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ISOO INTERNATIONAL SOCIETY of ORAL ONCOLOGY

Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
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?	**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.	IC	L	S
	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.	EB	H	S
	1.3. Clinicians evaluating ORN should utilize the ClinRad staging system for ORN, as should clinical trials.	EB	M	S
	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]	EB	M	S
	1.5. ORN case reporting and diagnosis should include formal informatics, ontology, and lexical standards consistent with the characterization noted in Recommendation 1.1.	IC	L	S
	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).	EB	M	S
	Qualifying statement: If either clinical or radiographic findings are initially detected, suspected or positive, subsequent confirmatory examination or imaging assessment is recommended.			

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	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).	EB	M	S
What are the recommended best practices for the prevention of ORN of the head and neck prior to RT?	**2.1.** Target coverage of tumor should not be compromised to avoid dose to bone.	EB	M	S
	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.	EB	M	S
	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.	EB	M	S
	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.			
	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.	EB	M	S
	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).	EB	M	S
	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.	EB	M	S
	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.	EB	M	S

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	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.	EB	M	S
	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.	EB	H	S
	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.	EB	H	S
What are the recommended best practices for the prevention of ORN after RT?	**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.	EB	M	S
	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.	EB	M	S
	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.	IC	L	W
	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.	IC	L	W

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	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.	EB	L	W
	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.			
	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.	EB	L	W
	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 RT.	N/A	N/A	N/A
How should ORN be managed non-surgically?	**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.	EB	M	W
	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.	IC	L	W
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.	EB	H	S
	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 <2.5cm in length may heal spontaneously with local measures. It is recommended that larger defects be covered with vascularized tissue.	EB	M	S
	5.2. In full thickness ORN (ClinRad selected Stage II and all Stage III), segmental maxillectomy or mandibulectomy with free flap reconstruction is recommended.	EB	H	S

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	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.	EB	H	S
	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.	EB	H	S
	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.	EB	H	S
	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.	IC	L	S
	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.	IC	L	S
	5.7.1. When patients are unfit to undergo definitive surgical treatment, the management should be focused on symptom control.	IC	M	S
	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.	IC	M	S

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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?	**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.	IC	L	S
	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.	IC	L	S

Abbreviations. EB, evidence based; H, high; HBO, hyperbaric oxygen; IC, informal consensus; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; L, low; M, moderate; N/A, not applicable; ORN, osteoradionecrosis; RT, radiation therapy; S, strong; W, weak

References. [1] Watson EE, Hueniken K, Lee J, et al: Development and Standardization of a Classification System for Osteoradionecrosis: Implementation of a Risk-Based Model. medRxiv, 2023

