Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE To provide evidence-based recommendations for prevention and management of osteoradionecrosis (ORN) of the jaw secondary to head and neck radiation therapy in patients with cancer.

METHODS The International Society of Oral Oncology-Multinational Association for Supportive Care in Cancer (ISOO-MASCC) and ASCO convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. PubMed, EMBASE, and Cochrane Library databases were searched for randomized controlled trials and observational studies, published between January 1, 2009, and December 1, 2023. The guideline also incorporated systematic reviews conducted by ISOO-MASCC, which included studies published from January 1, 1990, through December 31, 2008.

RESULTS A total of 1,539 publications were initially identified. There were 487 duplicate publications, resulting in 1,052 studies screened by abstract, 104 screened by full text, and 80 included for systematic review evaluation.

RECOMMENDATIONS Due to limitations of available evidence, the guideline relied on informal consensus for some recommendations. Recommendations that were deemed evidence-based with strong evidence by the Expert Panel were those pertaining to best practices in prevention of ORN and surgical management. No recommendation was possible for the utilization of leukocyte- and platelet-rich fibrin or photobiomodulation for prevention of ORN. The use of hyperbaric oxygen in prevention and management of ORN remains largely unjustified, with limited evidence to support its practice.
Additional information is available at www.asco.org/head-neck-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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TARGET POPULATION AND AUDIENCE

Target Population

Adult patients scheduled to receive or who have received at least 50 Gy head and neck RT for head and neck malignancies.

Target Audience

Radiation oncologists; medical oncologists; head and neck surgeons; otolaryngologists; other physicians; oral and maxillofacial surgeons; dental specialists including practitioners of oral medicine, oral and maxillofacial pathology, and oral and maxillofacial radiology; general dentists; oncology nurses; advanced nurse practitioners; nurse navigators; social workers; clinical researchers; and patients with HNC receiving RT.

INTRODUCTION

The purpose of this guideline is to provide contemporary recommendations for prevention, assessment, grading, and management of osteoradionecrosis (ORN) of the mandible and maxilla in patients with head and neck cancer (HNC) previously treated with head and neck radiation therapy (RT). ORN is a mechanistically complex, clinically impactful risk of head and neck RT in patients with HNC. An interprofessional Panel was assembled to develop clinical recommendations directed to this condition, on the basis of ASCO methods for guideline production.

ORN has been historically characterized by nonhealing exposed oral bone in a patient who has been treated with RT for HNC.[1,2] Treister et al[3] have reported that the 2-year incidence of exposed bone was 6.1%, with an incidence of confirmed ORN of 3.1%. Although and perhaps because of its relatively infrequent occurrence across at-risk patients, there continue to be varying approaches to diagnosis and management.[4] ORN can result in considerable morbidity, including a constellation of adverse events associated with and/or caused by the lesion. As reported by Tasoulas et al,[5] poor oral health, including ORN, can influence long-term survival of patients with HNC. Long-term effects of HNC treatment increase the costs of patient survivorship.[6] Prevention of oral complications in these patients, including prevention of ORN, would reduce costs associated with utilization of health care resources. However, barriers to interprofessional oncology practice continue to exist.[7] Addressing these collective issues continues to be of high importance, given the global, regional, and national burden of HNC.[8]

In this context, evidence-based interprofessional practice combined with ongoing patient and family education can substantially mitigate the clinical and cost-of-care impact for patients with HNC. This joint guideline between ASCO and the Multinational Association of Supportive Care in Cancer-International Society of Oral Oncology (MASCC-ISOO) is directed to this overarching theme.

GUIDELINE QUESTIONS

This clinical practice guideline addresses six overarching clinical questions: (1) How should ORN be characterized, graded, and reported? (2) What are the recommended best practices for the prevention of ORN of the head and neck prior to radiation therapy? (3) What are the recommended best practices for the prevention of ORN after radiation therapy? (4) How should ORN be managed nonsurgically? (5) How should ORN be managed surgically? (6) When, how, and by whom should patients diagnosed with ORN be assessed for adverse events associated with and/or caused by ORN?

METHODS

Guideline Development Process

Multinational Association of Supportive Care in Cancer-International Society of Oral Oncology (MASCC-ISOO) and ASCO convened an Expert Panel (Appendix Table A1, online only) to consider the evidence and formulate the recommendations. Members of the Expert Panel were identified from both community and academic settings and had collective expertise in dental medicine including oral medicine and oral and maxillofacial surgery, radiation oncology, surgical oncology, medical oncology, otolaryngology, head and neck surgery, and biostatistics. The Expert Panel also included a patient representative and an ASCO guidelines staff specialist with health research methodology expertise. The Expert Panel convened via teleconference and corresponded through e-mail. On the basis of the consideration of the evidence, authors were asked to contribute to the development of the guideline, provide critical review, and finalize guideline recommendations.

PubMed, EMBASE, and Cochrane library database were searched for randomized controlled trials (RCTs) or observational studies that were published from January 1, 2009, through December 2023. This systematic review was an update to a previous MASCC-ISOO review that was published in 2010.[1] The search strategy is provided in the Data Supplement (online only). The online software Covidence[9] was used for importing citations from literature searches, screening abstracts and titles, and screening full texts.

Inclusion criteria consisted of publications in the English language, in a peer-reviewed journal, and that assessed the oral manifestations of head and neck RT to the jaw in adult

patients undergoing cancer therapy. Exclusion criteria consisted of (1) preclinical studies; (2) non–head and neck cancer; (3) no history of RT to head and neck; (4) history of treatment with bone-modifying agents; (5) ORN not involving maxilla and/or mandible; (6) pediatric studies; (7) meeting abstracts not subsequently published in peer-reviewed journals; (8) editorials, commentaries, letters, news articles, case reports of less than five patients, and narrative reviews; (9) non-English language publication; and (10) sample size less than five participants. The systematic review of the evidence revealed a dearth of evidence on which to base the recommendations.

Members of the Expert Panel were responsible for reviewing and approving the final version of the guideline. This process involved the drafting of recommendations by a subgroup of the Expert Panel using clinical expertise and available evidence, followed by discussion and approval of the draft recommendations with the full Expert Panel.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from September 6 through 20, 2023. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 107 respondents and 227 written comments received. Of the 35 recommendations drafted, approximately 98% of the responses either agreed or agreed with slight modifications to the recommendations and 2% of the responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

All changes were incorporated into the final manuscript before ASCO EBMC, ISOO Board, and MASCC Guidelines Committee review and approval. In addition, before publication, this joint guideline was endorsed by the American Head and Neck Society, the American Society for Radiation Oncology, the American Association of Oral and Maxillofacial Surgeons, and the American Academy of Oral Medicine.

As with all ASCO guidelines, this guideline was ultimately reviewed and approved by the ASCO Evidence-Based Medicine Committee (EBMC) before submission to *Journal of Clinical Oncology* for editorial review and consideration for publication. The guideline was also reviewed and approved by the ISOO Board and MASCC Guidelines Committee. All funding for the administration of the project was provided by MASCC-ISOO and ASCO.

Guideline Updating

The International Society of Oral Oncology-Multinational Association for Supportive Care in Cancer (ISOO-MASCC)-ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ISOO-MASCC-ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

TABLE 1. Characteristics of Studies Identified in the Literature Search

Topics	RCT	Prospective (non-RCT)	Retrospective	Total
Grading				
Grading	0	0	2	2
Prevention				
Before RT	0	3	15	18
After RT	0	3	5	8
Mixed	0	0	2	2
Management				
Medication	0	2	6	8
HBO	6	1	4	11
Surgery	0	4	20	24
Combination	0	0	6	6
Laser (PBM)	0	1	0	1
Total	6	14	60	80

Abbreviations: RCT, randomized controlled trial; RT, radiation therapy; HBO, Hyperbaric Oxygen; PBM, photobiomodulation.

RESULTS

Characteristics of Studies Identified in the Literature Search

Eighty publications were identified on the basis of the search strategy described in the Methods section. Of these, six were RCTs, [10-15] 14 were prospective studies,[3,16-29] and 60 were retrospective studies.[30-50,51-89] The identified trials were published between 2004 and 2023. The studies compared different approaches in prevention, surgical, and nonsurgical management of ORN. The outcomes included incidence, duration, healing of ORN, and quality of life (QoL). The summary of the characteristics of studies by intervention is included in Table 1. Further characteristics of the studies' participants and systematic review flow diagram are presented in the Data Supplement.

Evidence Quality Assessment

The quality of evidence of the studies was evaluated via Risk of Bias methodology and instrument via the Covidence platform. This rating includes factors such as study design, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect. Refer to Appendix Table A2 for definitions of the quality of the evidence and the Methodology Manual for more information.

RECOMMENDATIONS

All recommendations are available in Table 2 and are derived from the 72 systematically reviewed publications.[3,10-40,41-70,71-89]

CHARACTERIZATION, GRADING, AND REPORTING OF ORN

Recommended Workup to Characterize ORN

Literature Review and Analysis

A review of the literature revealed a single study by Watson et al[83] with evidence in support of a particular system for the workup and characterization of ORN of the jaw (mandible, maxilla), the ClinRad classification system. Shaw et al[90] outlined ideal characteristics of a staging and grading system for ORN, and the new ClinRad system meets these criteria.

