Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy

ISOO-MASCC-ASCO Guideline

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1 Background & Methodology

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 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 head and neck cancer.
- Evidence-based interprofessional practice combined with ongoing patient and family education can substantially mitigate the clinical and cost-of-care impact for patients with head and neck cancer.
- This joint guideline between ASCO and MASCC-ISOO is directed to this overarching theme.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical 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 RT?
3. What are the recommended best practices for the prevention of ORN after RT?
4. How should ORN be managed non-surgically?
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?

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 head and neck cancer receiving RT.

2 Summary of Recommendations

Summary of Recommendations

Clinical Question 1

- How should ORN be characterized, graded, and reported?
  - Which patients should be considered at high risk for ORN?
  - What is the recommended workup to characterize ORN?

Recommendation 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 RT.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Low	Strong

Summary of Recommendations

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 1.3

- Clinicians evaluating ORN should utilize the ClinRad staging system for ORN, as should clinical trials.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 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.[1]

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Low	Strong

Summary of Recommendations

Recommendation 1.6

- Recommended initial evaluation of ORN should include one or more of the following: (1) clinical intra-oral examination (including direct visual or endoscopic examination and/or formal periodontal assessment); and/or (2) formal radiographic examination (i.e., x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging).

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Qualifying statement: If either clinical or radiographic findings are initially detected, suspected or positive, subsequent confirmatory examination or imaging assessment is recommended.

Summary of Recommendations

Recommendation 1.7

- Recommended serial characterization or surveillance of ORN should include clinical intra-oral examination (including direct visual, endoscopic examination, and/or comprehensive periodontal assessment) and comprehensive radiographic examination (i.e., x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging).

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Clinical Question 2

- What are the recommended best practices for the prevention of ORN of the head and neck prior to RT?

Recommendation 2.1

- Target coverage of tumor should not be compromised to avoid dose to bone.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 2.2

- Advanced radiation planning techniques (e.g., IMRT, IMPT) should be employed to deliberately reduce radiation dose to the jaw at risk as much as possible.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Qualifying statement: While tumor site (e.g., 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.

Summary of Recommendations

Recommendation 2.4.1

- A dental assessment by a dentist (with a dental specialist if possible) is strongly advised prior to therapeutic-intent RT 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 2.4.2

- Dental extraction, if clinically indicated, should occur at least 2 weeks prior to commencement of RT. In the setting of rapidly progressing tumor, extractions should be deferred and not cause a delay in the initiation of RT (see dental clearance, Table A3 in the guideline manuscript).

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 2.5.1

- (general dentists and dental specialists) Teeth with poor prognosis including moderate-severe periodontal disease, within a field of therapeutic-intent RT 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

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 RT. Information about the planned volume to be irradiated, anticipated dose to the mandible and maxilla, and RT start date should be provided to the dentist or dental specialist.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 2.6

- A two week healing period between time of dental extraction and start of RT 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 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 post-radiation caries, which in turn decreases risk of post-radiation extractions and ORN.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Recommendations

Recommendation 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 RT.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Recommendations

Clinical Question 3

- What are the recommended best practices for the prevention of ORN after RT?

Recommendation 3.1

- Prior to finalizing dental treatment plans in patients with a history of head and neck RT, review of the RT plan should be performed with particular attention focused on dose to mandible and maxilla.

Evidence-based

Evidence Quality	Strength of Recommendation
Moderate	Strong

Summary of Recommendations

Recommendation 3.2

- For teeth in areas at high risk for ORN, alternatives to dental extraction (e.g., 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 3.3

- It is recommended that patients considered to be at higher risk for ORN due to prior RT 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

Evidence Quality	Strength of Recommendation
Low	Weak

Recommendation 3.4

- Patients at risk for ORN who have delayed healing after dental extraction may be prescribed antiseptic mouth rinses. Chlorhexidine gluconate (e.g., 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

Evidence Quality	Strength of Recommendation
Low	Weak

Summary of Recommendations

Recommendation 3.5

- It is recommended that pentoxifylline (400 mg twice daily) and tocopherol (1000 IU once daily) be prescribed for at least one week before and four weeks after invasive dental procedures (preferably until the dental socket has healed) in cancer-free patients.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Qualifying statement: This should be considered for patients at elevated risk for ORN due to prior RT 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.

