.

KEYWORDS

deep learning, xerostomia, oropharyngeal cancer, CT images, CNN—convolutional neural network

Introduction

Oropharyngeal squamous cell carcinomas (OPCs) are tumors that could be located in the soft palate, the pharyngeal wall, the tonsils, or the base of tongue (1).

Treatment-related toxicity is a significant problem due to the close proximity of the tumor mass to normal tissues and organs. Modern radiotherapy techniques, such as volumetric modulated arc therapy (VMAT) or intensity modulation radiotherapy (IMRT), have overcome the conventional techniques, in attempting to reduce the toxicities induced by radiation (2).

Nonetheless, RT treatments are still associated with severe toxicity, including dysphagia, mucositis, and xerostomia. In particular, xerostomia, i.e., dryness of the oral cavity caused by reduced or absent saliva flow, is common late toxicity that negatively affects patients' quality of life either by impairing speech or swallowing or even chewing (3). This toxicity occurs especially when median doses above 26 Gy are applied to both parotids with the volume irradiated above a patient-individual threshold which is probably the most relevant predictive parameter (4, 5).

An accurate and personalized prediction of radiation-induced toxicity could support clinicians in planning an optimal treatment path. Although radiation-induced xerostomia mainly results from damage to the major salivary glands that are usually included in radiation fields, other factors are notoriously associated with the likelihood of developing toxicity in the parotids, such as parotid volume, parotid eccentricity heterogeneity, salivary gland density, amount of predisposed fat, etc. Recently, several radiomic-based models have been proposed for the prediction of late xerostomia in patients with head and neck cancer, also achieving promising performances. They showed that there is a personal risk factor for developing toxicity related to the texture of the organs at risk (OARs). Typically, most of these methods are based on the designing of the so-called handcrafted features, which have a physical meaning of the measure being considered. More recently, cutting-edge deep learning models have been used to automatically extract more sophisticated and higher-level hierarchical characteristics (6–9). These features can be lost in interpretation because they are extracted from images that undergo many processing and convolution steps, but allow the evaluation of finer and informative characteristics that cannot be quantified on the original image. Models trained on radiomic features extracted from computed tomography (CT)/magnetic resonance imaging (stocktickerMRI) and combined with clinical and dose characteristics have recently been proposed for predicting toxicity in head and neck tumors (10–14).

To the best of our knowledge, the xerostomia predictive models proposed in the literature are designed for head and neck tumors which include several locations anatomical sites of the primary tumor. There is a lack of models tailored for patients with OPC (15, 16). Compared to treatment in other areas of the head and neck, the oropharynx represents the most frequently treated site for which the definition of a plan that preserves the functionality of the parotid is more complex (17, 18). Therefore, in this work, we proposed a transfer learning approach for the definition of an accurate radiomic-based model trained on pre-treatment CT with the goal of predicting late xerostomia in patients with OPC. The radiomic features were extracted by using a pre-trained convolutional neural network (CNN) and subsequently processed by different state-of-the-art machine learning algorithms (19–21).

We also evaluated the predictive power of dosimetric parameters and clinical features, both separately and in conjunction with radiomic features. Furthermore, since the contouring of both OARs and the target is an operator-dependent process, we have investigated the strength of the model with respect to the manual contouring processes of the

parotid. The results obtained were achieved on a multicenter dataset and validated both in cross-validation and on an independent set.

Materials and methods

Enrolled patients and collected data

For this study, we performed a multicenter data collection. We enrolled 61 patients from Apulia, Italy, out of which 32 patients were referred to Istituto Tumori "Giovanni Paolo II" in Bari (Apulia, Italy), 15 patients to Casa Sollievo della Sofferenza Hospital in San Giovanni Rotondo (Apulia, Italy), and 14 patients to "Monsignor Raffaele Dimiccoli" Hospital in Barletta (Apulia, Italy). Patients were enrolled according to the following criteria:

- histologic diagnosis of squamous cell carcinoma of the oropharynx
- treatment with primary radiotherapy, with or without concomitant chemotherapy or cetuximab,
- follow-up period (with the evaluation of xerostomia) of at least 3 months,
- availability of pre-treatment CT.

All patients were consecutively included in a data registration program as part of routine clinical practice. The study was approved by the Institutional Review Board of Istituto Tumori "Giovanni Paolo II" Bari, Italy (Approval Code: 24269/21). All the centers involved in the study signed a data transfer agreement.

The collected clinical features were: age at diagnosis, tumor size (T: T1a, T1b, T1c, T2, T3, T4), lymph nodes stage (N: 0, 1, 2, 3), surgery (Yes/NO), induction chemotherapy (induction CHT: Yes, No), concurrent CHT during RT (concurrent CHT: Yes, No), platinum-based CHT (Yes/NO), weight pre-RT (Kg), smoking history (Yes, No, Ex), and alcohol history (Yes, No, Ex). Hereinafter, this dataset consisting of 11 characteristics is referred to as the *Clinical Feature Set* (abbr. *Clin_FS*).

Among the enrolled 61 patients, 34 patients were treated with the VMAT RT technique, while 27 patients were treated with IMRT RT technique. All treatment plans included a simultaneous integrated boost and tried to spare a dose to the parotid glands without compromising the dose to the target volumes. For both parotids, the mean dose (left and right mean dose), volume receiving 20 and 40 Gy of radiation (left and right V20, left and right V40), and dose received by 20 and 40% of the volume (left and right D20, left and right D40) were extracted from dose-volume histograms (DVHs). **Figure 1** shows the contouring of the parotids and how the dose map was overlaid to illustrate the calculation of the dose features set. Previous studies have shown that these dose features were the most important parameters in the prediction of long xerostomia after RT (22). Hereinafter, this dataset consisting of 10 dose features is referred to as the DVH Feature Set (abbr. DVH_FS).

Moreover, for each patient, a planning pre-treatment CT was acquired and used to extract radiomics features, as described in the following section.

Radiomic feature extraction

All pre-treatment CT images were acquired at the time of simulation, prior to the beginning of the treatment. Pre-treatment CT was used for contouring and RT planning. All CT images were acquired using dedicated and customized immobilization and reproducibility systems (SIRs) (versaboard and 9-point thermoplastic mask). The pre-treatment CT series is generated by an area subtended between the keel bifurcation and the vertex of the head, using an acquisition spiral with a thickness of 3 mm with pitch equal to 1 (contiguous scans), 120 kV, and 350 mAs. The FOV used is the maximum one (600 mm) with a standard brain acquisition filter and a 512 $\times$ 512 matrix.

The parotids are contoured by expert radiotherapists of the involved Institutes. The parotids were then automatically segmented by extracting a binary mask for the structures of interest. For each patient, radiomic features were extracted by a transfer learning approach from both left and right parotids. Transfer learning approach is usually used when relatively small-size datasets are analyzed. Specifically, we made use of the high-performing pre-trained CNN, called AlexNet, as a feature extractor. AlexNet is a CNN with eight deep layers (23, 24). It has previously been trained on more than a million images to solve image classification tasks. Such a network constructs a hierarchical representation of input images: deeper layers contain higher-level features, constructed using the lower-level features of earlier layers.

The knowledge learned by the network during the training phase was here transferred to our images to extract features useful to train a classification model for predicting late xerostomia. Since AlexNet requires an image input size of 227-by-227, parotids segmentation has previously been resized to patches of this size to be given as input to the network. The radiomic features were extracted from planning DICOM files.

In this work, we extracted features from the "*pool1*" layer of the network architecture which corresponds to the first pooling layer. The "*pool1*" layer had an output with dimensions of 27 $\times$ 27 $\times$ 96 that was flattened to a single 69984-length features vector. The "*pool1*" layer is one of the initial layers of the network. Thus, the corresponding extracted features are low-level features, namely, representations of local details of an image, such as edges, dots, and curves. We extracted the features not directly from a convolution layer that returns the feature

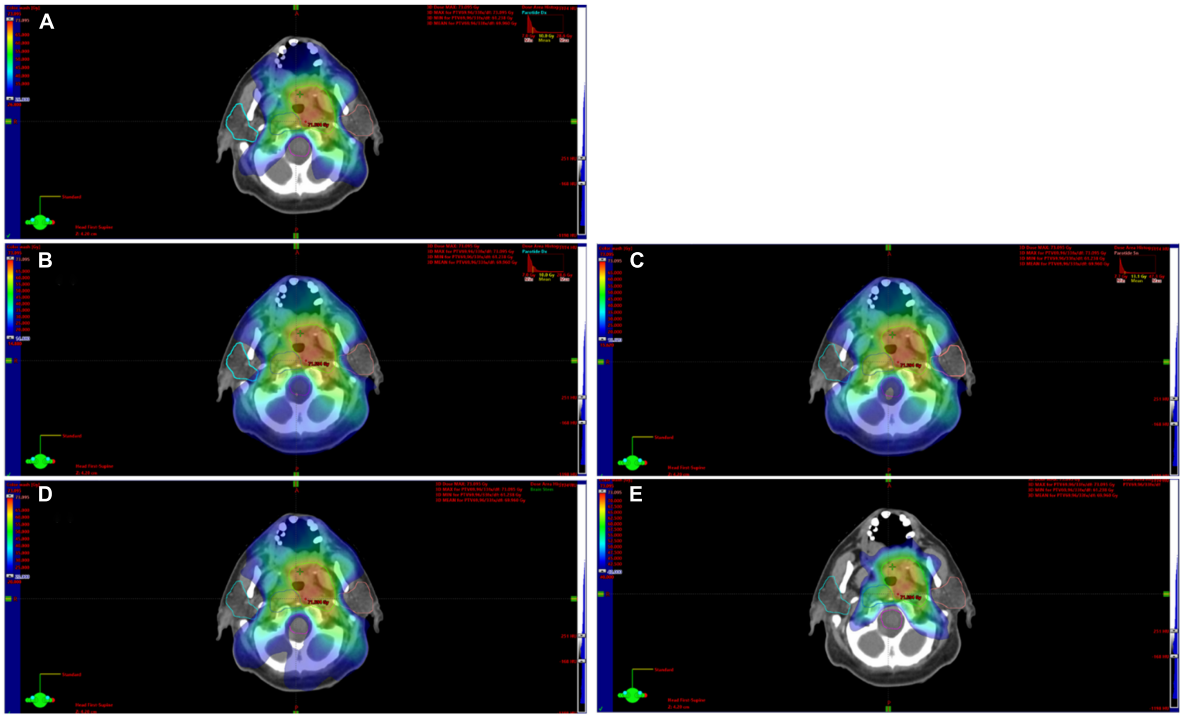

FIGURE 1
Contouring of the parotids on CT images and the related dose map. In this explanatory case, both the left and right parotid showed a D20 equal to 26.8 Gy **(A)**. The D40 of the right parotid was equal to 14.88 **(B)** the left one was 15.62 **(C)**. Panels **(D,E)** show the volume covered by an isodose of 20 and 40 Gy, respectively.

maps but after the application of pooling that, as well-known in deep learning theory, makes features invariant to truncation, occlusion, and translation (25).

