

Review Article

Modern Radiation Therapy for Head and Neck Cancer and the Management of Radiation-Induced Oral Complications

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Abstract

Background: The management of head and neck cancers is a unique crossroads between the dental and oncology disciplines. In the following manuscript, a summary of the modern advances in radiation treatment of head and neck cancers as well as a brief overview of some of the most common adverse effects will be reviewed with special emphasis on osteoradionecrosis.

Types of Studies Reviewed: We reviewed the literature regarding major dental events after head and neck radiotherapy, which include 4 major categories including: 1) osteoradionecrosis, 2) gingival recession, 3) caries, extractions, tooth loss and 4) oral mucositis.

Results: We summarized herein the literature behind the pathophysiology, risk factors and management options for major dental events after head and neck radiotherapy. We also have organized the major guidelines published for dental management before, during and after head and neck radiotherapy.

Practical Implication: The cooperation between dentistry and oncology is paramount considering the advancements regarding overall survival and outcomes in cancer patients. Patients are expected to deal with the sequelae of the long-term, post-treatment effects of radiation therapy. Younger, healthier individuals are being diagnosed with head and neck cancers given the rise of HPV infections, which portends longer survival and the greater need to improve long-term dental health in this group. We hope that this review will be a resource to dental providers to help provide excellent care for head and neck cancer radiotherapy patients.

Keywords: Radiation Therapy; Oral Cancer; Oropharyngeal Cancer; Radiation-Induced Dental

complications

Introduction

About 68,000 new cases of head and neck cancers occur annually and account for about 3-4% of all cancers in the United States [1]. HPV-related oropharyngeal cancers have risen from 16.3% of all oropharyngeal cancers in the 1980s to more than 72.5% in the 2000s; an uptick that reflects the near-found awareness, identification and diagnostic evaluation for HPV [1]. The overall incidence of HPV-related head and neck cancers is growing while the incidence of HPV-unrelated head and neck cancers is decreasing with the declining use of tobacco. The survival at 3 years for low-risk HPV-related oropharyngeal cancers is >90% compared to HPV-unrelated oropharyngeal cancers where the survival is <50% (Table 1) [1,2].

	Epidemiology	Survival
Oral Cavity and Pharynx Cancer	54,540 new cases/year 2.8% of all new cancer cases 11,580 deaths/year 1.9% of all cancer deaths ³	5-year relative survival: 68.5% ³
HPV-related oropharyngeal cancer	~70% of all oropharyngeal cancers ⁴	3-year overall survival: 93% (low risk only*) ² 8-year overall survival: 70.9% ⁶
HPV-unrelated oropharyngeal cancer	Tobacco significant risk factor	8-year overall survival: 30.2% ⁶ 3-year overall survival: >90% ⁷
Nasopharynx	3,200 cases per year in the US and 133,000 cases worldwide (endemic in South China, Hong Kong, Southeast Asia and North Africa due to EBV) ⁵	
Larynx cancer	12,380 new cases/year 0.6% of all new cancer cases 3,820 deaths/year 0.6% of all cancer deaths ⁸	5-yr relative survival: 61.6% ⁸
*low-risk as defined in RTOG 0129 retrospective analysis (HPV-positive tumors and ≤10 year pack-year history, or HPV-positive tumors and > 10 pack-year history and N0-2a nodal status) ²		

Table 1: Epidemiology and survival data from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program database and from various sources.

Indications for Radiotherapy and Overview of Radiotherapy delivery techniques

Multidisciplinary team discussions are essential for assessing need for radiotherapy for head and neck cancers. Stage, extent of disease, functional status, surgical outcomes and pathological findings are all determinants in management. Radiotherapy for head and neck cancers is most frequently delivered with a linear accelerator, which is a device that accelerates charged particles using high-frequency electromagnetic waves to produce therapeutic X-rays (Fig. 1).