Clinical Interpretation

ORN of the jaw should be operationally characterized as:

radiographic lytic or mixed sclerotic lesion of bone
and/or
visibly exposed bone
and/or
bone probed through a periodontal pocket or fistula (Figs 1A and 1B)

occurring within an anatomical site previously exposed to a therapeutic dose of head and neck RT.

To facilitate clinical implementation of the enclosed recommendations, the Panel has adopted the ClinRad classification system. The Panel arrived at this decision through examination of existing literature. ORN has a widely divergent series of definitions, diagnostic criteria, and related diagnoses described in the medical literature. Current clinical definitions can be collectively summarized insofar as the majority infer a temporal relationship to RT, occurrence within bone, evidence of devitalization, devascularization, or necrosis. However, some definitions utilize differential clinical, radiographic, or therapeutic criteria, and there is divergence regarding duration of observed clinical, radiographic, or therapeutic features. The ClinRad system addresses the recommendations made by Shaw et al[90] and demonstrated superior statistical performance when analyzed against other ORN classification systems in the medical literature.

The Panel also favored the ClinRad system as it was designed in order to be comprehensive enough to be used across providers and specialties (eg, including oral health, dental, surgical, and oncology providers) who might use different assessment methods (eg, oncologists are unlikely to probe periodontal pockets, while many dentists do not routinely order tomographic imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) used by oncologists in postradiation surveillance), and yet simple enough to communicate a stable intrinsic description of ORN as a recognizable disease state (which prior literature review has shown is, in fact, quite challenging).

This is not trivial, given that ORN is typically defined through the incipient causative event (RT exposure to bone). Unlike other necrotic states, direct biopsy or tissue sampling is neither routinely used nor recommended by this Panel, as the biopsy or tissue excision itself might engender disease progression. Moreover, there is a lack of concordance regarding the temporal or causal relationship between pathognomonic injury (ie, devascularized or devitalized bone) and apparent clinical presentation (eg, cortical thinning, mandibular fracture, or mucosal ulceration), and the presence or absence of alternative criteria (eg, infection, secondary malignancy). That is, patients may, in fact, exhibit marrow changes or vascular alterations on CT or MRI for months or years before clinically evident ORN. Thus, our goal was to arrive at a formalism that would allow clinicians to define ORN not as a pathophysiologic process or specialty-specific diagnostic criteria, but rather as a coherent and easily recognizable clinical event.

Notably, ORN, unlike medication-related osteonecrosis of the jaw (MRONJ, International Classification of Diseases M87.180), until recently has lacked a formal designation in the International Classification of Diseases. However, the 11th edition[91] cospecifies two designations (FB81.5 Osteonecrosis due to ionizing radiation, "Necrosis of bone attributable to ionizing radiation, most commonly seen affecting the mandible following radical radiation therapy for the treatment of head and neck cancer or the chest wall following radiation therapy for breast cancer" with specific anatomy code XA51B7, "Mandible"; alternatively, the nonspecific coding DA06.0, "Inflammatory conditions of jaws" includes "osteoradionecrosis" as one of many synonyms).

To provide a practical and working clinical construct for the implementation of the proposed guidelines, we have arrived at the listed characterization using the following premises:

- The characterization should be clinically relevant and reflect current clinical practice [practical]
- The characterization should be readily understandable by managing clinicians using referential language, without qualifying quantitative measurement components (such as centimeters of exposed bone or probe depth) [semantic]
- The characterization should be reasonable, comprehensive, and scalable using clinical or radiographic methods without specialty-specific devices or additional testing (eg, biopsy, pathologic confirmation) [clinical]
- The characterization should be assessable independently on a given clinical examination visit or assessment, without requiring knowledge of duration or prior severity of the condition [time-independent]

TABLE 2. Summary of Recommendations

Clinical Question	Recommendation	Type	Evidence Quality	Strength of Recommendation
1. How should ORN be characterized, graded, and reported? a. Which patients should be considered at high risk for ORN? b. What is the recommended workup to characterize ORN?	1.1. Osteoradionecrosis of the jaw (mandible, maxilla) should be characterized as a radiographic lytic or mixed sclerotic lesion of bone and/or visibly exposed bone and/or bone probed through a periodontal pocket or fistula, occurring within an anatomical site previously exposed to a therapeutic dose of head and neck radiation therapy	Informal consensus	Low	Strong
	1.2. A patient with radiation dose to the jaw of 50 Gy or higher should be considered at risk for development of ORN. Modifiable risk factors including poor oral hygiene, dentoalveolar surgeries, and/or tobacco use, should be considered as further increasing this lifelong risk	Evidence-based	High	Strong
	1.3. Clinicians evaluating ORN should utilize the ClinRad staging system for ORN, as should clinical trials	Evidence-based	Moderate	Strong
	1.4. ORN assessment should have a defined formal characterization for disease evaluation at each visit which is usable across members of the clinical care or provider specialty spectrum. The panel recommends utilizing the ClinRad Classification system for ORN developed by Watson et al[83]	Evidence-based	Moderate	Strong
	1.5. ORN case reporting and diagnosis should include formal informatics, ontology, and lexical standards consistent with the characterization noted in Recommendation 1.1	Informal consensus	Low	Strong
	1.6. Recommended initial evaluation of ORN should include one or more of the following: (1) clinical intraoral examination (including direct visual or endoscopic examination and/or formal periodontal assessment) and/or (2) formal radiographic examination (ie, x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging)	Evidence-based	Moderate	Strong
	Qualifying statement: If either clinical or radiographic findings are initially detected, suspected or positive, subsequent confirmatory examination or imaging assessment is recommended			
	1.7. Recommended serial characterization or surveillance of ORN should include clinical intraoral examination (including direct visual, endoscopic examination, and/or comprehensive periodontal assessment) and comprehensive radiographic examination (ie, x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging)	Evidence-based	Moderate	Strong
2. What are the recommended best practices for the prevention of ORN of the head and neck prior to radiation therapy?	2.1. Target coverage of tumor should not be compromised to avoid dose to bone	Evidence-based	Moderate	Strong
	2.2. Advanced radiation planning techniques (eg, IMRT, IMPT) should be employed to deliberately reduce radiation dose to the jaw at risk as much as possible	Evidence-based	Moderate	Strong
	2.3. Focused effort should be made to reduce the mean dose to the jaw and the volume of bone receiving above 50 Gy, whenever possible	Evidence-based	Moderate	Strong
	*Qualifying statement: While tumor site (*eg, *oropharynx, oral cavity) and size impacts the specific dosimetric parameters that are achievable in each patient, the overall goal of reducing as much volume of bone receiving higher doses applies uniformly*			
	2.4.1. A dental assessment by a dentist (with a dental specialist if possible) is strongly advised prior to therapeutic-intent radiation therapy to identify and remove teeth which will place the patient at risk of ORN during the patient's lifespan, and to comprehensively educate the patient about lifelong risk of ORN	Evidence-based	Moderate	Strong
	2.4.2. Dental extraction, if clinically indicated, should occur at least 2 weeks prior to commencement of radiation therapy. In the setting of rapidly progressing tumor, extractions should be deferred and not cause a delay in the initiation of radiation therapy (see dental clearance, Appendix Table A3)	Evidence-based	Moderate	Strong
	2.5.1. (general dentists and dental specialists) Teeth with poor prognosis including moderate-severe periodontal disease, within a field of therapeutic-intent radiation therapy should be removed prior to RT to reduce the risk of ORN. In addition, teeth with periapical disease, caries and partially erupted third molars should be considered for treatment depending on tooth location, patient risk factors for ORN, and timing available for healing	Evidence-based	Moderate	Strong

(continued on following page)

TABLE 2. Summary of Recommendations (continued)