The CT image of each patient is made up of a different number of 2D slides. From each slide, radiomic features were extracted by transfer learning approach, i.e., using a pre-trained network. As a result, several vectors of radiomic features, as many as the number of slices that make up the CT, are associated with each patient. To obtain only one vector radiomic feature in correspondence to each single patient, we computed the maximum value of each feature. Hence, the final vector was composed of the maximum values for each feature.

Although multicenter studies are necessary to demonstrate the potential clinical value of radiomics as a prognostic tool, the variability factors introduced by scanner models, acquisition protocols, and reconstruction settings need particular attention. Indeed, it is well-known that radiomic characteristics are very sensitive to these factors. We then applied a statistical harmonization method called ComBat which was first developed to treat the "batch effect" in gene expression microarray data and is also effectively used in radiomics-based studies (26–28).

During the analysis and evaluation of the collected data, a discrepancy was found in the contouring of the volumes of interest (targets and OARs) and the related geometric expansions of the radiotherapy planning target volume (PTV) which may depend on the extent of the disease, on partial discretion within the expansion limits defined by the guidelines and the type of pre-treatment checks adopted by the various centers (29–32).

In order to evaluate the robustness of the proposed model with respect to different manual contouring practices, we repeated the image analysis pipeline on "fake" parotid contours. To obtain these "fake" parotid contours, we changed the contour of the segmented parotids from each of the three centers, called center 1, center 2, and center 3, by applying dilation or erosion processes by 10% of the volume of interest compared to the original one.

All the analyses were performed by using MATLAB R2022a (MathWorks, Inc., Natick, MA, USA) software.

Classification model design

The primary objective of the present work was the prediction of xerostomia 3 months after RT in patients with OPS. As schematically illustrated in **Figure 2**, the classification method was developed in three phases: (i) for each dataset, a feature reduction or selection was performed, (ii) different

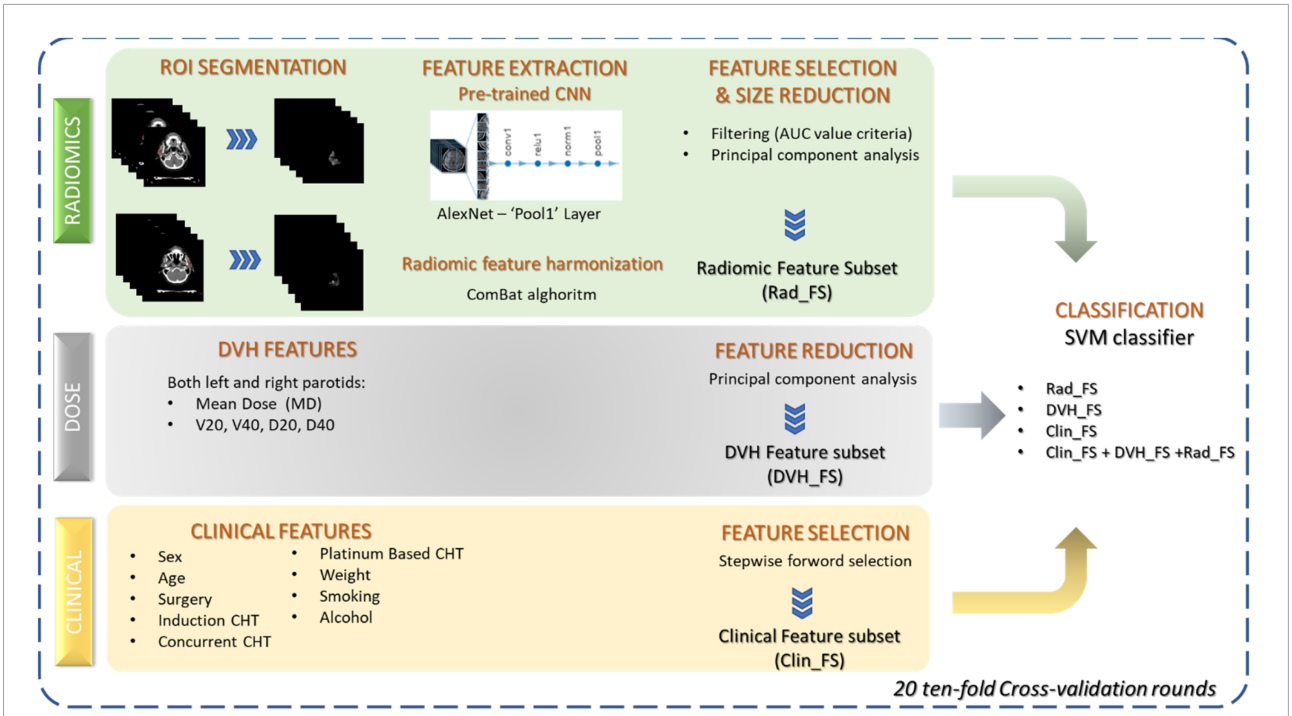

FIGURE 2
Workflow of the proposed classification approach. Three sets of features were considered: radiomic features extracted from parotid images by means of a pre-trained CNN, dose features extracted from DVH, and clinical features before RT beginning. Feature reduction and selection techniques were applied to the three sets of features to identify three subsets of significant features. SVM classifier was trained both on the individual feature subsets and using all the feature kinds jointly.

classification models were trained on each subset of features, and (iii) finally, a classifier was trained using the selected subsets jointly.

First, a subset of the clinical feature set was selected by a sequential forward feature selection algorithm: it identified a feature subset by sequentially adding one feature at a time during a fivefold cross-validation procedure until adding more features decreases the misclassification rate of the classification model used over the same training set. Specifically, we used a discriminant analysis (33). The selected features (*Clinical Feature Subset*, *Clin_FS*) were used to train the classification model. In order to further reduce the number of selected features, we implemented a nested feature reduction technique by principal component analysis (PCA) in cross-validation (34). Only the principal components with explained variance greater than 1 were chosen (*DVH Feature Subset*, *DVH_FS*) and used to train the classification model.

A subset of radiomic feature extracted from the CT images (see section "Radiomic feature extraction") was selected according to their discriminant power which was assessed through the computation of the area under the receiver operating curve (AUC) (35). Features whose AUC value was less than 80% were dropped from the feature radiomic set. However, these features showed a strong correlation between them. Therefore, after standardizing each feature, we implemented a nested feature reduction technique by principal component analysis (PCA) and selected the principal components with explained variance greater than one (*Radiomic Feature Subset*, *Rad_FS*) and used them to train the classification model.

The feature subsets identified are used to train a well-known machine learning algorithm, i.e., support vector machine (SVM). Specifically, we used SVM with the linear basis kernel function (36). Other classifiers known to the state of the art have been implemented but have not shown a significant performance improvement. In order not to burden the discussion, these results have not been reported either.

Finally, in order to evaluate the overall performance of all identified subsets of features, we jointly used them and trained a classification model.

A double validation of the model was carried out: (i) 20 ten-fold cross-validation rounds on 43 patients, equal to about 70% of the entire sample available and (ii) independent sample consisting of 18 patients (equal to about 30% of the entire sample available) randomly drawn and stratified with respect to the number of individual centers. The classification performances related to the iterated cross-validation procedure were evaluated in percentage terms of AUC, F-score, and accuracy, sensitivity, and specificity calculated by identifying the optimal threshold using Youden's index on the ROC curves (37). The feature reduction or selection procedure implemented for each feature

set has been nested\into the iterated cross-validation procedure. In order to evaluate the robustness of the model when the training set changes, we have calculated the same performance metrics of the same independent test set on each round of the cross-validation procedure.

Statistical analysis and performance evaluation

The association between parotid volume of two different centers was evaluated by means of the Wilcoxon–Mann–Whitney non-parametric test (38). The same non-parametric test was used to evaluate the association between continuous features and toxicity at 3 months, whereas we used Chi-square test for those features measured on an ordinal scale (39). Correlation between continuous features was measured by Pearson's correlation coefficient (40).

Due to the relatively small size of the sample population, a result was considered statistically significant when the p-value was less than 0.10 (41).

Results

Patients' characteristics are summarized in **Table 1**. A total of 61 patients with a median age at diagnosis of 59 years afferent to three different care centers was collected. Among them, 22 patients (36.07%) have shown xerostomia 3 months after RT. None of the collected clinical characteristics was statistically associated with the manifestation after 3 months from the end of the RT of the considered toxicity, except for Induction CHT (p-value < 0.10).

Classification performance using the parotids real contours

As described in section "Materials and methods," an SVM classifier algorithm was trained both on the three subsets of features identified individually (*Rad_FS*, *DVH_FS*, and *Clin_FS*) and jointly. The performances of the different prediction models were evaluated both in cross-validation and on an independent test stratified random sample from the entire dataset of 61 patients.

The sample used in the cross-validation procedure consisted of 43 patients, out of which 15 patients (34.88%) had experienced xerostomia after 3 months from RT.

Figure 3 shows the correlation among the collected DVH features: the dose features resulted as strongly correlated with each other, especially when they refer to the same area. The average number of principal components on radiomic features and selected DVH features in the different cross-validation rounds implemented were 4 and 1, respectively. **Figure 4** shows the statistical frequency of the clinical features, which were selected on 20 ten-fold cross-validation procedures by means of the feature selection algorithm. The weight at the start of the RT treatment, induction CHT, and sex is the features selected with a frequency equal to 100%.