Summary of Recommendations

Recommendation 3.6

- Routine use of prophylactic hyperbaric oxygen (HBO) therapy prior to dental extractions in patients who received prior head and neck RT is not recommended.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
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.

Summary of Recommendations

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 RT.

Summary of Recommendations

Clinical Question 4

- How should ORN be managed non-surgically?

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Recommendations

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Recommendations

Clinical Question 5

- How should ORN be managed surgically?

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
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.

Summary of Recommendations

Recommendation 5.1.2

- Small defects <2.5cm in length may heal spontaneously with local measures. It is recommended that larger defects be covered with vascularized tissue.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
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.

Summary of Recommendations

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Recommendations

Recommendation 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

Evidence Quality	Strength of Recommendation
High	Strong

Recommendation 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

Evidence Quality	Strength of Recommendation
Low	Strong

Summary of Recommendations

Recommendation 5.6

- Pre-operative radiographic interpretation of extent of compromised bone, with intra-operative confirmation via bleeding bone endpoint, should be utilized in determination of resection borders. The potential for intra-operative findings to alter the resection margin should be a consideration in planning. If prefabricated cutting guides are used, contingency planning is recommended.

Informal consensus

Evidence Quality	Strength of Recommendation
Low	Strong

Recommendation 5.7.1

- When patients are unfit to undergo definitive surgical treatment, the management should be focused on symptom control.

Informal consensus

Evidence Quality	Strength of Recommendation
Moderate	Strong

Summary of Recommendations

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Clinical Question 6

- When, how, and by whom should patients diagnosed with ORN be assessed for adverse events associated with and/or caused by ORN?
- If ORN-associated adverse events are identified, how should they be managed?

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Low	Strong

Summary of Recommendations

Recommendation 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	
Evidence Quality	**Strength of Recommendation**
Low	Strong

3 Discussion

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 head and neck cancer survivors.
- Based on prospective data, PRO measures need to be developed to screen for ORN-associated symptoms following which clinical trials investigating management strategies for ORN-related supportive care issues can be designed and implemented.
- Research opportunities should ideally be addressed in large, prospective, multi-center, 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 strategic value to this dynamic as well.
- The oncology team should orient the patients and their caregivers regarding achieving consistent, and long-term interactions.
- Patents should be assured that there are resources 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 continued 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 as well as internationally, principally due to differences in habits of tobacco, alcohol, and betel-quid chewing.[2]
- By comparison, there is a HPV-related increase in the population-level incidence and survival in patients with oropharyngeal cancer in the United States.[3]
- Hallmarks of these two dynamics are patient-based habits, access to care including prevention and early detection of malignancy, and health cost coverage.
- 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.[4]
- Similarly, nonwhite race and uninsured status were associated with worse cancer-specific mortality in HPV-positive oropharyngeal squamous cell carcinoma; in contrast, this association was not observed in HPV-negative or non-oropharyngeal squamous cell cancers.[5]

Cost Implications

- Besides causing prolonged illness and a lower quality of life, ORN also places an additional financial burden on patients due to the costs associated with its prevention and treatment.
- Despite the undeniable link between cancer treatment and dental issues, coverage for prevention & treatment in the US 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.
- Conservative management of ORN, involving antibiotics and debridement, can cost between $4,000 and $35,000 (or even up to $74,000), and the addition of HBO therapy can increase these costs by $10,000 to $50,000.[6]
- Addressing this issue requires a multifaceted approach, but at its core is a fundamental need to reevaluate and restructure reimbursement policies by medical insurers, specifically for dental diseases directly linked to underlying medical conditions like head and neck cancers.[6]

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines

- Patient information is available at www.cancer.net

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Abbreviations

- ASCO, American Society of Clinical Oncology
- EBMC, Evidence Based Medicine Committee
- HBO, hyperbaric oxygen
- HNC, head and neck cancer
- HPV, human papillomavirus
- IMPT, intensity-modulated proton therapy
- IMRT, intensity-modulated radiation therapy
- ISOO, International Society of Oral Oncology
- MASCC, Multinational Association of Supportive Care in Cancer
- ORN, osteoradionecrosis
- PRO, patient-reported outcome
- RT, radiation therapy
- US, United States

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