Clinical Question	Recommendation	Type	Evidence Quality	Strength of Recommendation
	2.5.2. (radiation oncologists) Oral assessment, including a comprehensive dental, periodontal, and oral radiographic exam when feasible, should be performed by a dentist or dental specialist as early as possible prior to initiation of head and neck radiation therapy. Information about the planned volume to be irradiated, anticipated dose to the mandible and maxilla, and radiation therapy start date should be provided to the dentist or dental specialist	Evidence-based	Moderate	Strong
	2.6. A 2-week healing period between time of dental extraction and start of radiation therapy is advised only when this does not result in a delay to starting RT which may compromise oncologic control. If planned extractions will alter the vertical dimension of occlusion, they should be performed prior to fabrication of the immobilization mask that will be worn during RT	Evidence-based	Moderate	Strong
	2.7. Patients at risk of radiation-induced salivary hypofunction should be instructed to use prescription-strength topical fluoride applied to the teeth daily to reduce the risk of postradiation caries, which in turn decreases risk of postradiation extractions and ORN	Evidence-based	High	Strong
	2.8. Modifiable risk factors that place patients at risk of ORN, like those listed in Recommendation 1.2, should be addressed prior to, during, and after radiation therapy	Evidence-based	High	Strong
3. What are the recommended best practices for the prevention of ORN after radiation therapy?	3.1. Prior to finalizing dental treatment plans in patients with a history of head and neck radiation therapy, review of the radiation therapy plan should be performed with particular attention focused on dose to mandible and maxilla	Evidence-based	Moderate	Strong
	3.2. For teeth in areas at high risk for ORN, alternatives to dental extraction (eg, root canal, crown, filling) should be offered unless the patient has recurrent infections, intractable pain, or other symptoms that cannot be alleviated without extraction. Similarly, dental implants in high-risk zones for ORN should be avoided unless alternatives to restoring oral function are not possible	Evidence-based	Moderate	Strong
	3.3. It is recommended that patients considered to be at higher risk for ORN due to prior radiation therapy encompassing the mandible and/or maxilla at site(s) of planned dental intervention receive oral antibiotics before and after invasive dental procedures, such as dental extraction and/or implant placement	Informal consensus	Low	Weak
	3.4. Patients at risk for ORN who have delayed healing after dental extraction may be prescribed antiseptic mouth rinses. Chlorhexidine gluconate (eg, 0.12% or 0.2%) solution or povidone-iodine mouth rinses should be performed at least twice daily until sufficient healing has been achieved based on close follow-up evaluation with the treating dentist or oral surgeon	Informal consensus	Low	Weak
	3.5. It is recommended that pentoxifylline (400 mg twice daily) and tocopherol (1,000 IU once daily) be prescribed for at least 1 week before and 4 weeks after invasive dental procedures (preferably until the dental socket has healed) in cancer-free patients	Evidence-based	Low	Weak
	Qualifying statement: This should be considered for patients at elevated risk for ORN due to prior radiation therapy dose ≥50 Gy to the mandible or maxilla at site of the dental intervention unless the patient has contraindications to pentoxifylline and/or tocopherol such as increased bleeding risk			
	3.6. Routine use of prophylactic hyperbaric oxygen (HBO) therapy prior to dental extractions in patients who received prior head and neck radiation therapy is not recommended	Evidence-based	Low	Weak
	Qualifying statement: Prophylactic HBO may be offered to patients undergoing invasive dental procedures at site(s) where a substantial volume of mandible and/or maxilla received >50 Gy			
	No recommendation. Due to limited, low-quality available evidence, no recommendation can be made regarding utilization of leukocyte- and platelet-rich fibrin or photobiomodulation therapy to prevent ORN for patients undergoing dental procedures after head and neck radiation therapy			
4. How should ORN be managed nonsurgically?	4.1. Pentoxifylline may be used in cancer-free patients with mild, moderate, and severe cases of ORN and is most likely to have a beneficial effect if the treatment is combined with tocopherol, antibiotics, and prednisolone	Evidence-based	Moderate	Weak
	4.2. HBO therapy in conjunction with surgical intervention may be used in cancer-free patients with mild, moderate, and severe cases of ORN. Potential benefit is most likely to be observed in mild cases	Informal consensus	Low	Weak

(continued on following page)

TABLE 2. Summary of Recommendations (continued)

Clinical Question	Recommendation	Type	Evidence Quality	Strength of Recommendation
5. How should ORN be managed surgically?	5.1.1. In partial thickness ORN (ClinRad stage I or II), surgical management can start with transoral minor intervention which can lead to resolution. This may include debridement, sequestrectomy, alveolectomy, soft tissue flap closure	Evidence-based	High	Strong
	Qualifying statement: Partial thickness ORN is defined as disease extent whereby removal of all necrotic bone leaves native jaw with enough structural integrity such that oroantral or oronasal defect is unlikely in the maxilla, and pathological fracture in unlikely in the mandible			
	5.1.2. Small defects <2.5 cm in length may heal spontaneously with local measures. It is recommended that larger defects be covered with vascularized tissue	Evidence-based	Moderate	Strong
	5.2. In full thickness ORN (ClinRad selected stage II and all stage III), segmental maxillectomy or mandibulectomy with free flap reconstruction is recommended	Evidence-based	High	Strong
	Qualifying statement: Full thickness ORN is defined as disease extent whereby removal of all necrotic bone is likely to result in oroantral or oronasal defect in the maxilla or pathological fracture in the mandible			
	5.3. In full thickness ORN or extensive partial thickness ORN where conservative therapy has not yielded appropriate disease control (ClinRad stage II or III), segmental resection is recommended	Evidence-based	High	Strong
	5.4.1. Maxillectomy defects that extend into the sinus (ClinRad stage III) can be reconstructed with myocutaneous flaps or osteomyocutaneous flaps, whereby the latter has the additional benefit of allowing dental implantation where desired. Obturation of the defect with a prosthetic appliance may also be done for those patients who are poor candidates for microvascular surgery	Evidence-based	High	Strong
	5.4.2. Osteomyocutaneous free flap reconstructions are recommended for mandibular continuity defects. A spanning reconstruction plate across a segmental defect covered by a myocutaneous flap may be an alternative in select settings where the medical status of the patient is compromised, or the treating institution has a limited scope of maxillofacial reconstruction	Evidence-based	High	Strong
	5.5. Free flaps are recommended over pedicle flaps. Free flaps offer greater versatility and improved outcomes. Pedicle flaps can be used, especially in salvage procedures, with some limitations	Informal consensus	Low	Strong
	5.6. Preoperative radiographic interpretation of extent of compromised bone, with intraoperative confirmation via bleeding bone endpoint, should be utilized in determination of resection borders. The potential for intraoperative findings to alter the resection margin should be a consideration in planning. If prefabricated cutting guides are used, contingency planning is recommended	Informal consensus	Low	Strong
	5.7.1. When patients are unfit to undergo definitive surgical treatment, the management should be focused on symptom control	Informal consensus	Moderate	Strong
	5.7.2. Removal of superficial bony sequestra should be performed if viewed as low risk by the clinician. Reduction of the disease burden and the biofilm environment can be synergistic with the ongoing systemic therapy	Informal consensus	Moderate	Strong
6. When, how, and by whom should patients diagnosed with ORN be assessed for adverse events associated with and/or caused by ORN? (a) If ORN-associated adverse events are identified, how should they be managed?	6.1. Patients should be assessed by their healthcare providers for presence of adverse events at the time of ORN diagnosis, and periodically thereafter until resolution based upon patient status including response to intervention	Informal consensus	Low	Strong
	6.2. Given lack of data specific to management of adverse events associated with ORN, management should be informed by pertinent available guidelines developed for analogous symptoms and/or disease states	Informal consensus	Low	Strong

Abbreviations: HBO, hyperbaric oxygen; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; ORN, osteoradionecrosis; RT, radiation therapy.

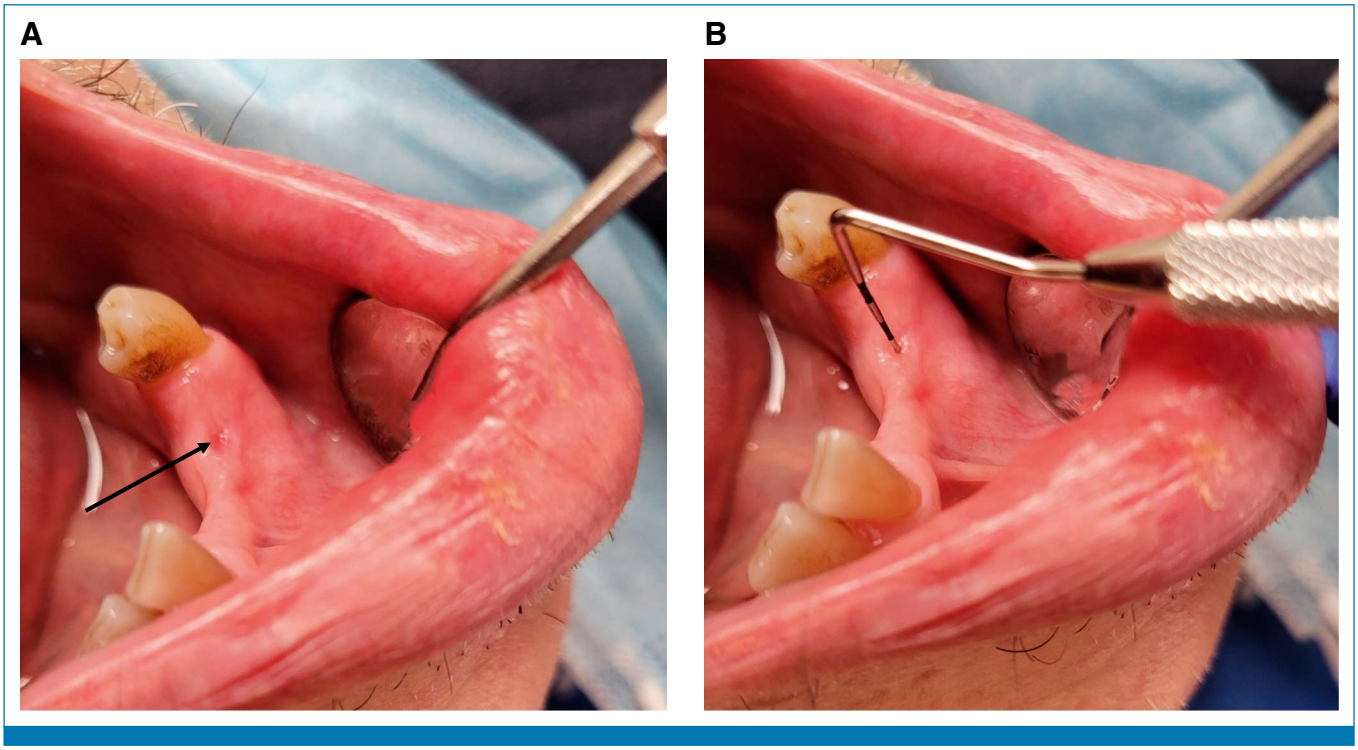

FIG 1. (A) Fistula present in edentulous anterior left mandible (arrow), without using a dental instrument probe. The lesion is subtle in clinical presentation. (B) The same fistulous lesion seen in (A), using a dental instrument probe to facilitate clinical visualization.