Table 2 summarizes the results achieved in cross-validation. The clinical features alone did not exceed 50%, the dose features settled around 60%, while the radiomic-based model achieved the best performances with a median value of AUC, accuracy, sensitivity, and specificity of 84.17, 88.37, 66.67, and 100%, respectively, with an F-score of 80%. The joint use of all three sets of features allows an improvement in the performance of over 5 percentage points in terms of sensitivity, reaching 73.33%.

The proposed models were also validated on an independent sample consisting of 30% of the total sample of 61 patients. Among the 19 patients in the independent test, seven (36.84%) had experienced xerostomia 3 months after RT. The encouraging performances of the radiomic features were also confirmed on independent tests: the SVM classifier achieves an accuracy of 83.33%, a sensitivity of 71.43%, and a specificity of 90.91%. However, the improvement in sensitivity on the independent test using all three feature sets was not confirmed.

It is emphasized that both *Clin_FS* and *DVH_FS* showed a particularly variable sensitivity on the training set (53.33 and 80.00, and 40.00 and 53.33, respectively, as 1st and 3rd quantile values) and even more marked on the independent set (14.29 and 1, and 0 and 57.14, respectively, as 1 st and 3rd quantiles values).

Classification performance using the parotid "fake" contours

The contouring of the target and organs is an operator-dependent operation. The median volume and interquartile range of the three centers were 19.25 (13.65–27.8), 24.15 (20.4–27.5), and 23.19 (17.36–29.30), respectively (**Figure 5**). The volume distribution of center 1 differs significantly from the other two centers (p-value 0.097 and 0.015), while center 2 and center 3 do not show a significant difference in distribution (p-value 0.575). Since the most performing and stable model in external validation is the radiomic model, we wanted to evaluate the robustness of the model with respect to variations in parotid contouring. Therefore, to obtain these "fake" parotids, we dilated the volumes of patients in center 1 which showed smaller volumes on average and eroded those in centers 2 and 3 (which showed larger volumes on average) by 10% of the area of interest compared to the original one.

We then reposted the same previously proposed analysis pipeline on the parotid "fake" contours. The performances of the radiomic features still show their predictive power also following a variation of the contours of the parotids both in

TABLE 1 Sample dataset characteristics.

Characteristic	Distribution	*P*-value
Xerostomia at 3 months after RT		
Yes (abs. %)	22 (36.07)	
No (abs. %)	39 (69.93)	
Sex		0.52
Male (abs. %)	47 (77.05)	
Female (abs. %)	14 (22.95)	
Age at diagnosis		0.31
Median (1th–3th quantile)	59.00 (54.00–68.25)	
T		0.84
T1	2 (3.28)	
T2	21 (34.43)	
T3	25 (40.98)	
T4	10 (16.39)	
NaN	3 (4.92)	
N		0.37
N0	6 (9.84)	
N1	13 (21.31)	
N2	35 (57.38)	
N3	3 (4.92)	
NaN	4 (6.56)	
Surgery		0.31
Yes	53 (86.89)	
No	8 (13.11)	
NaN	–	
Induction CHT		0.07
Yes	26 (42.63)	
No	35 (57.38)	
NaN	–	
Current CHT		0.31
Yes	55 (90.16)	
No	6 (9.84)	
NaN	–	
Platinum based CHT		0.36
Yes	52 (85.25)	
No	7 (11.48)	
Nan	2 (3.28)	
Weight pre-RT (Kg)		0.26
Median (1th–3th quantile)	69.50 (60.35–80.40)	
Smoking history		0.61
Yes	25 (40.98)	
No	13 (21.31)	
Ex	16 (26.23)	
NaN	8 (13.11)	
Alcohol history		0.62
Yes	15 (24.59)	
No	33 (54.10)	
Ex	1 (1.64)	
NaN	10 (16.39)	

For categorical variables, absolute (abs.) and percentage (%) counts are reported. For continuous values, the median value and interquartile range (1st–3rd quantiles) are indicated. *P*-value related to the association test between each feature with xerostomia at 3 months after RT is shown.

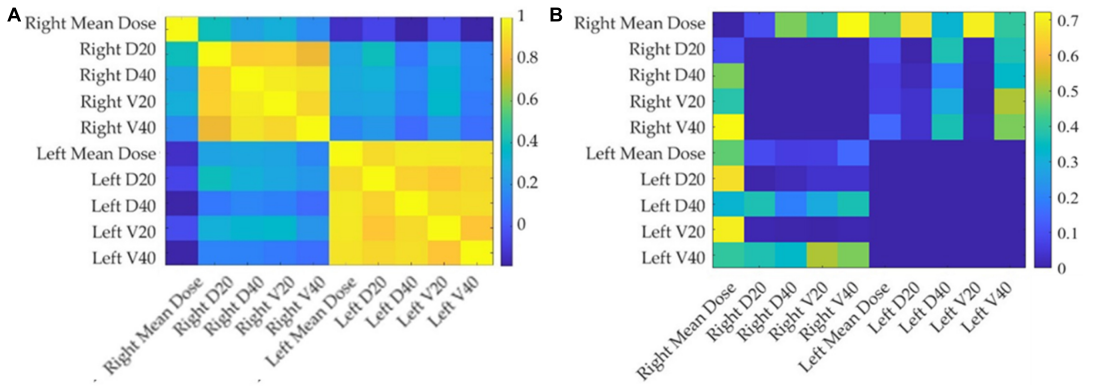

FIGURE 3
Correlation and *p*-value matrix plot of DVH features. The left panel **(A)** depicts the Pearson's coefficients among DVH features considered in this study, while the right panel **(B)** shows the corresponding *p*-values. The DVH-extracted parotid-related dose features considered in this study show strong positive correlations.

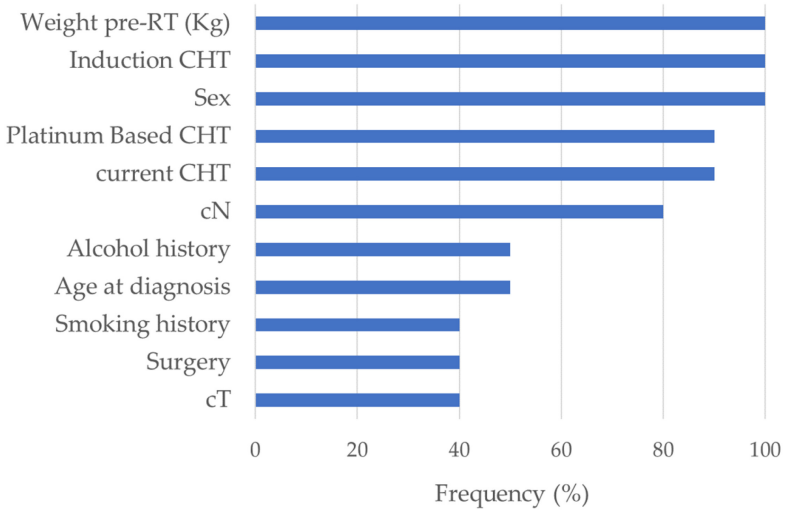

FIGURE 4
Feature selection. Statistical frequency of the clinical features selected on 20 ten-fold cross-validation rounds by means of the sequential feature selection algorithm.

cross-validation and on the independent test with a median accuracy value of 81.40 and 94.44% in cross-validation and on the independent test, respectively (**Table 3**). It should be noted that on the independent test set, the accuracy reached using the adjusted ROI was greater than that obtained when we used the original ROI by more than 10 percentage points.

Discussion

Radiotherapy, possibly joined with chemotherapy, represents the standard of care in patients with locally advanced oropharyngeal cancer (OPC) (42). However, RT is often associated with substantial acute and late toxicity, including xerostomia (43). Xerostomia is a frequent side effect of RT for head and neck cancer and is due to damage to the irradiated salivary glands with a relevant impact on patient s' quality of life (44).

The latest advancement in radiotherapy techniques has improved the rate of acute adverse events in long-term survivors, yet there is a need for better identification of patients with higher risk of toxicity. In order to minimize the toxicity burden for patients with OPC, an individual toxicity risk assessment is required to adequately plan radiation treatment and any supportive therapy. Recently, computational models based on the quantitative analysis of biomedical images, i.e., radiomic analysis, have been effectively proposed to address unmet clinical needs, mainly in the field of oncological imaging

TABLE 2 Classification performances of the late xerostomia predictive models in terms of median percentage and interquartile range (1st–3rd quartiles) AUC, accuracy, sensitivity, and specificity evaluated on real parotid counters.

	AUC	f-score	Accuracy	Sensitivity	Specificity
20 ten-fold cross-validation rounds					
Clin_FS	48.57 (45.00–54.76)	50.00 (48.10–50.95)	48.85 (41.86–55.81)	73.33 (53.33–80.00)	35.71 (21.43–57.14)
DVH_FS	59.40 (55.95–61.43)	50.33 (44.45–55.17)	69.77 (65.12–72.09)	43.33 (40.00–53.33)	80.36 (78.57–85.71)
Rad_FS	84.64 (84.29–86.66)	80.00 (78.57–80.00)	88.37 (86.05–88.37)	66.67 (66.67–73.33)	100 (92.86–100)
All FS	84.17 (82.38–85.71)	76.92 (75.86–78.57)	86.05 (83.72–86.05)	73.33 (66.67–73.33)	92.86 (89.29–96.43)
Independent test set					
Clin_FS	50.00 (42.86–56.49)	51.08 (38.75–56.00)	50.00 (38.89–61.11)	42.86 (14.29–1)	50.00 (0–72.73)
DVH_FS	75.97 (74.03–79.22)	62.02 (54.55–66.67)	66.67 (61.11–72.22)	42.86 (0–57.14)	90.91 (81.82–90.91)
Rad_FS	81.17 (79.22–81.82)	76.92 (76.92–78.69)	83.33 (83.33–83.33)	71.43 (71.43–71.43)	90.91 (90.91–90.91)
All FS	81.82 (81.82–88.31)	71.43 (71.43–76.92)	77.78 (77.78–77.78)	71.43 (67.14–71.43)	86.36 (81.82–90.91)

The results are evaluated both on 20 ten-fold cross-validation rounds and independent test. The related 1st and 3rd quantiles are reported in round brackets.