Radiotherapy techniques have tremendously improved since the inception of therapeutic radiation for head and neck cancers that have allowed for intensification and precision. The current standard of practice for head and neck radiotherapy uses a technique called Intensity-Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) for definitive and post-operative settings (Fig. 1). The conformal radiotherapy treatment plan is determined by optimizing radiation beam parameters, which include beam shape and intensity. The delivery of photon beams was revolutionized with the advent of Multi-Leaf Collimators (MLC) (Fig. 1) [3-9]. These tungsten alloy "leaves" shape and modulate the photon beams allowing for fine control of the beam profile. Multi-leaf collimation is one of the poignant examples of the improved design of modern linear accelerators; other advances in radiation oncology that compliment this feature include automated optimization of MLC field shaping and modulation, image guidance and adaptive techniques [9]. In comparison to three-Dimensional Conformal Radiotherapy (3D-CT), the predecessor to IMRT, there have been comparative studies that show better tumor coverage, more sparing of normal tissue and lower toxicity after treatment (Fig. 2) [10-12].

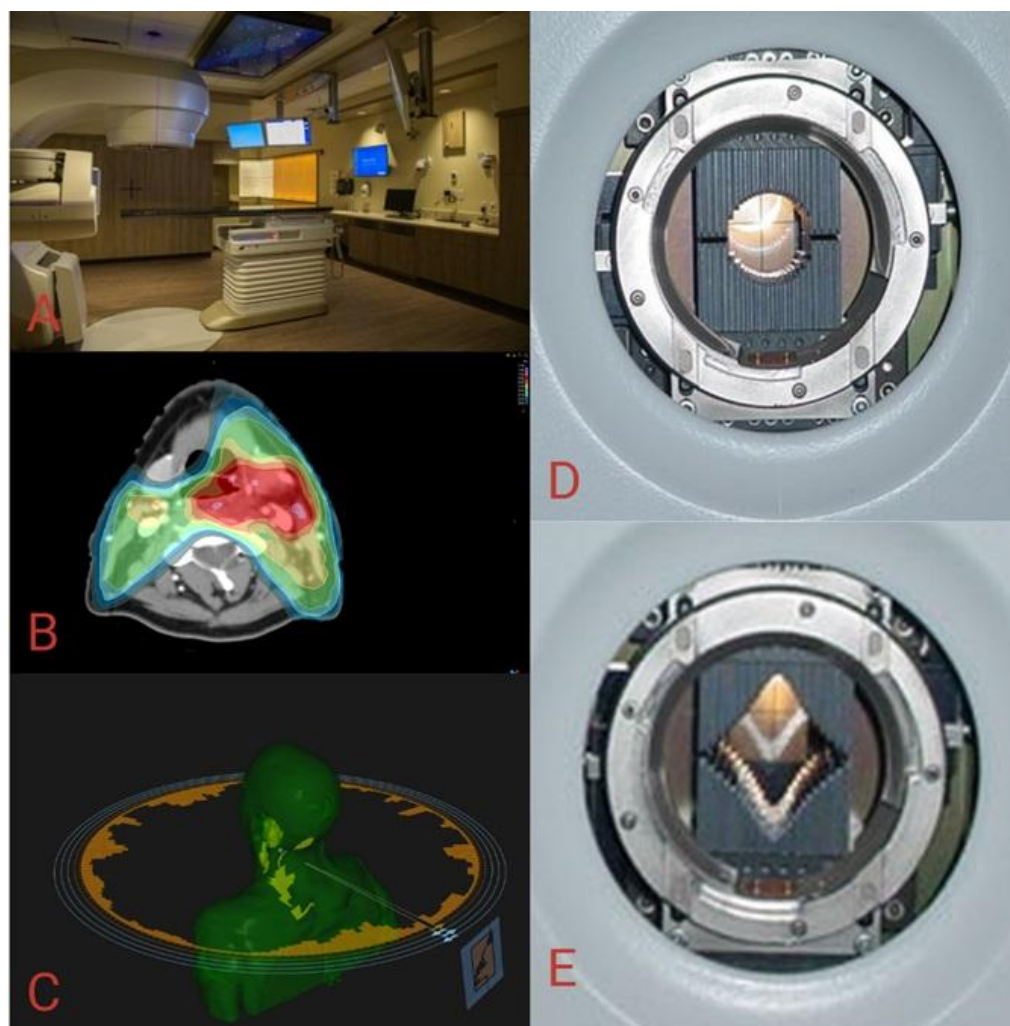


Figure 1: A) Modern linear accelerators deliver therapeutic x-rays. These devices employ high-frequency electromagnetic waves to accelerate electrons. The high-energy electrons hit a target that is made of material that has a high atomic number (Z), which produces a spectrum of x-ray energies. B) This is an IMRT treatment plan for a patient with