- The characterization should be nonsyndromic and include directly observable physical examination or radiographic features, rather than including associated patient- or clinician-reported symptoms (eg, pain) [objective]
- The characterization should be sufficiently broad to be integrated within both Panel-derived and independent severity scales and staging systems [flexible]
- The characterization should be sufficiently descriptive as to encompass disease states reasonably attributable as ORN across human- and machine-interpretable nomenclatures and/or ontologies [scalable and interoperable]
- The characterization should be based on meeting one or more of the listed criteria, rather than a diagnosis of exclusion (eg, "non-septic and unrelated to synchronous malignancy") [affirmative]

During Panel discussion, there was a consensus to place emphasis on clinical signs and symptoms in conjunction with radiographic findings as a practical approach in diagnosing ORN. This is not to underestimate the importance of histology or specialized imaging and the role they can play when available in a more advance care setting. Practically, biopsy adds potential for initiating loss of tissue, and current imaging biomarkers for post-RT bone alteration are utilized rarely outside research centers. Consequently, the characterization was decided to be rooted on *post-RT consequential injury* that centers around *observable loss of bone and periosteal integrity* as the key construct for the transition from potential precursor injury states (ie, post-RT tissue changes, vascular alteration of bone, or profibrotic marrow and/or tissue alterations) toward *ORN as a distinct clinical condition*, without using a time factor or duration, nor incorporating "syndromic" definitions by requiring the presence or absence of commonly associated signs (eg, mucosal ulceration, or frank mandible fracture) or frequently noted consequential symptoms (ie, the presence or absence of associated pain or trismus).

PREVENTION OF ORN OF THE HEAD AND NECK PRIOR TO RT

Radiation Dosimetry

Literature Review and Analysis

No randomized trials were identified by the systematic review. Several retrospective reviews have been performed investigating this question. Intensity-modulated radiation therapy (IMRT) reduces dose to organs at risk, which should be contoured based on consensus guidelines.[92] Several comparative reviews of IMRT to three-dimensional conformal RT demonstrated significant reduction of rates of ORN in patients treated with IMRT, while others have failed to show a difference.[84,85] However, rates of ORN have decreased over time, which is thought to be at least in part due to the increasing use of IMRT.[3,28] The largest study that has examined dosimetry parameters for bone avoidance was a study of 1,259 patients with HNC treated with chemoradiation, which showed that limiting no more than 30% of

the mandible to receive a dose of 35 Gy or more confers a <5% risk of ORN for patients undergoing pretreatment dental extractions. For patients without pretreatment dental extractions, limiting no more than 30% of the mandible to receive a dose of 42 Gy or more confers a <5% risk of ORN.[29] This study and several others have shown that the volume of mandible receiving at least 50 Gy (V50Gy) is significantly associated with ORN risk.[29,86-89] Another dosimetric parameter identified with lower risks of ORN in several studies was lowering the mean dose to the mandible. While this holds qualitatively across several studies, the absolute quantitative planning goal is less clear. Similarly, a recent review of relevant studies demonstrates a variety of different dosimetric parameters associated with mandibular ORN, such as mean dose <37 Gy, V44Gy <42%, and V58Gy <25%.[93]

Clinical Interpretation

These recommendations were formulated by extrapolating the best available data and incorporating expert consensus. A patient with radiation dose to the jaw of 50 Gy is at higher risk of developing ORN.

Dental Interventions

Literature Review and Analysis

Seven studies were included that reviewed preventive dental interventions or extractions prior to head and neck RT. No randomized trials were identified. Two prospective observational cohort studies[22,81] and five retrospective cohort studies [37,40,50,63,82] were included. In the prospective study by Lalla et al,[81] 572 patients were examined prior to RT and followed prospectively over 2 years. Tooth-level predictors of tooth loss and bone exposure post-RT were reviewed. Pre-RT tooth-level predictors of tooth-loss post-RT included hopeless teeth not extracted pre-RT (hazard ratio [HR], 17.1), untreated caries (HR, 5.0), periodontal pockets 6 mm or greater (HR, 3.3) or equaling 5 mm (HR, 2.2), recession over 2 mm (HR, 2.9), furcation score of 2 (HR, 3.3), and any mobility (HR, 2.2). Pre-RT tooth-level predictors for bone exposure post-RT included hopeless teeth not removed prior to RT (risk ratio [RR], 18.7) and periodontal pockets 6 mm or greater (RR, 5.4) or equaling 5 mm (RR, 4.7). In the prospective study performed by Muraki et al,[22] oral care protocols and dental intervention before and after RT were reviewed with 39 (58%) of 67 patients undergoing pre-RT dental extractions. Within the first 2 years after RT, 7% of patients developed bone exposure which had resolved in all patients by 2 years.

The retrospective study by Chang et al[37] reviewed national insurance data of 17,290 control cases and 941 ORN cases and found an association between pre-RT scaling, use of chlorhexidine, and ORN. The study had several methodological issues that make it difficult to interpret the results, with scaling and chlorhexidine likely acting as surrogate markers for periodontal disease, which was not controlled for. Liao et al[50] retrospectively compared timing of pre-RT extractions and risk of ORN in 5,010 controls and 52 cases with ORN using the staging system developed by Tsai et al.[86] Pre-RT extractions were not associated with risk of ORN even when occurring within 7 days of RT initiation, and no difference was observed in rates of ORN between groups who had teeth removed 1-7 or 8-21 days prior to RT, respectively. Rather, ORN risk was significantly associated with pre-RT tumor excision, mandibulectomy, and tumor site. Shih et al[63] performed a retrospective analysis of national insurance data for a cohort of 24,353 patients.[63] They found that a 2 week interval between tooth extractions and initiation of RT did not significantly reduce the incidence of ORN, with no significant difference in ORN rates between patients with extractions within 2 weeks of starting RT and extractions occurring prior to 2 weeks. Dumoulin et al[40] retrospectively assessed pre-RT interventions in 384 control cases and 31 ORN cases. Despite methodological issues, there was evidence to support the notion that post-RT extractions are associated with an increased risk of ORN. Most recently, Lee et al conducted a retrospective review of 879 patients who underwent extractions prior to radiation for HNC, of whom 3% developed ORN related to the preradiation extraction. They found a strong association between extractions performed within 7 days of starting radiation and risk of ORN.[63,82]

In addition to the studies included in the evidence base for this guideline, the formal consensus process guidance document by Watson et al[94] suggests which teeth to remove prior to RT based on location (maxilla *v* mandible), position (anterior or premolar *v* molar), patient risk factors (smoking, poor compliance with dental care, prognosis) and tooth-level factors (caries, periapical disease, periodontal disease). All teeth with periodontal disease stage III or greater were recommended for removal, while partially erupted third molars were only recommended for removal if adequate healing time existed between extraction and RT start date.

In contrast, no recent studies were identified that evaluated the impact of fluoride gels on the risk of ORN. A 2019 Cochrane review performed by El-Rabbany et al[95] reviewed a randomized control trial between two fluoridation methods, with no difference noted in rates of ORN. The ASCO guideline for salivary hypofunction did not make recommendations for prevention of post-RT caries.[96]

Clinical Interpretation

The results of the prospective observational study[81] confirm many of the recommendations from the formal consensus process.[94] Both hopeless teeth and periodontally involved teeth not removed prior to RT will place a patient at significantly increased risk of ORN. This finding supports the importance of referral to an appropriate dental specialist (including hospital-based dental oncologists) to perform a

complete dental, periodontal, and radiographic exam, as well as careful review of patient risk factors, to detect teeth such as these that, if not removed, will place the patient at increased risk of ORN post-RT. Patients require significant education about the lifelong risk of ORN and strategies to mitigate risk, including the importance of good oral hygiene, in particular maintenance of periodontal condition, regular clinical and radiographic exams to detect any developing dental issues at an early stage, and the importance of avoiding dentoalveolar surgeries in the future. In some patients, for example, elderly patients with a limited prognosis, or patients with trismus complicating dental treatment, more limited evaluation protocols may be necessary. The reviewed studies provided conflicting evidence regarding a significant association between timing of pre-RT extractions and risk of ORN. In addition, the reported rates of ORN associated with pre-RT extraction were low (2%-3%). The panel recommends a 2-week period of healing, if oncologically safe, should be provided between date of dental extraction and start of RT to reduce the risk of ORN. However, the Panel strongly agreed that RT should not be delayed solely based on dental extractions when delay could compromise oncologic control. In situations where a patient does not have one to 2 weeks of healing available and presents with hopeless teeth within the planned radiation field, the Panel recommends removal.

In contrast, there is insufficient evidence to make a recommendation for the use of high-concentration fluoride gels or toothpastes to prevent the development of ORN. However, the Expert Panel strongly recommends use of high-concentration fluoride gels or toothpastes for the prevention of post-RT caries to reduce the need for future extractions that can place the patient at risk of ORN.