(45, 46). Table 3 summarizes radiomic-based research works addressing the prediction of RT-related toxicity in head and neck patients. The models proposed at the state of the art refer in general to head and neck tumors (9–12). However, compared to treatment in other areas of the head and neck, the oropharynx represents the most frequent challenge for the preservation of radio-induced xerostomia. Therefore, the goal of our research activity was the development of a support system tailored to give an early prediction of the risk of late xerostomia after 3 months of radiotherapy treatment in patients with OPC. Specifically, we developed a deep learning-based model which exploited pre-treatment CT images. Radiomic features were extracted by a pre-trained CNN and analyzed jointly with both clinical and dose features. The usage of a transfer learning approach was here preferred to a customized CNN, i.e., to extract features and then give a prediction, because it provides some benefits especially when, as in our case, a relatively small amount of data is available. When a pre-trained network is used as a feature extractor only, no training phase is required; therefore, a drastic reduction of the computational time occurs. Moreover, for datasets counting small samples, pre-trained net allows us to obtain high generalizability of the results.

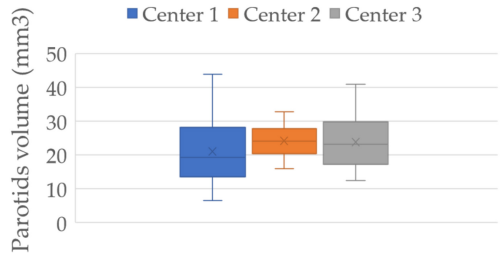

FIGURE 5
Parotids volume distribution of three centers. Center 1 shows a significantly smaller volume of the parotids than that of the other two centers (p-value 0.097 and 0.015), while centers 2 and 3 show no significant difference between them (p-value 0.575).

Our experimental results show that the radiomic signature has a predominant predictive potential with respect to both clinical and dose characteristics. Indeed, in the cross-validation, the radiomic features alone showed median values of AUC, accuracy, sensitivity, and specificity, 84.64, 88.37, 66.67, and 100%, respectively. The addition of the clinical and dose features only contributes to an increase in the sensitivity value (73.33%). However, this advantage on the independent test is

TABLE 3 Classification performances of the late xerostomia predictive models in terms of median percentage AUC, accuracy, sensitivity, and specificity evaluated on "fake" parotid counters.

	AUC	f-score	Accuracy	Sensitivity	Specificity
20 ten-fold cross-validation rounds					
Rad_FS	80.24 (78.93–82.14)	71.43 (71.43–74.07)	81.40 (81.40–83.72)	66.67 (66.67–66.67)	91.07 (89.29–92.86)
All FS	68.10 (66.90–73.10)	58.20 (55.56–60.61)	69.77 (67.44–72.09)	60.00 (53.33–66.67)	75.00 (71.43–78.57)
Independent test set					
Rad_FS	94.16 (93.51–94.81)	92.31 (83.33–92.31)	94.44 (88.89–94.44)	85.71 (71.43–85.71)	100 (100–100)
All FS	95.86 (88.31–970.81)	74.83 (60.00–80.00)	83.33 (77.78–83.33)	71.43 (42.86–85.71)	95.45 (81.82–100)

The results are evaluated both on 20 ten-fold cross-validation rounds and independent test. The related 1st and 3rd quantiles are reported in round brackets.

lost, probably due to the high variability of the performances of these two data sets.

Probably, DVH_FS does not provide an added value to the prediction performance of radiomic features alone because clinicians follow the constraints defined by the guidelines in defining a treatment plan (47, 48). Rather, it seems that there is a strong predisposition to the risk of toxicity linked to the texture of the organ at risk.

The performances of the proposed radiomic model trained on CT images are encouraging if compared to the state-of-the-art models, both when trained on the same type of images (7–9) and on magnetic resonance imaging (10, 11). A classification performances overview of late xerostomia state-of-the-art predictive models is provided by **Table 4**. It should be emphasized that the comparison with the state of the art is purely qualitative, since in this work we considered the prediction of xerostomia at 3 months as an endpoint and the model is dedicated only to patients affected by OPC. Relevant studies currently proposed to refer to a different follow-up time and refer to the larger population of patients with head and neck cancer.

Moreover, in this article, we also wanted to verify how robust the model was in relation to strongly operator-dependent contouring procedures. We have artificially segmented "fake" contours of the parotids and repeated the process of extracting the features and training the classification models. To the best of our knowledge, no studies for this purpose have been carried out. Even using the "fake" contours, the performances of the radiomic model are highly performing. Specifically, the results obtained using the adjusted ROI

TABLE 4 Classification performances of the late xerostomia predictive models in terms of median percentage AUC, accuracy, sensitivity, and specificity evaluated on "*fake*" parotid counters.

References	Imaging modality	Study population and sample size	Endpoint Time of assessment	Statistics and modeling	Features	Results
MEN et al. (10)	Pre-treatment CT	784 H and N cancer patients	Xerostomia at 12th months	Model 1: 3D rCNN Model 2: Logistic Regression	3D CT 3D dose D20, V20 parotid D20, V20 submandibular Clinical data: sex, age, race, treatment arm, treatment technique, tumor site, T, N, Zubrod performance score	AUC: 0.84 Acc: 0.76 Sens: 0.76 Spec: 0.76 F-score: 0.70 AUC: 0.74 Acc: 0.64 Sens: 0.72 Spec: 0.59 F-score: 0.60
Gabryś et al. (11)	Pre-treatment CT	153 H and N cancer patients	Xerostomia at 0–6 months	Gradient tree boosting	Demographic: Age, sex 6 Handcrafted radiomics features DVH: Mean, spread, skewness	AUC: 0.65
Van Dijk et al. (12)	Pre-treatment CT	249 H and N cancer patients	Xerostomia at 12 months	Logistic regression	142 Handcrafted radiomics features DVH: Mean dose Clinical: age, sex, WHO stage, weight, length and BMI, tumor characteristics (TNM stage, tumor location) and treatment characteristics	AUC: 0.76
Sheikh et al. (13)	Pre-treatment CT MRI	249 H and N cancer patients	Xerostomia at 12 months	Generalized linear model	2877 Handcrafted radiomics features (PyRadiomics software): CT features MRI features DVH: 48 features	AUC: CLIN + CT + MR 0.73 CLIN + DVH + CT + MR 0.68
van Dijk et al. (14)	T1 weighted MRI	249 H and N cancer patients	Xerostomia at 12 months	Logistic regression	64 Handcrafted radiomics features	AUC: 0.83

The results are evaluated both on 20 ten-fold cross-validation rounds and independent test. The related 1st and 3rd quantiles are reported in round brackets.

achieved very high performances in the independent test set. Our intent with the analysis of the "fake" ROI was to evaluate how much the model was still highly performing with variations on the contouring which is a notoriously operator-dependent operation.

In light of the results obtained, it would seem in fact that the erosion and dilation carried out have led to an improvement in the forecast results, that is to say, that with too many or too large contours there is a loss of information.

This result, which we have underlined in the results and discussions, offers food for thought for future works, e.g., by evaluating a forecasting model based on optimal automated segmentation.

The proposed model seems to provide reliable support regardless of the clinical contouring practice used by the operator.

Therefore, the model could accurately support clinicians in the decision-making process by providing a personal risk score for the development of toxicity, to improve the quality of life, without compromising patient care. Such a support system, if applied to clinical practice, it would allow clinicians to define a personalized radiotherapy plan by reducing the doses of the parotids as much as possible and to associate pharmacological support therapies to be carried out before and during the radiotherapy treatment.

Although our study is multicentric, the limited sample size represents a limitation of the study which, therefore, requires further validation studies. In future studies, we intend to generalize the model also for observation times and toxicities different from those considered here.

Conclusion

In this article, we proposed a deep learning-based model to predict late toxicity after radiotherapy in patients with OPC. Specifically, we developed a radiomic-based model using pre-treatment CTs to give an early prediction of xerostomia in 3 months after RT treatment. The achieved experimental results are promising in terms of prediction accuracy. Moreover, the model is robust with respect to the manual parotid contouring procedure. Therefore, the proposed model could help to develop a valid support tool for clinicians in planning radiotherapy treatment.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The raw data supporting the conclusions of this article will be made available by the corresponding authors, without undue reservation. Requests to access these datasets should be directed to SB, s.bove@oncologico.bari.it and MC, m.c.comes@oncologico.bari.it.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Scientific Board of Istituto Tumori "Giovanni Paolo II," Bari, Italy–Protocol number 24269/21. Informed consent was obtained from all subjects and/or their legal guardian(s).

Author contributions

AF and RM: conceptualization, writing—original draft preparation, and supervision. AF, SBo, and MC: methodology. AF: software and validation. AF, GS, AN, PT, and RM: formal analysis. RM: resources. AF, GS, AN, SBa, CC, AD, AE, LP, PT, MT, SP, RV, and RM: data curation. AF, GS, AN, SBa, SBo, MC, CC, VD, AD, AE, LP, PT, MT, SP, RV, AZ, ML, and RM: writing—review and editing. All authors have read and agreed to the published version of 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.

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Present and future of extraoral maxillofacial prosthodontics: Cancer rehabilitation

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Historically, facial prosthetics have successfully rehabilitated individuals with acquired or congenital anatomical deficiencies of the face. This history includes extensive efforts in research and development to explore best practices in materials, methods, and artisanal techniques. Presently, extraoral maxillofacial rehabilitation is managed by a multiprofessional team that has evolved with a broadened scope of knowledge, skills, and responsibility. This includes the mandatory integration of different professional specialists to cover the bio-psycho-social needs of the patient, systemic health and pathology surveillance, and advanced restorative techniques, which may include 3D technologies. In addition, recent digital workflows allow us to optimize this multidisciplinary integration and reduce the active time of both patients and clinicians, as well as improve the cost-efficiency of the care system, promoting its access to both patients and health systems. This paper discusses factors that affect extraoral maxillofacial rehabilitation's present and future opportunities from teamwork consolidation, techniques utilizing technology, and health systems opportunities.