oropharyngeal cancer showing the dose distribution that is produced with automated inverse planning and volumetric modulate arc delivery. C) This figure shows the modulated fluences for a single beam using a full arc trajectory. D) Multileaf collimators are made of tungsten alloy and allow the shaping and modulation of photon beam profiles. The MLCs are arranged in a circular pattern. E) MLCs arranged in a diamond-shaped pattern.

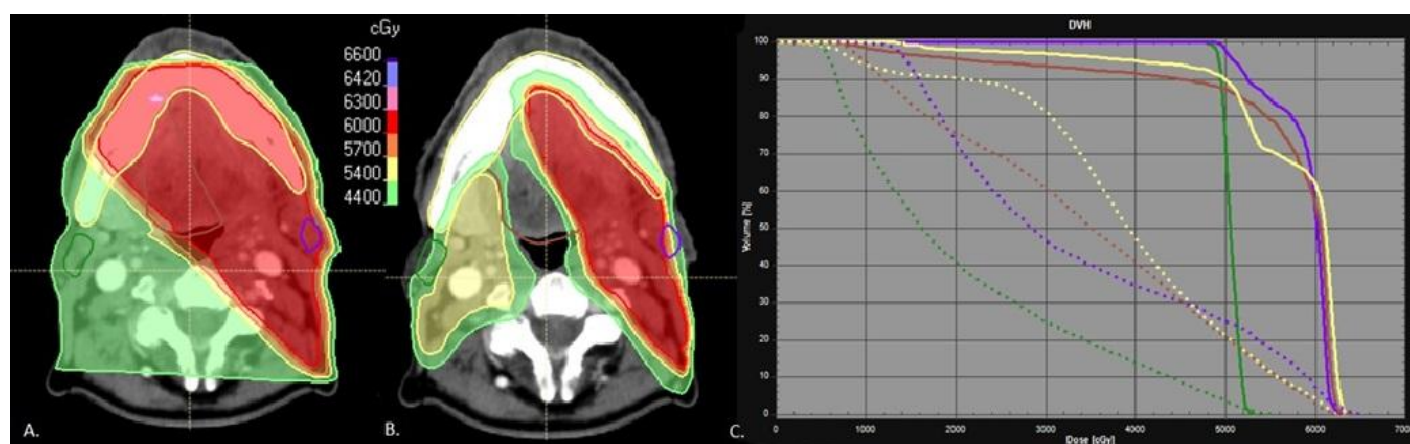


Figure 2: Radiation treatment plan for a post-op oral cavity cancer. A. 3D plan B. IMRT plan C. Dose-Volume Histogram (DVH) comparing 3D (solid line) vs IMRT (dotted line). Purple: left parotid; Green: right parotid; Yellow: mandible, Brown: Oral Cavity.

Other Modalities: SBRT, Proton Therapy and Brachytherapy

Stereotactic Body Radiation Therapy (SBRT) is a technique often employed in the setting of re-irradiation after recurrence or in the palliative setting. The regimen uses higher doses per fraction and shorter treatment regimens to allow for high biological equivalent doses while sparing normal tissues. Other forms of radiotherapy in the head and neck region can be delivered using brachytherapy, which involves using radioactive sources that can be implanted in the body. Proton beam therapy is still an area of active investigation for head and neck cancers; however, this technique has been adopted into clinical use when normal tissue constraints cannot be met by photon beam therapy techniques. However, proton beam therapy is only available in around 42 centers across the United States. The first carbon ion therapy facility in the United States is under construction in Florida.