PREVENTION OF ORN AFTER RT

RT Plan Review to Inform Dental Treatment Plan

Literature Review and Analysis

No relevant randomized trials or cohort studies were identified by the systematic review. Therefore, recommendations are based on informal consensus.

Clinical Interpretation

Recommendations for interventions to prevent ORN in patients with a history of head and neck RT require personalized risk assessment based on the radiation dose and volume received by the mandible and/or maxilla at the site(s) of invasive dental intervention.

Communication between the radiation oncologist and dental specialist is essential to determine whether special precautions or alternative treatment plans are indicated based on radiation dose distribution and the location of planned dental extraction(s) or implant placement. Dental extractions and implant placement in areas of the mandible (including grafted bone, ie, fibula or scapula mandibular reconstruction) or maxilla that received ≥50 Gy should be avoided to reduce risk of ORN if other therapeutic options are available. For patients undergoing reirradiation, review of the cumulative dose to mandible and maxilla on the plan sum should be evaluated when available. One should be cognizant that anterior mandibular sites may be at risk for development of ORN even if the high radiation dose was administered to only the posterior mandible, due to the uniarterial blood supply to the right and left mandible. Root canal, crown placement, or dental filling should be offered as noninvasive alternatives to dental extraction for problematic teeth in areas at high risk for ORN. Patients requiring dental extraction in a high-risk region due to recurrent infection, intractable pain, or other symptoms that cannot be alleviated without extraction should be monitored closely for healing with frequent irrigation of the surgical site(s). Additionally, patient education regarding abstinence from tobacco use and avoiding particle and debris collection is recommended. If patients lack options for restoring oral function aside from dental implants, then the benefit of dental implants may outweigh the increased risk of ORN due to improved QoL.

Perioperative Prophylactic Antibiotics

Literature Review and Analysis

No randomized trials were identified by the systematic review. One prospective cohort[17] and one retrospective cohort study[58] utilizing different antibiotic regimens were identified. In the prospective study by Al-Bazie et al,[17] 89 patients with a history of head and neck radiation dose >60 Gy underwent extraction of 232 teeth (n = 78 maxillary, n = 154 mandibular). Time range between prior RT and extraction ranged from 12 to 33 months (mean = 15 months). Patients received amoxicillin 500 mg once (or clindamycin 300 mg if allergic to penicillin) every 8 hours starting 10 days before the extraction through 7 days after the extraction. Patients also performed rinses with chlorhexidine gluconate 0.2% mouth washes every 12 hours for 10 days prior to extraction and 7 days after extraction. Patients received close follow-up with once weekly visits for 1 month after the procedure, then once monthly visits up to 6 months, then once every 3 months for 2 years. With a mean follow-up of 63 months, no ORN cases were reported. In the retrospective cohort study by Palma et al,[58] 49 patients with a history of 3D conformal head and neck RT underwent extraction of 107 teeth (n = 58 maxillary, n = 49 mandibular). All patients received clindamycin 300 mg once every 8 hours for 3 days prior to extraction and 7 days after extraction. Two of 49 patients (4.1%) developed ORN at sites of two adjacent mandibular tooth extractions (3.7% of extracted teeth).

Clinical Interpretation

To date, no randomized trials have evaluated periprocedural antibiotics in patients at risk for ORN. The prospective and

retrospective cohort studies discussed previously did not include a comparator group without antibiotics; therefore, the benefit from antibiotics in ORN reduction cannot be estimated. Additionally, risk assessment for ORN in these studies is limited by the lack of information on radiation dose at the site(s) of dental extraction. Notably, inclusion criteria for the Al-Bazie et al[17] prospective study required a history of head and neck RT with dose exceeding 60 Gy, while no minimum radiation dose was reported in the Palma et al[58] retrospective study. The recommendations for perioperative antibiotics were formulated by extrapolating the best available data and informal consensus among experts on this Panel, who recommend tailoring the duration of preoperative antibiotics based on whether the patient has any evidence of pre-existing infection. While the two studies discussed previously included 3 or 10 days of preoperative antibiotics, experts on the Panel recommend a shorter preoperative duration with antibiotics initiated either 1 hour or 1 day before the procedure. Given that surgical site infection significantly increases the risk of ORN, Panel members reached informal consensus that the benefit of perioperative antibiotics outweighs the risks of promoting antimicrobial resistance by antibiotic overuse in this relatively rare patient population.

Antiseptic Mouth Rinses

Literature Review and Analysis

No randomized trials evaluating perioperative antiseptic mouth rinses in the postradiotherapy setting were identified by the systematic review. The prospective cohort study by Al-Bazie et al[17] discussed previously included mouthwashes with 10 ml chlorhexidine gluconate 0.2% every 12 hours for 10 days prior to extraction and 7 days after extraction, in addition to perioperative oral antibiotics. It is unclear whether the addition of antiseptic mouth rinses contributed to the absence of ORN development among patients undergoing a total of 232 tooth extractions in the setting of prior head and neck radiation dose exceeding 60 Gy. As discussed in the "Prevention of ORN of the head and neck prior to radiation therapy" section, the retrospective study by Chang et al[37] showed an association between chlorhexidine use within 2 weeks prior to radiotherapy and ORN risk. However, similar associations have not been reported in the post-RT setting, and Chang et al[37] indicate that chlorhexidine use may have been "a surrogate marker for poor oral hygiene" in their retrospective analysis.

Clinical Interpretation

These recommendations were formulated by informal consensus among experts on the Panel. There was consensus that the extraction site should be kept clean by irrigating the site regularly with an antiseptic rinse (eg, chlorhexidine or povidone-iodine oral rinse).

Perioperative Prophylactic Pentoxifylline and Tocopherol

Literature Review and Analysis

No randomized trials evaluating the utility of pentoxifylline and tocopherol for prevention of ORN were identified by the systematic review. Four retrospective cohort studies were identified.[16,23,52,62] In the 2023 study by Lombardi et al,[52] ORN was defined as an "area of exposed necrotic bone in the maxillofacial area, lasting for at least 3 months with no evidence of clinical healing, in patient who underwent RT of the head and neck and in absence of local neoplastic recurrence or metastatic disease not explicitly defined in these studies." The other three studies did not include any definition or grading system for ORN. Only one study by Samani et al[62] included a comparator group that did not receive pentoxifylline and tocopherol, with all patients in the other three studies receiving perioperative pentoxifylline and tocopherol. In the retrospective cohort study by Samani et al,[62] 219 patients underwent a total of 1,079 extractions between 2009 and 2020 after prior head and neck RT (42% IMRT). Patients without contraindications (eg, pregnancy, breastfeeding, history of cerebral hemorrhage, acute myocardial infection, severe cardiac arrhythmia, impaired renal or hepatic function, allergy, or sensitivity) received pentoxifylline 400 mg twice daily and tocopherol 1,000 IU once daily for at least 1 week before dental extraction and at least 1 month after the procedure, with 3 months of postoperative treatment in the absence of adverse events. Patients also received 1 week of postoperative antibiotics. Patients were categorized based on compliance to the pentoxifylline and/or tocopherol regimen (n = 148 fully compliant; n = 19 partially compliant), and patients who did not receive pentoxifylline and/or tocopherol due to contraindications to taking this regimen were considered the control group (n = 52). ORN rates were significantly lower in patients with full compliance to the pentoxifylline and tocopherol regimen compared to the control group (3.4% *v* 11.5% at the patient level, $P < .03$; 1.0% *v* 3.5% at the tooth level, $P < .01$), with intermediate ORN rate of 5.3% at the patient level in patients with partial compliance. While these data are limited by the retrospective nature of the study and potential confounding biases in the comparator group (eg, history of cardiovascular comorbidities that may affect ORN risk), they suggest reduced ORN risk with pentoxifylline or tocopherol for at least 1 week before and 1-3 months after dental extraction.

The retrospective study by Lombardi et al[52] utilized a similar regimen of pentoxifylline 400 mg twice daily and tocopherol 1,000 IU once daily for at least 1 week before the dental procedure and 9 weeks after the procedure. A total of 29 patients underwent 71 dental extraction procedures (152 teeth extracted with a maximum of 6 teeth per procedure; n = 65 maxillary; n = 87 mandibular) and four dental implant procedures between 2011 and 2018. Among the 12

patients with RT data available, the mean radiation dose was 59.5 Gy. While oral antibiotics were used starting the day of the procedure for implants, only 44.5% of patients received postoperative antibiotics. All patients received chlorhexidine 0.2% mouthwash and/or 1% gel for 7-14 days after the procedure. ORN occurred after 5.6% of the dental extraction procedures and 25% of the implant placements, with a nonsignificant trend toward longer duration between RT and surgery for patients who developed ORN. In the Patel et al[23] retrospective study of 82 patients with prior head and neck RT (7% IMRT) who underwent 390 dental extractions (n = 232 mandibular; n = 158 maxillary) between 2009 and 2014 with perioperative pentoxifylline and tocopherol treatment, ORN rates were low at 1.2% (0.26% at the tooth level). Patients received pentoxifylline 400 mg twice daily and tocopherol 1000 IU once daily for a mean of 11 weeks preoperatively and 13.6 weeks postoperatively. Most patients also received perioperative antibiotics (27% preoperatively; 97% postoperatively). The retrospective study by Aggarwal et al[16] utilized a similar regimen of pentoxifylline 400 mg twice daily and tocopherol 1000 IU once daily for a mean of 12 weeks preoperatively and 14 weeks postoperatively. A total of 110 patients with prior head and neck RT (47.3% IMRT) underwent 450 dental extractions between 2010 and 2015 with preoperative and postoperative antibiotics used in 36.4% and 63.6% of patients, respectively. ORN rates were higher among patients with a longer time interval between RT and dental extraction: 6% if within 1 year of RT, 12% if ≥2 years after RT, and 16% for ≥5 years after RT. Notably, rising use of IMRT within the period for this study may have contributed to the lower ORN risk for patients undergoing extraction with more recent RT.