KEYWORDS
maxillofacial prosthodontics, facial prosthetics, 3D technologies, oral cancer, head and neck cancer, anaplastology

Introduction

Head and neck cancer management requires a reconstruction and rehabilitation multidisciplinary plan to transform the original oncological pathology and disability toward restored bio-psycho-social functioning (1, 2). Most head and neck oncology services that want to promote this multiprofessional approach do not have the necessary in-house professionals to address the patients' broad scope of needs. Therefore, patients are often referred externally or directed to rehabilitation services remotely located (3–6).

The teamwork composition around maxillofacial patients' needs must include oncology surveillance, systemic physiologic patient condition complications and microbiology, advanced 3D workflow technologies, biomaterials, advanced restorative techniques, osseointegration, and hyper-realistic artistic skills (7–9). All these professional competencies may be concentrated in a system with one or more

professionals possessing the competence and legal responsibility necessary for the patient's care. The United States, United Kingdom, and other developed regions are examples of how an education and certification structure has been established for healthcare professionals who must face specializations, subspecializations, and board certification programs to allow patients and health systems to trust their skills and multiprofessional capabilities (10–14). However, this is a specific reality for unique countries that do not necessarily match most parts of the world's public health coverage, needs, and level of education. Furthermore, worldwide professionals cannot justify professions like anaplastology and ocularists in their own countries if their laws cannot support and protect them. Worldwide, dabbler practices are illegal and a public health risk. This is the case when insufficiently trained or supervised lab technicians are treating patients or self-taught people provide care with a self-claimed professional status. They are both dabblers and illegal practitioners facing a severe risk and possible felony. If the country's law does not recognize anaplastology or ocularistry, they have no legal foundation to provide legal patient healthcare in these regions. On the other hand, multiprofessional management empowers individual skills and, under a coordinated intervention and delimitation of responsibilities, allows patients to have a secure rehabilitation process with professionals who exercise their vocation within their defined scope of service.

The American Academy of Maxillofacial Prosthodontics was founded in 1953 when dentists' first education and training in maxillofacial prosthodontics was of significant concern. In the United States, from 1958 to 1977, 2-year teaching programs were offered. From 1977 to 1984, 3-year programs were offered, and the ADA Commission accredited these on Dental Education (15). Maxillofacial prosthodontists obtain their title after a subspecialization of prosthodontics. This is possible after a dentistry program confers a degree that allows the professional to care for the patient's health as a doctor. The International Anaplastology Association was founded in 1980 as the American Anaplastology Association. Its consolidation as a formal profession in the Unites States arose from wartime necessity. Military hospitals provided care to veterans and identified the need for even more specialized care in both laboratory and clinical setups for the artificial replacement of more complex structures of the face requiring more artistic skills. Thanks to Walter Spohn and Stanford University in 1971, the anaplastology profession started as a formal training program. This 2-year degree course included art and basic sciences, materials and methods, ethics, and business practices. Today, very few places in the world offer formal degree training, usually a 2-year master's program with a previous bachelor's in art, technology, or other medically related fields (6, 16).

In under-resourced regions, a vicious circle is occurring. The lack of formal education and legal framework maintains professionals without formal training. As a result, fewer professionals remain insufficient to sustain the necessary professional structure within most healthcare systems. Yet, it is a day-to-day reality worldwide among appropriately trained and certified maxillofacial prosthodontists, anaplastologists, and ocularists who are working on solving these real-life problems to serve expanding patient populations.

Facial prosthetics production

No other body part can reveal feelings, emotions, and character like the face of a person. Therefore, its alteration comes with a solid and intrinsic need to hide facial defects and seek restorative care. Ancient registers support this statement, like the Chinese using resins and metallic parts to hide eyes and faces. Egyptian mummies have been discovered with stone and mosaic replicas of facial parts. Romans documented "eye makers," "doctors of the eye," and much more. Restoring anatomy to enable function, cognition reinforcement, and esthetics is a human need (17–20).

Facial prostheses are customized medical-grade devices used to restore severe functional, cognitive, and esthetic alterations to positively impact the patient's daily living activities in a bio-psycho-social way. Three significant steps are well described in the literature to produce facial prosthetics (17, 18, 21, 22). The analog manufacturing process starts with a molding of the facial defect. With the obtained gypsum working model, a sculpture can be fabricated with a thermoplastic material that will mimic the lost anatomy, respecting functional and esthetic principles. Once finished, a mold is created as a negative version of the sculpture. Multiple layers of intrinsically characterized medical-grade silicone are packed accordingly to replicate the patient's skin color. However, in most regions of the world, the prosthetic context requires manufacturing them by analog processes such as manual molding, sculpting, and coloring, as well as using acrylic resin materials, as has been done since the origin of this specialty, among other adaptations of the procedure to the local reality (18, 23–25).

High learning curves exist to exact this technical task and to reduce the chances of a mistake or remakes of the prosthesis. To overcome this artisanal and time-consuming process, specialists have looked to digital technologies to assist or replace some steps in the process, like molding and sculpting (26–35).

3D data acquisition

Molding processes have been utilizing different 3D image acquisition methods

The first 3D data acquisition trials and digital workflows were performed using MRI data and CT scans because they were the most well-known imaging methodologies to capture the anatomy, becoming more prevalent as cone-beam

computed tomography (CBCT) emerged on the market with up to 10% of the radiation dose. Its main advantage is the precision and veracity of the acquired external surface, as well as the possibility of capturing negative areas such as lumens or ears with capricious anatomies. However, nowadays, there is no indication to irradiate a patient with a CT scan for extraoral surface scanning or use expensive MRI technology, both of which lack sufficient image resolution and color information to adequately replicate the level of detail required in a surface scan in facial prosthetics. CT scans have a unique use for extraoral surface data acquisition only when osseointegrated implants are being planned. It can help transport the head's position and allow the designer to mirror the healthy anatomy with just one scan (23, 26, 27, 36–41).

In addition, DICOM images require a thorough segmentation process that can add or remove information from the surface if not handled properly. To segment the facial anatomy, the Hounsfield threshold is used on an appropriate scale. Depending on the application, there are situations where semiautomatic and automatic segmentation tools could be used, but this is at the discretion and responsibility of the treating medical staff. There is no superior tool at present that beats a trained professional with extensive software and anatomy experience performing manual segmentation. Automatic segmentation systems through artificial intelligence are an evolving present. Eventually, automatic systems with artificial intelligence will be sufficiently accessible so that they can be used routinely (42–46).

Laser scanning has been used as an alternative mobile resource to scan extraoral surface structures, with the advantage of not irradiating patients but with the limitation of a noncolored image and limitations for open-eye scanning. Industrial-grade laser scanners were outstanding regarding trueness and precision but were costly and not easily portable given their size. Therefore, they have been replaced by other optic 3D scanning technologies that allow the acquisition of color (UV-map) and were more portable. Recently, the Lidar technique of laser usage has demonstrated potential when combined with optical resources to enhance the best of two data acquisition technologies. However, more studies are necessary to understand its cost-efficiency better (35, 47–49).

The stereophotogrammetry technique is the fastest scanning system because multiple synchronized cameras acquire all of the captures needed in a fraction of a second. It became popular over the last 20 years because of its colored facial scanning. In addition, the standardized hardware presents a low learning curve and reproducibility of its trueness and precision. However, the high-cost investment and the dedicated infrastructure and space needed for a scan rig must be considered. More simplified versions are being developed to reduce space requirements and costs (34, 50–56).

In the past decade, structured light scanners came into the facial prosthesis digital workflows as an active scanning method that creates a 3D stitching process, while the scanner is focused and displaced around the subject. As an optic resource, it produces a colored 3D model. The industry around this technology claimed to be an accessible solution due to the comparison of stereophotogrammetry systems that may cost exponentially more. However, structured light scanners were still not inexpensive enough to become a widespread technology used in most hospitals and under-resourced regions. Additionally, an intermittent flash is not comfortable for an opened eye posture of the patient. Also, the stitching process may accumulate errors in more expansive areas, creating unnoticed errors and holes in the mesh. Finally, the first structured light scanners were not calibrated for facial scanning. Designed primarily for intraoral dental applications, the optical properties may not have the optimal focal distance to obtain the most delicate details of the skin (57, 58).

Lacking the need for special equipment, monoscopic photogrammetry is the most accessible 3D facial surface scanning technique. A unique camera and specific software can be used. Smartphones and open-source software have proven their value in this workflow. When properly used, they have no limit in the computing graphic possibilities, which can manually produce professional and high-resolution 3D images for free. The consideration needed is appropriately controlling the variables with respect to protocols for precision and trueness optimization and a high learning curve to expertly operate the open-source software for rapid data manipulation and satisfactory results (31, 59–66).

Face scans with techniques such as monoscopic photogrammetry, precisely executed, are getting closer in precision and accuracy compared to tomographic methods. Even so, in cases such as the evaluation of craniofacial implants, there is an opportunity to compose 3D scans with those of surface scans. In this way, it is possible to obtain the best advantages of multiple systems and technologies in a more digital and integrated treatment. There is no single best technology for every case. It is necessary to intelligently use all the available resources that the patient and the context allow (**Figure 1**) (67–73).