Clinical Interpretation

These four retrospective cohort studies included patients who had previously undergone head and neck RT and received pentoxifylline and tocopherol for varying durations before and after dental extractions or implant procedures. To date, no RCTs have evaluated pentoxifylline and tocopherol in this patient population. All studies included prior head and neck RT as an eligibility criterion, but detailed data regarding radiation dose were not available and frequency of IMRT use varied across studies. The weak recommendation in favor of perioperative pentoxifylline and tocopherol is primarily based on the study by Samani et al[62] showing lower ORN rates among patients who were fully compliant with the regimen. Notably, antibiotic use may be a confounding factor in these studies, with lower ORN rates in the two studies that reported more consistent use of postoperative oral antibiotics. Individualized evaluation of ORN risk level should be considered to determine which patients are most likely to benefit from preoperative and postoperative pentoxifylline and tocopherol. Additionally, this regimen should be avoided in patients with active cancer or contraindications to pentoxifylline, including increased bleeding risk, grade 4-5 chronic kidney disease, severe coronary artery disease, or cirrhosis.

Prophylactic Hyperbaric Oxygen Therapy

Literature Review and Analysis

One prospective RCT[12] and two retrospective cohort studies without nonhyperbaric oxygen (HBO) comparator groups[49,73] were identified by the systematic review. The RCT enrolled 144 patients undergoing dental extraction or implant placement in the setting of previously receiving >50 Gy to the mandible with modern RT techniques.[12] ORN was classified using the modified Notani Score,[97] with the primary endpoint being presence or absence of ORN at 6 months after surgery based on blinded review of photographs and radiographs. All patients were prescribed perioperative chlorhexidine mouth rinses (prior to the procedure and three times daily for 5 days postoperatively) and amoxicillin (1 hour before the procedure, three times daily for 5 days postoperatively). Patients assigned to the HBO group received oxygen at 2.4 atmospheres for 80-90 minutes once daily for 20 sessions preoperatively and 10 sessions postoperatively. Among the 100 patients evaluable for the primary endpoint, ORN incidence did not differ by treatment group (6.4% for HBO group *v* 5.7% for control group; odds ratio, 1.13 [95% CI, 0.14 to 8.92]). In a retrospective study by Heyboer et al,[73] 40 patients underwent HBO (2.5 atmospheres, 90 minutes) for 20 sessions before and 10 sessions after dental extractions between 1995 and 2005. Among 19 patients with >6 months of follow-up, ORN incidence was 15.8%. A similar retrospective study by Kaur et al[49] evaluated ORN in 26 patients with a history of head and neck RT (30-72 Gy) who underwent HBO with the same protocol between 2003 and 2006. Only one patient developed ORN (3.8%), but interpretation of this study is limited by the lack of information on follow-up duration. In a 2016 Cochrane systematic review,[98] HBO use was associated with improved healing of dental extraction sites within a prior RT field (RR, 1.4 [95% CI, 1.1 to 1.7]; P = .009), but risk of ORN was not evaluated.

Clinical Interpretation

Available data suggest limited benefit of perioperative HBO for prevention of ORN in patients with a history of head and neck RT undergoing dental extraction. However, HBO does improve the probability of dental socket healing within an irradiated area and may benefit a small subset of patients at elevated risk for ORN.

Leukocyte- and Platelet-Rich Fibrin

Clinical Interpretation

Due to limited, low-quality available evidence, no recommendation can be made regarding utilization of leukocyte- and platelet-rich fibrin[10,13] or photobiomodulation therapy[11]

to prevent ORN for patients undergoing dental procedures after head and neck.

NONSURGICAL MANAGEMENT OF ORN

Pentoxifylline and PENTOCLO

Literature Review and Analysis

Nine studies of pentoxifylline and potentiation by clodronate (PENTOCLO) were identified.[19,20,26,44,59,60,69,75,77] In one controlled study, pentoxifylline was used in combination with surgery and doxycycline, which led to inconclusive results regarding the effect of pentoxifylline in mild, moderate, and severe ORN cases.[69] The remaining two prospective[19,26] and six retrospective studies[20,44,59,60,75,77] of pentoxifylline in mild, moderate, and severe ORN cases reported healing rates of 60%-100% in studies that also administered clodronate, ciprofloxacin, amoxicillin and/or prednisolone.

Many studies that did not include either clodronate, antibiotics, or prednisolone reported lower healing rates, while two studies reported similar successful healing rates. None of these eight studies was controlled and collectively included few patients.

Clinical Interpretation

Evidence remains limited for pentoxifylline and PENTOCLO. With respect to mild to moderate grades of ORN, PENTOCLO may be a useful tool in managing ORN without surgery. However, due to the considerable variation in the studies, it should be further investigated in well-designed randomized clinical trials.

HBO

Literature Review and Analysis

Two randomized trials regarding HBO treatment were identified by the systematic review.[14,15] One of these showed a significantly better recovery in the control group,[14] while the other showed healing in favor of HBO.[15] This was, however, not statistically significant and may be due to underpowering because of recruitment difficulties. Additionally, four retrospective studies[41,53,71,76] reported either high rates of improvement for mild, moderate, and severe grades of ORN or no effect of the addition to surgery in cases of moderate to severe ORN or free flap surgery. Only two[53,76] of these four studies included a control group. All these studies included surgery in combination with HBO.

Five retrospective studies of HBO without surgery reported high healing rates after HBO, particularly in mild grades of ORN. However, the studies were uncontrolled and generally included a low number of patients.[18,21,42,72,80]

Clinical Interpretation

The current literature is inconclusive regarding the effect of HBO, combined with surgery or alone. Evidence remains limited. This should be further investigated in well-designed randomized clinical trials. It is unknown whether the healing rate is similar in mild, moderate, or severe ORN.

SURGICAL MANAGEMENT OF ORN

Management of Partial Thickness Mandibular ORN

Literature Review and Analysis

No relevant randomized trials or cohort studies were identified by the systematic review. Therefore, recommendations are based on informal consensus. Lyons et al[99] managed 28 patients in which bone affected was 2.5 cm in length, including that covered by mucosa, with pentoxifylline and vitamin E (tocopherol) alone. ORN in 17 of 28 patients resolved, and the remaining 11 either improved or stabilized. Patients with more advanced disease proceeded to surgical care. Jin et al[47] treated 31 patients with sequestrectomy, curettage, and marginal mandibulectomy, of which 24 patients had resolution or improvement of their ORN. Arianpour et al[100] described 52 cases where mandibular ORN was arrested with the use of anterolateral thigh fascia lata rescue flap. Many centers adopt an approach of minor intervention for smaller lesions, with advancement to more definitive surgical care when nonresponsive.

Clinical Interpretation

There is general agreement in the literature that the most severe cases of ORN require segmental resection with reconstruction, but the severity threshold is defined using different staging systems or in some cases not defined. The Panel did not find consensus in an established staging system that suited this severity threshold and as such used the partial thickness and full thickness descriptors that may be the most intuitive.

The Panel defines partial thickness ORN as *disease extent whereby removal of all necrotic bone leaves native jaw with enough structural integrity such that oroantral or oronasal defect is unlikely in the maxilla, and pathological fracture is unlikely in the mandible.* In this disease severity, various authors have described successful management with nonsurgical therapy and local wound care as summarized in the prior sections of this article. There is no clear consensus in the literature on which modality of nonsurgical treatment, surgical treatment, or combination thereof is superior. Many approaches are overall successful in resolving, improving, or stabilizing the ORN.

Determinants of Full Thickness (segmental resection) of Mandibular ORN

Literature Review and Analysis

The resection of necrotic, irradiated bone that has not responded to nonoperative therapies has a robust level of support in the surgical literature. Multiple, large, single-institution retrospective studies with long follow-up periods have demonstrated consistent success rates at 90%. This includes cases that required segmental resection with free flap reconstruction.

In a multi-institutional retrospective review of 260 patients undergoing free flap reconstruction of ORN, Mayland et al[55] found a free flap success rate of 92%. O'Connell et al[57] reported on 49 patients undergoing free flap reconstruction for ORN, also finding 92% flap success. Contrera et al[38] reported on 76 patients undergoing free flap reconstruction for ORN, where total flap loss was only observed in 4% of patients. The most common complications in all three studies were wound site infection, metal exposure, and fistulation, which ranged from 20%-47%.

Clinical Interpretation

There is consensus in the literature that the most advanced cases of ORN require definitive segmental resection.[25,27,30,31,33-35,38,39,43,47,48,51,55-57,61,64,65,68,70,78,101] However, use of a variety of staging systems for ORN across studies complicates this analysis.

The Panel felt the delineation between those benefitting from segmental resection and those who do not need it as a critical issue, as it determines a significant departure in treatment modality. The Panel has described this group needing segmental resection as full thickness ORN, defined as *disease extent whereby removal of all necrotic bone is likely to result in oroantral or oronasal defect in the maxilla or pathological fracture in the mandible.*

Options For Reconstruction Following Segmental Resection

Literature Review and Analysis

Liu et al[102] described 244 consecutive cases of pectoralis major myocutaneous pedicled flap for reconstruction after HNC, where total flap loss occurred in only nine (3.6%) of cases. In the posterior mandible with a segmental defect, this would include a spanning metal plate across a segmental defect covered by a myocutaneous pedicle flap. Metal fatigue (eg, wear and tear due to repeated cyclical loading) and fracture can occur with function.

Clinical Interpretation

If systemic conditions permit, reconstruction of segmental defects of the mandible and maxilla are best treated with osteomyocutaneous vascularized flaps. Advantages to vascularized bony reconstruction include the ability to support dental implant reconstruction. In those patients with compromised medical status, or when institutional resources do not allow for free flap surgery, alternatives to free flap reconstructions should be considered. Segmental resection of advanced ORN lesions that have failed nonoperative therapies is associated with high rates of success.

Pedicle Flap Versus Free Flap for Reconstruction of ORN

Literature Review and Analysis

No relevant randomized trials or cohort studies were identified by the systematic review. Therefore, recommendations are based on informal consensus.

Clinical Interpretation

Free flaps offer greater versatility and improved outcomes and are recommended where possible. Pedicle flaps can be used, with some limitations. Larger pedicle flap (eg, pectoralis flap) may result in facial asymmetry and malocclusion. Smaller pedicle flaps (eg, sternocleidomastoid flap, facial artery flap) have limited applications. They may offer an alternative where free flap resources do not exist, *in patients with compromised medical status, or as part of salvage surgery after definitive therapy has failed and the patient's medical status precludes having further free flap intervention.*

Radiographic and Clinical Parameters for Determining Extent of Resection

Literature Review and Analysis

No relevant randomized trials or cohort studies were identified by the systematic review. Therefore, recommendations are based on informal consensus.

Clinical Interpretation

Preoperative radiographic interpretation of extent of compromised bone, with intraoperative confirmation via bleeding bone endpoint, continues to be the gold standard in determination of resection borders. The potential for intraoperative findings to alter the resection margin should be a consideration in planning. If prefabricated cutting guides are used, contingency planning is recommended.

Role of Surgery in Management of Severe ORN in Patients for Whom Major Free Flap Surgery is Not Indicated, Due to Their Medical Complexity

Literature Review and Analysis

No relevant randomized trials or cohort studies were identified by the systematic review. Therefore, recommendations are based on informal consensus.

Clinical Interpretation

Subtotal necrotic bone removal under local anesthesia can still be tolerated by most patients in this demographic. For patients who are not candidates for resection and reconstruction, reduction of the necrotic bone burden may be effective in alleviating the symptoms of localized infection and pain.

These patients often have a resultant heavier dependence on prolonged antibiotic therapy to manage the persistent inflammation and episodic acute infection. The presence of a bacterial biofilm on the surface of necrotic bone has been shown to reduce penetration of, and directly inactivate antibiotics. Maximizing reduction of the burden of the necrotic bone is a key step of source control, which translates to better efficacy of the accompanying antibiotic therapy.[103]

Malnutrition, aspiration pneumonia, and spontaneous pathological fracture are secondary complications that may copresent and will require management.

ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH OR CAUSED BY ORN

Management of Adverse Events Associated With ORN

Literature Review and Analysis

Symptoms and supportive care needs associated with ORN include but are not limited to the following: pain, impaired mastication, dysphagia, weight loss, trismus, dysarthria, taste alterations, compromised oral hygiene, poor bone health, and psychosocial impairment.[3,15,95]

Table 3 provides a summary of relevant guidelines that address these symptoms and supportive care needs.

Clinical Interpretation

There is a paucity of data describing symptoms and supportive care needs associated with ORN. The preponderance of reports of ORN in HNC survivors are retrospective studies describing disease outcomes with varied treatment regimens. Retrospective medical record review rarely captures supportive care outcomes in a manner that provides useful and/or interpretable results. This is due to lack of routine systematic and comprehensive reporting of symptoms or adverse events.

A limited number of prospective clinical trials evaluating interventional approaches for treating ORN include supportive care outcomes as secondary aims. Most of these studies use clinician-reported toxicity rating scales (such as the Late Effects Normal Tissue Task Force [LENT]-Subjective, Objective, Management, Analytic [SOMA]).[122] While a small number of these studies reported global improvement in symptoms with treatment of ORN, detailed descriptions of the type, severity, and trajectory of specific adverse events related to ORN were not provided. Potential barriers to reporting supportive care outcomes in prospective clinical trials include missing data, challenges associated with analysis of patient-reported outcomes (PRO) or toxicity reporting, and lack of prioritization of supportive care outcomes. Directly addressing these and related issues in future studies is essential, including for adolescents and younger adults.[123]

There are several barriers to symptom or adverse event assessment in patients with ORN. For example, although many PRO instruments have been developed for patients with HNC, only a limited number of these instruments have incorporated robust patient input during their development.[124] Supportive care issues arising from ORN in patients with HNC have thus not been clearly delineated. Without methodologically sound studies delineating ORN-associated symptoms and supportive care needs, development, and validation of ORN-specific PRO measures are not feasible. While PRO measures directed at the general HNC population are available, many include items that are not directly relevant to survivors with ORN. Furthermore, they may lack items that capture important ORN-related symptoms or adverse events. Tailored and appropriate outcome measures are needed to understand the impact of ORN and its treatment on symptoms or adverse events.

Currently, there are no reports of clinical trials evaluating management strategies for ORN-associated symptom burden and adverse events. While ORN-associated symptoms may respond to interventions in a similar manner to the general oncology patient population, this cannot be assumed. ORN-associated symptoms may result in unique management challenges and thus merit investigation in prospective clinical trials.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Prospective studies are needed to evaluate the clinical presentation, trajectory, and response treatment of ORN-related symptoms and function impairment. In addition, social determinants of health, quality of life, and psychosocial impact warrant further investigation in HNC survivors. On the basis of prospective data, PRO measures need to be developed to screen for ORN-associated symptoms, after which clinical trials investigating management strategies for ORN-related supportive care issues can be designed and implemented. One possible strategy is to build specific PRO-Common Terminology Criteria for Adverse Events related to ORN, building a form leveraging the most frequent symptoms of which patients with ORN complain.

TABLE 3. Summary of Guidelines That Address Symptoms and Supportive Care Needs Associated With ORN

Adverse Event Associated With or Caused by ORN	Organization	Title
Pain	ASCO	Use of Opioids for Adults with Pain from Cancer or Cancer Treatment[104]
	ASCO-SIO	Integrative Medicine for Pain Management in Oncology[105]
	MASCC	Cannabis for cancer-related pain and risk of harms and adverse events[106]
		Cannabis for psychological symptoms including insomnia, anxiety, and depression[107]
	ESMO	Management of cancer pain in adult patients[108]
	NCCN	Adult Cancer Pain[109]
Dysphagia	AAO-HNS	Expert Consensus Statement: Management of Dysphagia in Head and Neck Cancer Patients[110]
	ESSD	European white paper: Oropharyngeal dysphagia in head and neck cancer[111]
Oral care	MASCC-ISOO	Management of Oral Problems in Patients with Advanced Cancer[112]
	ISOO-MASCC-ASCO	Salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies[96]
Nutritional deficiencies and weight loss	ESPEN	Clinical nutrition in cancer[113]
Dysarthria	UK National Multidisciplinary Guidelines	Speech and swallow rehabilitation in head and neck cancer[114]
Psychosocial impact on survivorship	ASCO	Management of Anxiety and Depression in Adult Survivors of Cancer[116]
		Head and Neck Cancer Survivorship Care[117]
	ASCO-SIO	Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults with Cancer[118]
	MASCC	Cannabis for psychological symptoms including insomnia, anxiety, and depression[107]
	NCCN	Survivorship[119]
	ESMO	The role of patient-reported outcome measures in the continuum of cancer clinical care[120]
		Anxiety and depression in adult cancer patients: ESMO Clinical Practice Guidelines[121]

Abbreviations: AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery; ESMO, European Society for Medical Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism; ESSD, European Society for Swallowing Disorders; ISOO, International Society of Oral Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; ORN, osteoradionecrosis; SIO, Society for Integrative Oncology; UK, United Kingdom.

From a rehabilitative standpoint, the use of dental implants in irradiated bone warrants further investigation with well-designed studies. Optimal prevention and treatment of patients with ORN remain to be established in the research. New research, including RCTs and prospective multicenter trials, on systemic and surgical treatment is warranted. HBO has been a longstanding standard of care in the management of ORN with poorly designed trials to support it. The Expert Panel encourages the creation of predictive tools for the development, grading, and staging of ORN, such as bone turnover markers and genetic markers.

Drugs such as bone-modifying agents have been associated with medication-related osteonecrosis of the jaw. The research opportunities described here should ideally be addressed in large, prospective, multicenter, observational studies of risk, outcomes, and cost of ORN for various treatment strategies.