3D modeling

Independent of the chosen technology for 3D facial scanning, the virtual 3D model needs to be manipulated within a CAD program. The standard tools necessary are duplicating, cutting, transforming, sculpting, and Boolean operations, which can be performed in almost any CAD software, apart from whether it is freeware like Meshmixer or high-cost commercial license software like Zbrush. Of course, previous user experience, learning curve, and user interface are individual criteria contributing to the designer's software selection. On the other hand, professional open-source software like Blender allows senior designers to take advantage

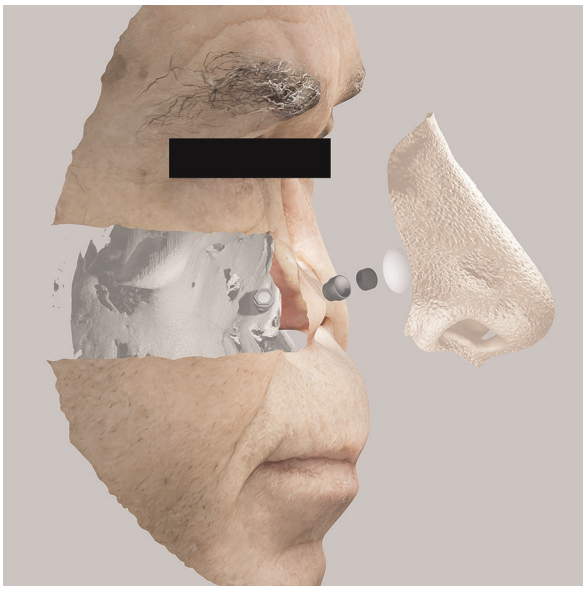

FIGURE 1
Integration of medical images with planning of implants, components, and prosthetic design for extraoral bucco-maxillofacial rehabilitation on implants.

of much more complex operations like modifiers, physic simulation, animations, merging, CMYK color model data in virtual reality modeling language (VRML) exportation, and others. The +Plus ID Institute programmed the first facial prosthetic design software as an add-on in Blender, which can be used for free (62, 63). Also, some algorithms are being developed to automatically detect the coloring of the facial prosthesis thanks to a deep artificial neural network approach to coloration in a facial prosthesis (74).

3D digital fabrication

Different digital manufacturing technologies have been described for facial prosthetic digital workflows, from subtractive techniques of wax, metals, and polyether ether ketone (PEEK) to additive manufacturing with fused filament fabrication (FDM), stereolithography/liquid-crystal display/digital light processing (SLA/LCD/DLP), polyjet, selective laser sintering (SLS), selective laser melting (SLM), and, more recently, silicone 3D printing (31, 63, 75–77).

FDM has been the most popular 3D printing technology since the Stratasys patent release. The thermoplastic filament is the most accessible 3D printing material that can replicate the macroanatomy of a facial structure but has a limitation on the microanatomy due to the evident layers and its staircase effect. On the other hand, all resin 3D printing technologies (SLA, LCD, DLP, Polyjet) have demonstrated their ability to reproduce the most delicate details of facial skin microanatomy characteristics (78).

Medical-grade silicone 3D printing is the most desired and expected technology consolidation. Some efforts have been made with success, although challenges still exist (79–83). However, voxel-colored Polyjet 3D printers may have a future in this realism and reliability where the +ID institute enabled the translation of color from smartphone captures into a 3D printed colored orbital prosthesis used by the patient with no complications (64).

Discussion

The future is technological and in teamwork. The ideal coming landscape for maxillofacial prosthodontists, anaplastologists, and ocularists is having worldwide opportunities for formal and accessible education. This will allow future professionals to fulfill the health system and patient needs, working together in an integrated health system with patient coverage of their advanced and accessible treatments. The next generations of 3D image acquisition systems bring an automated and self-calibrated, self-scaled 3D model that can mix more than one technology and dynamics with no high cost in a mobile and portable scenario. The next advances in 3D modeling of facial prostheses will make possible an open-source automated design created by artificial intelligence that can recognize the patient's anatomy and replace the missing part with self-created 3D meshes. The future of the 3D manufacturing process of the facial prosthesis is the final and direct 3D printed prosthesis with the high manual capacity of a gold standard exhibited by the most skilled prosthetists.

Author contributions

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.

Publisher's note

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Oral infections in oral cancer survivors: A mini-review

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The oral cancer survivors are a group of special individuals whose disease affect anatomical structures with a key role in identity and communication and a fundamental role in basic human functions such as speaking, eating, swallowing and breathing. Thus, quality of life of these individuals can be impaired by the consequences of disease and treatments, in particular surgery and radiotherapy. Among others, infectious conditions of any nature, bacterial, viral, fungal, are a frequent finding among oral cancer survivors. In fact, the peculiar systemic and local conditions of these subjects are known to significantly modify the microbiota, which, besides facilitating opportunistic infections, can affect the cancer microenvironment, as well as alter the effects of the anti-cancer therapies. Similarly, mouth infections can also affect the prognosis of oral cancer survivors. Among the opportunistic infections, fungal are the most common infections affecting these subjects, since neutropenia resulting from cancer, as well as chemotherapy and/or radiotherapy treatments, promote the shift from the carrier state of Candida species, to pathogen state. Treatment of oral candidiasis can be difficult in oral cancer survivors, and good evidence supports clotrimazole as the most effective for prevention, and fluconazole as the one with the best risk-benefit profile. Probiotics, although promising, need better evidence to be considered an effective treatment or preventive measure.

KEYWORDS
oral cancer, candidiasis, oral infections, cancer survivors, oral tumour

Introduction

According to the GLOBOCAN 2020 estimates produced by the International Agency for Research on Cancer, in 2020 19.3 million new cancer cases were diagnosed worldwide, a figure that in 20 years' time could reach 28.4 million (1). Thanks to ageing populations, advances in early diagnosis, and treatment effectiveness, the number of cancer survivors is rapidly increasing worldwide. "Cancer survivor" refers to anyone who has ever received a diagnosis of cancer, regardless of where they are in the course of their disease: the estimated 5-year prevalence of all cancers is 50.5 million (2). The Institute of Medicine (nowadays National Academy of Medicine, www.nam.edu) listed the following aims of a correct cancer survivor care: surveillance for recurrence, screening for spreading, or new primary cancers, assessment and management of the consequence of cancer and treatment, health promotion, and coordination between specialists and primary-care providers (3, 4). The oral cavity

and pharynx cancer males survivors are about 250,000 in the US only, and they are expected to increase significantly by 2030 (5). Cancer of the mouth and its treatments can affect a number of structures involved in key functions, such as speaking, eating, swallowing, breathing, as well having a central role in identity and communication of the individual. Thus, oncological surgery of the oral and perioral structures, chemotherapy with both traditional and biological drugs, and radiotherapy of the head and neck can significantly affect the quality of life of oral cancer patients (6). In addition, the high proportion of subjects over the age of 65 among them (59%), makes comorbidities highly common, further complicating the follow-up of this special group of cancer survivors (5).

One of the most relevant factors affecting the quality of life of oral cancer survivors is dental and oral health. Infective conditions of the soft and hard tissues of the mouth are common findings among those patients, and they include healthcare-associated infections (7), infectious complication of the surgical site, the most common reason for 30-day all-cause readmissions among patients surgically treated (8), or opportunistic infections which are extremely common during and after cancer treatment. In addition, common infectious conditions of teeth and gums, namely caries and periodontal diseases, have higher incidence, among cancer survivors. The susceptibility to infections of the oral cancer survivors depends on a number of factors including the age of patient, comorbidities, tobacco and alcohol use, oral health conditions at the time of diagnosis, stage and location of cancer, type of surgical intervention, dose and modalities of radiotherapy and consequent hyposalivation, drugs used for chemotherapy. Besides some common infections affecting the oral cancer survivor, this mini-review will address some less debated issues related to the infections in cancer survivors, such as their putative prognostic role and the changes in microbiota of these patients.

Microbiota modifications in cancer patients

The human microbiome is composed by the genome of the entire microbiota, which is represented by the ecological community of commensal, symbiotic and pathogenic microorganisms residing within and on the human body. Cancer therapies, mainly chemotherapy, immunotherapy and radiotherapy may affect the composition of microbiota, which can mediate both the therapeutic response and toxicity, also predisposing patients to infective complications. Qualitative and quantitative variations in bacterial communities as well as changes in the host environment can transform fungal commensals into opportunistic pathogens in the upper and lower gastrointestinal tract (9). Pioneering studies have shown that Streptococcus oralis has a mutualistic relationship with *C. albicans: C. Albicans* enables streptococcal biofilm growth at mucosal sites, while S. oralis facilitate invasion of the oral and esophageal mucosa by *C. albicans* (9).

In the gut, chemotherapy has been reported to produce severe dysbiosis, which may be further worsened by the concomitant use of antibiotics (10); the latter associated with a decrease the clinical activity of cancer immunotherapy (11). Several gut bacterial taxa appeared protective against the cancer immunotherapy's toxic effects and Bacteroidetes appeared abundant in patients resistant to ipilimumab-induced colitis, and Bifidobacterium can abrogate pathology in a mouse model of immunotherapy-induced colitis (10). Other taxa were, contextually, associated with both immunotherapy success and toxicity as Firmicutes case in immunotherapy and, in preclinical models, the gut dysbiosis associated to oxaliplatin (10). However, the mechanisms through which the gut microbiota influences response to cancer therapies remain not entirely understood (10, 12). About the role of microbiome in immunotherapy, literature supports the interaction of microbial products and components with antigen-presenting cells and innate effectors, which can enhance the adaptive immune response and the induction of cytokine production, besides local or distant effects of microbial metabolites (10). Most of studies focuses on the adaptive immunity induced by the gut microbiota during immunotherapy, suggesting that microorganisms may promote antitumor CD8 + T cell responses during treatment (12). The influence of gut microbiota on TH1 immune response and its modulation of TH17 cells have also been proposed as mechanisms, which may regulate the tumor microenvironment (12). Microbiota can also influence responses to a range of chemotherapy regimen; beneficial responses to cyclophosphamide were associated with increased intestinal permeability, producing bacterial translocation that can result in the maturation of TH17 cells (10).

Radiotherapy is also responsible of a proinflammatory dysbiosis, impairing intestinal mucosa and related functions (13). In preclinical models, radiotherapy changed the composition of gut microbiota, reducing the abundance of Firmicutes and increasing that of Proteobacteria, favoring the susceptibility to radiation-induced colitis (10). No studies directly investigated the impact of gut microbiota on radiotherapy efficacy and little is still known about how it can regulate the response to this cancer therapy (14, 15). However, some studies support that gut microbiota influence normal tissue radiosensitivity. In mice, the disruption of the circadian rhythm led to reduction of gut microbe species, which is associated with increases mouse sensitivity to gamma-ray irradiation (14). This suggests that alterations in gut microbiota may affect the response to radiotherapy modulating radio-sensitivity of the tissue (14). Consistently, gut microbiota also influences the intestinal barriers and modulates the inflammatory responses, which have impact on

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the sensitivity or resistance of tumors to radiotherapy. On these bases, it has been speculated that gut microbiota may influence the radiotherapy efficacy, although the role of gut microbiota in radio-sensitivity remains a new concept and the underlying mechanisms are still obscure. Much more research is needed on this topic (15).