PATIENT AND CLINICIAN COMMUNICATION

Clinician and patient communications are extremely important, because of the multiple clinical issues that will likely occur over time. A well-organized, cohesive interprofessional practice approach brings additional, strategic value to this dynamic as well. Patients will typically interact with a variety of clinical personnel over many years. The oncology team should orient the patients and their caregivers regarding achieving consistent and long-term interactions. Small steps are certainly more comprehensible and easier for the individual to understand. However, whether the patient wishes to join some type of support group or look solely to their team, they need the assurance that there are resources, both for the short and long term, that they can access. Their learning of important innovations that are constantly being adopted to improve their lives can also provide hope that represents realistic optimism. Many patients discontinue treatment and/or their 3- to 5-year follow-ups believing that there is no hope for the conditions they are experiencing. Keeping the patient informed of continuous evolution in the science and clinical translation of studies can offer encouraging promise for the future.

HEALTH EQUITY CONSIDERATIONS

Rates of oral cavity cancer vary in the United States and internationally, principally because of differences in habits

of tobacco, alcohol, and betel-quid chewing.[125] By comparison, there is a human papillomavirus (HPV)–related increase in the population-level incidence and survival in patients with oropharyngeal cancer in the United States.[126] Hallmarks of these two dynamics are patient-based habits, access to care including prevention and early detection of malignancy, and health cost coverage. As with selected other cancers, most oral and oropharyngeal cancers are preventable but require opportunity for patients to achieve health literacy in these realms. Health insurance literacy is a key factor in this regard.

The relationship between income and oral health has been well established, including low individual or household income being associated with the development of oral cancer.[127] Similarly, non-White race and uninsured status were associated with worse cancer-specific mortality in HPV-positive oropharyngeal squamous cell carcinoma; by contrast, this association was not observed in HPV-negative or nonoropharyngeal squamous cell cancers.[128] Although treatment of HPV-positive cancers is often effective, non-White patients with HPV-positive cancer have inferior clinical outcomes compared with their White peers.

Social determinants of health are thus a key driver in determining who does and does not develop oral and/or oropharyngeal cancer. In addition to continuous basic, translational, and clinical research directed to achieving optimal cancer cures, additional research is needed to address the health equity considerations associated with the disease, health literacy, and access to care. Prevention of ORN is a key yet not exclusive component of this modeling.

MULTIPLE CHRONIC CONDITIONS

Patients with multiple chronic conditions (MCC; two or more chronic conditions) might have additional complexities and needs when clinicians are developing treatment and follow-up plans, including those related to impaired lung, cardiac, renal, neurologic, and other organ functions. The complexity and uncertainty created by MCC highlight the importance of shared decision making regarding implementation of guideline-recommended care.[129] Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of the results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

TABLE 4. Risk Factors for Development of Osteoradionecrosis

Nonmodifiable Risk Factor	Modifiable Risk Factor
Age	Uncontrolled diabetes mellitus
Sex at birth	Performance status
History of alcohol use	Pre-RT dental evaluation
Exsmokers	Pre-RT tooth extraction
Tumor-related variables (primary tumor site, T-stage, nodal status)	Treatment-related variables (pre-RT surgery, pre-RT mandible surgery, induction chemotherapy, concomitant chemotherapy, RT technique, and DVH parameters of the jaw)
	IMRT dose
	Current smokers
	Stage III-IV periodontal disease

Abbreviations: DVH, dose-volume histogram; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

In patients with HNCs, the risk of developing ORN is increased by the presence of modifiable and nonmodifiable risk factors that are usually present in patients with MCC. Table 4 provides a summary of these risk factors on the basis of the studies by Kubota et al[130] and Watson et al.[83]

Clinicians should review all chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan. This may mean that some or all the recommended care options are modified or unable to be applied, as determined by best practice in consideration of any MCC. This is an area in need of further evidence-informed development, including the future development of practice guideline recommendations for this population of patients.

COST IMPLICATIONS

Besides causing prolonged illness and a lower QoL, ORN also places an additional financial burden on patients because of the costs associated with its prevention and treatment. Extensive research has convincingly established a direct connection between cancer treatment, poor oral health, and the incidence of ORN.[6] Despite this clear causality, the responsibility for preventing and treating these cancer-related complications has often fallen on patients. Remarkably, despite the undeniable link between cancer treatment and dental issues, coverage for prevention and treatment in the United States remains largely absent from standard medical insurance policies. Even for patients with dental insurance, annual payment caps often fall far short of covering the actual costs of necessary care. Moreover, these patients often have multiple teeth at risk, exacerbating the financial burden. Preventative protocols that reduce risk do exist, but regrettably, they too are not covered by medical insurers. As such, survivors of HNC face an alarming risk of financial hardship, the significance of which should not be underestimated. The percentage of patients at risk of bankruptcy is

staggering, and tragically, suicides among survivors are not uncommon.

It is worth noting that conservative management of ORN, involving antibiotics and debridement, can cost between $4,000 US dollars (USD) and $35,000 USD (or even up to $74,000 USD), and the addition of HBO therapy can increase these costs by $10,000 USD to $50,000 USD.[131] Addressing this issue requires a multifaceted approach, but at its core is a fundamental need to re-evaluate and restructure reimbursement policies by medical insurers, specifically for dental diseases directly linked to underlying medical conditions, such as the treatment of HNCs.[131]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the Panel. The additional role of this PGIN representative on the guideline Panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/head-neck-cancer-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit http://www.asco.org/head-neck-cancer-guidelines. The Data Supplement for this guideline includes additional evidence tables. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from Panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net. The ASCO Survivorship Care Plan and the ONCOllab app are also available to clinicians.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the online form.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Care[132] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[133] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx[134] (http://ascopubs.org/doi/10.1200/JCO.18.01921)
- Human Papillomavirus Testing in Head and Neck Carcinomas[135] (http://ascopubs.org/doi/10.1200/JCO.18.00684)
- Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck[136] (http://ascopubs.org/doi/10.1200/JCO.20.00275)
- Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma[137] (http://ascopubs.org/doi/10.1200/JCO.20.03237)
- Management of Salivary Gland Malignancy[138] (http://ascopubs.org/doi/10.1200/JCO.21.00449)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[139] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between sex and anatomy.[140-143] With the acknowledgment that ASCO guidelines may affect the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data on the basis of gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/head-neck-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Patents, Royalties, Other Intellectual Property: EA025592B1 Eurasian Patent Office Bioactive white oil and method for production thereof. Abstract This invention relates to biologically active substances derived from native naphthalan and can be used in medicine, pharmacology, and cosmetology. Claimed is bioactive white oil "Gazelli White Oil," representing a naphthalan fraction with a boiling point of 350-450°C and a density of 875-879 kg/m, containing condensed polycyclic natural naphthenic hydrocarbons consisting of at least 80% tetracyclic naphthenes of steroidal type. Also claimed is a method for producing biologically active white oil comprising pretreating native naphthalan, distillation fractionation separating the distillate fraction having a boiling point of 350-450°C, which is subjected to a hydrodynamic cavitation and then treated with sulfuric acid, then neutralized with bentonite clay, and post-treated with an activated silica gel

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No other potential conflicts of interest were reported.

APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting, or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Shlomo A. Koyfman, MD, cochair	Cleveland Clinic, Cleveland, OH	Radiation Oncology
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Nofisat Ismaila, MD, MSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook.[144]

TABLE A3. Descriptions of Complete, Partial, and Minimal Dental Evaluation Protocols on the Basis of the Type of Dental and/or Periodontal Pathology[81,94]

Dental Pathology	Complete Dental Clearance	Partial Dental Clearance	Limited Dental Clearance
Caries	Restore all teeth	Restore deep caries; mild/moderate caries restored if time permits	Intervention only if symptomatic
Severe caries/pulp involvement/ dental abscess	Extraction	Extraction	Intervention only if symptomatic
Apical periodontitis—previous endodontic treatment	Extraction of symptomatic lesions and lesions ≥5 mm	Extraction of symptomatic lesions and lesions ≥5 mm	Intervention only if symptomatic
	Surveillance of asymptomatic lesions <5 mm	Surveillance of asymptomatic lesions <5 mm	Intervention only if symptomatic
Apical periodontitis—no previous endodontic treatment	Extraction or endodontic therapy for restorable, periodontally sound teeth	Extraction or endodontic therapy of restorable, periodontally sound teeth	Intervention only if symptomatic
Advanced periodontal disease	Extract teeth with	Extract teeth with	Intervention only if symptomatic
	Probing depth ≥5 mm	Probing depth ≥5 mm	
	Furcation II, III; Mobility II, III	Furcation II, III; Mobility II, III	
	Severe inflammation	Severe inflammation	
Partially erupted third molars	Extract	Extraction of symptomatic teeth; consider requesting radiation delay	Intervention only if symptomatic

NOTE. The proper protocol should be selected by the oncologist and dentist according to the patient's medical status. Limited clearance would be indicated for patients treated with noncurative intent. Partial and complete clearance protocols are based on patients being treated with curative-intent radiotherapy and appropriate access to care. In general, patients with at least 2 weeks of healing available before radiation can be treated with complete clearance and those with less than 2 weeks of time can be treated with partial clearance.

[a]Clearance protocols should be applied to teeth that will receive a therapeutic dose of radiation. For teeth that will receive below a therapeutic dose, minimal clearance protocols can be applied.