Oral microbiome has been also investigated, even if literature is still scanty. In 2018, a systematic review (16) evaluated the specific effect of systemic chemotherapy on the microbiota of the oral cavity: 17 studies were included, 5 were on pediatric patients, 12 were on adult patients. They overall reported, during chemotherapy, a higher proportion of gram-negative bacteria of the Enterobacteriaceae family and gram-positive Streptococcus; these variations could predispose the patient to the occurrence of systemic (septicemia or localized infections) and local (acute oral infections, oral mucositis) complications (16). The disruption of the balance between bacterial load and the immune status which is compromised allows certain bacteria and Candida species to multiply and overwhelm other resident microorganisms. Head and neck radiotherapy for oral cancer causes severe alteration in oral microbiota and, after radiotherapy, the patient may acquire drug-resistant opportunistic infections, which may cause systemic complications and high morbidity (17). *Candida albicans* and *Klebsiella species* and *Pediococcus species* are, in particular, the most important pathogens isolated in post-radiotherapy cancer patients (17).

To corroborate these findings, a further clinical study showed that the combined chemotherapy-radiotherapy treatment protocols, often used in case of oral and oropharyngeal cancers at advanced stages, altered the oral microbiome and metabolomic profiles for 24-month post-treatment. Nitric oxide (NO−) homeostasis is crucial to mammalian physiology: as a free radical signaling molecule, NO− regulates cellular processes such as angiogenesis, smooth muscle tone, immune response, apoptosis, and synaptic communication (18). The recently described enterosalivary nitrate–nitrite–nitric oxide pathway has been shown to provide bioactive NO− from dietary nitrate source. This pathway is dependent upon oral nitrate-reducing bacteria, since humans lack this enzyme activity (18). The majority of downregulated metabolites, after chemotherapy-radiotherapy regimens, were nitric oxide-related precursor, modulator, and/or catalyst such as aspartic acid, phenylalanine, L-ornithine, L-proline, xanthine, tyrosine, and glycine (18). The salivary metabolites reflected the oral microbiome communities and supported the hypothesis of the loss of NO- bioavailability in oro-pharyngeal cancer patients post-chemotherapy-radiotherapy, due to the reduction of oral nitrate-reducing bacteria (18). chemotherapy-radiotherapy, indeed, resulted in oral dysbiosis associated with the specific depletion of genera regulating the enterosalivary nitrate–nitrite–nitric oxide pathway (18).

Opportunistic fungal infections

Cancer patients are at risk in developing opportunistic fungal infections and in particular oral candidiasis (OC) which can involve only the oral cavity or, more often, extend towards the oropharynx and esophagus or result in systemic infection. Neutropenia resulting from cancer as well as chemotherapy and/or radiotherapy treatments will promote the shift from the carrier state of Candida species (*Candida spp*), to pathogen state, leading to clinical debilitating infections (19).

The prevalence of OC in these patients may vary from different studies in literature, depending on populations studied and diagnostic criteria adopted (20). Overall, oropharyngeal candidiasis is reported to be present in 5%–60% of patients affected by solid tumors and in 20%–80% of patients underwent autologous bone marrow transplantation (21).

Diagnosis of OC is mainly based on clinical sign and symptoms in association with medical history of the patient: however, in immunocompromised patients, where fungal infections tend to recur and become chronic, the microbiological evaluation of the *Candida spp* involved, as well as their susceptibility to antifungal treatment, may be of help in the management of these infections, avoiding the emergence of resistant strains (22).

Three main clinical forms of OC have been described in cancer patients: pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis. The most typical and easy to recognize form is the pseudomembranous (also known as oral thrush), characterized by the presence of whitish pseudomembranes that can be removed by scraping and leading to an erythematous base (**Figure 1**). Lesions tend to spread on all the mucous membranes of the oral cavity including tongue, cheeks, lips, palate and pharyngeal tissues. Often, in patients undergoing chemotherapy or radiotherapy

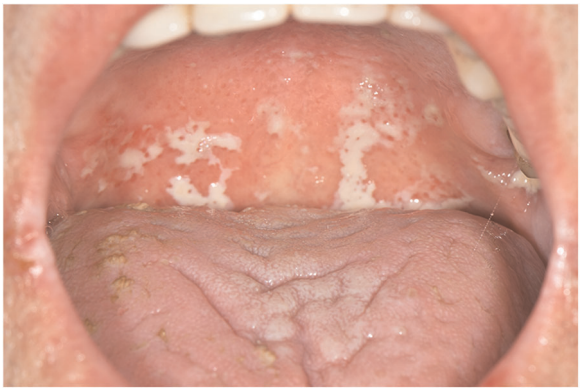

FIGURE 1
Oral pseudomembranous candidiasis of the soft palate in a cancer patient.

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of the head and neck region, this form of OC can also be observed as superinfection of oral mucositis. Erythematous candidiasis may present as acute or chronic form: it is generally associated with broad spectrum antibiotics or corticosteroids, commonly used in cancer patients. Dorsum of the tongue is the most common localization of this infection: it appears as dry, red, and shiny; palate is often simultaneously involved (kissing lesions) (20, 23).

Angular cheilitis is classified as a Candida-associated lesion: the presence of yeast is not the unique etiological agent and bacteria, mainly *Staphylococcus aureus*, are implicated in its etiology. Clinically it appears as chronic erythematous inflammatory lesion of the labial commissures (both unilaterally or bilaterally), with painful fissures that tend to bleed with time.

Symptoms associated with fungal infections can be more or less pronounced, but cancer patients affected by chronic OC complain of burning, dysphagia and difficulty in feeding, with the need to start appropriate antifungal treatment and sometimes to suspend ongoing drug therapies.

The therapy of choice for superficial oral candidiasis is topical, due to a lower risk of side effect and drug interactions, while systemic therapy is generally reserved for recurrent infections or in immunocompromised patients with already extensive infections (19, 24). Polyenes (nystatin and amphotericin B) and some topical forms of azoles (clotrimazole, miconazole) are commonly used for OC: prolonged contact of drugs with the oral mucosa is recommended, repeated several times during the day. It should be noted that not all the formulations of the different antifungal agents are always available: for example, topical formulations of amphotericin B are not available in several countries and its use is reserved as systemic treatment in hospitalized patients with severe fungal infections (**Table 1**).

Due to the frequency of fungal infections in cancer patients, the need to evaluate the efficacy of treatments that can prevent the onset of OC in these patients has emerged in the literature. In particular, a recent systematic review and network meta-analysis on 20 RCTs (26), reported that clotrimazole, compared with placebo, was the most effective antifungal agent in preventing OC, while fluconazole has the most risk-benefit profile. Unfortunately, there were no RCTs comparing clotrimazole with other antifungal agents.

TABLE 1 Typical antifungal agents used for the treatment of oral candidiasis in cancer patients.

Antifungal agents	Form	Dosage	Advantages/Disadvantages
POLYENS			
Amphotericin B	Lozenges 10 mg[a]	Dissolve 1 lozenge in the mouth 3–4 times a day after meals	Scarse drug interactions, scarse strain resistance/short duration contact time, highly sucrose sweetened
	Suspension[a]100 mg/ml	Rinse the oral cavity 4–5 times a day after meals	Scarse drug interactions, scarse strain resistance/short duration contact time, highly sucrose sweetened
Nystatin	Pastilles[a] (200.000 U each)	Dissolve 1 pastille in the mouth 4 times a day after meals for 7–14 days	Scarse drug interactions, scarse strain resistance/short duration contact time, highly sucrose sweetened
	Suspension (100.000 U/ml)	Rinse the oral cavity with 4–6 ml 4–5 times a day after meals for 21 days	Scarse drug interactions, scarse strain resistance/short duration contact time, highly sucrose sweetened
AZOLES			
Myconazole	Gel 2%, cream 2%	Apply directly on the interested area	Low risk of fungal resistance, once daily application/possible drug interactions
	Mucoadhesive tablets, 50 mg	Apply 1 tablet a day on the canine fossa for 7–14 days	Low risk of fungal resistance, once daily application/possible drug interactions
Fluconazole	Suspension 50 mg/5 ml	Rinse the oral cavity with 4–6 ml 4–5 times a day after meals for 21 days	Risk of fungal resistance, possible drug interactions
	Capsules 100–200 mg	1–2 tablets daily for 7–14 days	Indicated for mild to severe diseases/Risk of fungal resistance, possible drug interactions
Clotrimazole	Troches 10 mg	Dissolve 1 troche in the oral cavity 5 times daily	Risk of fungal resistance, possible drug interactions
	Cream 1%	Apply to affected area 2–3 times daily for 3–4 weeks	Risk of fungal resistance, possible drug interactions
Itraconazole	Capsules 100 mg	1–2 capsules daily for 7–14 days	Indicated in fluconazole-resistant diseases, possible drug interactions
Ketaconazole	Cream 2%	Apply to affected area 2–3 times daily for 3–4 weeks	Possible skin irritations and headache
	Oral tablets 200–400 mg	4 tablets daily for 14 days	Indicated in systemic fungal infections; can cause severe hepatotoxicity, potential teratogenicity, possible drug interactions

[a]Not available in all countries.
Adapted from lombardi et al 2020 (25).

Finally, the use of some probiotics species in preventing and treating oral and oropharyngeal candidiasis in different patient populations has been investigated in several studies (27–29). In particular, recently, a RCT investigated the effect of probiotic bacteria on oral *Candida spp*. counts in a group of patients who underwent head- and neck- radiotherapy, suggesting that probiotics were effective, alone or in combination with conventional therapies, in reducing *Candida spp* (30). However, although promising, many of these studies were not specifically targeted at evaluating the effect of specific probiotics on a particular host immunodeficiency status. Furthermore, further researches are needed to identify more clearly the inhibitory effect of probiotics on *Candida spp*. in the oral cavity (31, 32).

Other opportunistic infections

During oral cancer therapy, the neutrophil reduction can put patients at risk for bacterial infections, particularly odontogenic infections. Moreover, the mucositis resulting from chemotherapy represents a big gateway for bacteria into the bloodstream. The inflammatory response is altered, and in the case of infections, the clinical manifestations can be highly variable (33). Besides, the chances of maintaining proper oral hygiene are compromised and depend on numerous factors. The invasiveness of the surgery often limits the opening of the oral cavity and the possibility of accessing the posterior areas. In addition, the onset of mucositis can make oral hygiene maneuvers very painful. These variables, in addition to the reduction of salivary flow, increase the risk of caries and endodontic lesions and expose patients to the onset of periodontal and peri-implant infections. Progression of periapical infections that are untreated or unresponsive to treatment may lead to osteomyelitis of the jaws, resulting in swelling, pain, suppuration, sinus tract formation, bone sequestration, and a radiographically characteristic "moth-eaten" appearance. There are numerous bacteria which constitute normal oral flora, but which may become pathogenic with immune suppression and can cause sepsis: *Viridans Strep*, *Prevotellae*, *Fusobacterium*, *Actinobacillus actinomycetemcomitans*, and *Actinomyces species* may cause oral mucosal infections (34).

The impaired T-cell activity also exposes to viral infections. The oral viral infections include Herpes Simplex virus (HSV), Varicella Zoster virus (VZV), Epstein–Barr virus (EBV), and Cytomegalovirus are often complications of oral cancer treatments. The most common infection is Herpes Simplex. It is frequent in cases where the patient has also undergone chemotherapy in addition to radiation therapy. In particular, chemotherapy seems to be the main cause of the appearance of herpetic lesions. Depending on the patient's level of immunosuppression, exuberant clinical manifestations may occur, such as to confuse these lesions with mucositis or aphthous ulcers (35). Herpes Zoster can induce chickenpox when first infected, and then remain dormant in the neuron of a dorsal root ganglion or a cranial nerve. Later in life, or under a state of compromised immunity, the virus can re-emerge and trigger a unilateral, painful, vesicular rash along the distribution of a dermatome. Oral cancer is associated with Herpes Zoster and in particular, radiotherapy appears to increase the incidence of Herpes Zoster infection in oral cavity (36). Infection by EBV is known to cause infectious mononucleosis and is associated with many human lymphoid and epithelial cancers. The viral prevalent rates varied greatly, ranging from 15% to 77% (37) but the etiologic and tumorigenic roles of the virus in oral cancer remain unclear. Cytomegalovirus infection symptoms are generally evident in immunocompromised patients. Intra-oral lesions appear as nonspecific painful ulcers, usually present for weeks or months, on any mucosal surface. They are often mistaken for, or co-infected with, other viral or fungal infections (38).

Infections as prognostic factors in oral squamous cell carcinoma

Viral infections

At least 3% of oral cancer and 30%–60% of oropharyngeal carcinoma cases are possibly caused by HPV infection even though medical literature is still controversial (39, 40). A recent meta-analysis (41) found that HPV-positive status is an adverse prognostic factor for oral squamous cell carcinoma (OSCC), in contrast to the literature demonstrating that HPV-positive oropharyngeal squamous cell carcinomas patients have favourable treatment and survival outcomes. In particular, the result of this meta-analysis showed that the overall survival decreased in HPV-positive OSCC patients compared with HPV-negative. Furthermore, there was also significant decrease of distant control, i.e., metastases, for the patients with HPV-positive OSCC. Exploring the reasons of the difference, the Authors suggested that the prevailing variant of HPV infection in OSCC could be different from those found in other areas of head and neck HPV-positive. Also, the inactivation of HPV genetic expression p16 *via* environment factors (tobacco and alcohol) could also contribute to the different prognosis.

Of interest, could be the possible role of HPV vaccination strategies in patients suffering from head and neck squamous cell carcinoma (HNSCC). While a recent review and meta-analysis demonstrates that adjuvant HPV vaccination is associated with a reduced risk of cervical cancer and cervical intraepithelial neoplasia recurrence, the role of HPV vaccination on primary lesions and recurrences of OSCC

remain unknown (42). Nevertheless, this strategy is considered promising since the FDA have recently included prevention of HNSCC among the indications for the 9-valent vaccine (https://clinicaltrials.gov/ct2/show/study/NCT04199689), and several studies are present in literature (43–45). To note, in a recent letter to the Editor, Yilong Hao and Colleagues reported, after the HPV vaccination, the appearance of a symptomatic form of oral lichen planus, a potentially malignant disorder (46).

The Epstein-Barr virus (EBV) was the first human virus associated to oncogenic potential. EBV infects approximately 90% of the world's adult population asymptomatically, and although EBV's role in oral carcinogenesis has not been established yet, its etiological role has been demonstrated in hairy leukoplakia, nasopharyngeal cancer, Burkitt's lymphoma, Hodgkin's disease, and B-cell lymphoma. In a paper aimed to collect data on the prevalence of EBV DNA in patients with OSCC, oral lichen planus, and oral leukoplakia in an eastern Hungarian population, the Authors (47) found that Epstein–Barr virus-positive and EBV-negative OSCC patients did not statistically differ in patient characteristics and exposure to risk factors (smoking and alcohol consumption). Furthermore, the presence of EBV in the tissues of the oral diseases and in OSCC did not increase, respectively, the risk of poor outcome or not influenced the survival (48).

Regarding the Human Immunodeficiency Virus-1 (HIV-1), the introduction of the antiretroviral combined therapy reduced the incidence of AIDS-associated cancers, in particular, Kaposi sarcoma and non-Hodgkin lymphoma. On the contrary, some others cancers, the so-called non-AIDS-defining cancers, have increased significantly (49). Among these, head and neck squamous cell cancers. A recent paper (50) explored the prognostic significance of the HIV infection in patient with head and neck cancer. The Authors, considering age at initial diagnosis, localization, and stage, found a significant difference in both overall survive and disease-free survival rates between patient living with HIV infection and HIV-negative well-matched patients.

Fungal infections

It is well known that chronic hyperplastic candidiasis is of particular significance due to the potential of malignant transformation that could be, in untreated patients, as high as 10% of the cases (51). Furthermore, several studies showed that Candida species are prevalent in oral squamous cell cancer patients as expected. Regarding the potential effects on oral cancer prognosis of fungal infection, recently, in a population of 100 patients suffering from OSCC the Authors did not observe a statistically significant effect of the yeast on the mortality rate (52).

However, the role of *Candida spp*. in the process of oncogenesis it has been studied and various pathogenic mechanisms involved in epithelial transformation have been investigated (53). Recently, candidalysin, a cytolytic toxin peptide exclusively secreted by pathogenical hyphal forms of *C. albicans*, it has been reported to be essential in epithelial damage and host recognition of candidiasis. This toxin is encoded by ECE1 gene, associated with fungal filamentation and host cell adhesion. Candidalysin damages the epithelial cells, inducing innate immune host response and promoting the expression of cytokines that can contribute to carcinogenesis (54, 55).

Bacterial infections

Syphilis is a chronic systemic infectious disease caused by the spirochaetal bacterium Treponema pallidum, that has predominant muco-cutaneous lesions, with or without systemic symptoms after the involvement of internal organs. In a recent paper (56), the authors aimed to verify if syphilis has an influence on prognosis in patients suffering from OSCC. Data were retrieved from the TriNetX network, a database that includes clinical data from many health care organizations from different countries. This study did not show a negative influence of syphilis on the five-year survival rate of patients with OSCC, compared to patients without syphilis.

Discussion

In order to assure a healthy mouth and a good quality of life, the management of oral cancer survivors requires a multidisciplinary approach and the involvement of specialist and non-specialist health care providers.

Because of a number of local and systemic conditions, subjects who received a diagnosis of mouth cancer, and have been treated for that, can be at high risk of local infections of any nature: bacterial, viral, mycotic, that can affect the wellbeing of these subjects, and complicate the course of the disease.

Thus, any health care provider involved in the management of oral cancer survivors should be aware of the infectious conditions that they can face and of the consequences that they might have on the oral and general health of this fragile subjects. That is clearly expressed by the American Cancer Society Head and Neck Cancer Survivorship Care Guidelines (endorsed by the American Society of Clinical Oncology) (57): besides recommending "to maintain close follow-up with

the dental professional", since "preventive care can help reduce caries and gingival disease", they state that "primary care clinicians should refer head and neck cancer survivors to a qualified dental professional for treatment and management of complicated oral conditions and infections" (recommendation 3.20) (58).

Author contributions

Conceptualization, GL, MM and AS; methodology, EMV and NL; data curation, GL, MM, AS and AP; writing—original draft preparation, MM, AS, NL, EMV, GL and AP; writing-review and editing, GL, NL and EMV. 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.

Publisher's note

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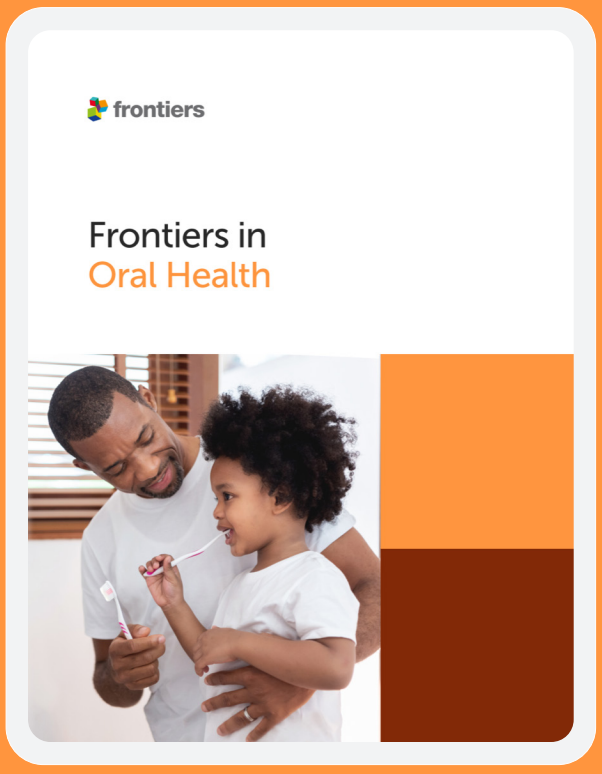

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