Dosimetric Parameters and Quality Assurance

It is standard practice for radiotherapy plans to delineate and calculate dosimetric parameters for critical organs at risk in the region of treatment. Dmax (max dose), volumetric and mean doses to organs at risk are monitored and accounted for when designing treatment plans. Not only are dosimetric goals set for target volumes, but there are also constraints placed on the organs at risk. Quality Assurance (QA) testing for precision and accuracy of therapy devices as well as image guidance are done on a daily routine basis. Patient specific QA is also performed before the first treatment is delivered.

Osteoradionecrosis

Pathophysiology

Osteoradionecrosis (ORN) is one the most feared complications of head and neck radiotherapy and commonly manifests as pain and denuded bone with a median time of 38 months after completion of radiotherapy but as soon as 6 months afterwards (Fig. 3) [13,14]. The buccal cortex of the premolar, molar and retromolar regions are the most vulnerable to ORN development due to the morbidity of ORN, understanding risk factors and especially radiation dosimetry is important to understand to avoid unnecessary complications [13]. On clinical exam there is ulceration and necrosis of the oral mucosa with exposure of underlying bone; sometimes this is also accompanied by purulent drainage and/or fistula formation [15]. Dental extractions are the most common initiating factor in development of ORN. Development of ORN is multifactorial and has purported to be a combination of radiation-induced hypo-vascularity, hypoxia, hypo-cellularity, fibrosis as well as an interplay with inflammatory and infectious processes. Histologically, there is destruction of osteocytes and osteoblasts. Punch biopsies taken from the mandible of irradiated patients found a decreased density of small diameter blood vessels as compared to non-irradiated controls, strengthening this potential link between radiation therapy and diminished blood supply [16]. Hypo-vascularity induced by radiation is due to impairment of angiogenesis and destruction of the microvasculature. Dosing greater than or equal to 50 Gy was linked to a smaller percentage of blood vessels and subsequent risk of hypo-vascularity [16]. At this point it becomes pertinent to mention that while ORN is a well-documented risk of HNRT, the risk is still relatively low in the setting IMRT [17]. In fact, in a retrospective study consisting of 168 patients who were previously treated with IMRT for head and neck cancers, only two subjects were found to have ORN with maximum mandibular doses of 72 and 58 Gy and both had oral cavity primary lesions. In fact, with the advent of more sophisticated radiation techniques and prophylactic dental treatment, recent studies have purported incidences as low as 1% and up to 7% after extractions [17,18]. The mandible is the predominant bone affected by ORN, but other bones can also be affected such as the maxilla and temporal bones after head and neck radiotherapy. The incidence of maxillary ORN is <1% [19].

The mandible is particularly susceptible to ORN as it has relatively poor vascularity as compared to other regions of the mouth [20,21]. At the onset of ORN regardless of severity, it is important to optimize modifiable risk factors including smoking and alcohol use, periodontal hygiene and overall patient health [21]. The vascular damage has been confirmed by MRI imaging studies reporting a significantly higher degree of leakiness in the mandibular vasculature that are associated with areas of advanced ORN compared to healthy mandible [13,22]. Imaging techniques helpful in evaluating for ORN include panoramic radiography, CT and Magnetic Resonance Imaging (MRI). The same clinical and radiological findings can be found with tumor recurrence. To differentiate tumor recurrence and ORN, the time of presentation after treatment and location are and advanced imaging techniques (MRI with diffusion weighted imaging and Positron Emission Tomography and Computed Tomography (PET-CT)) can be used to differentiate the two diagnoses [23]. A biopsy is usually warranted and definitive.

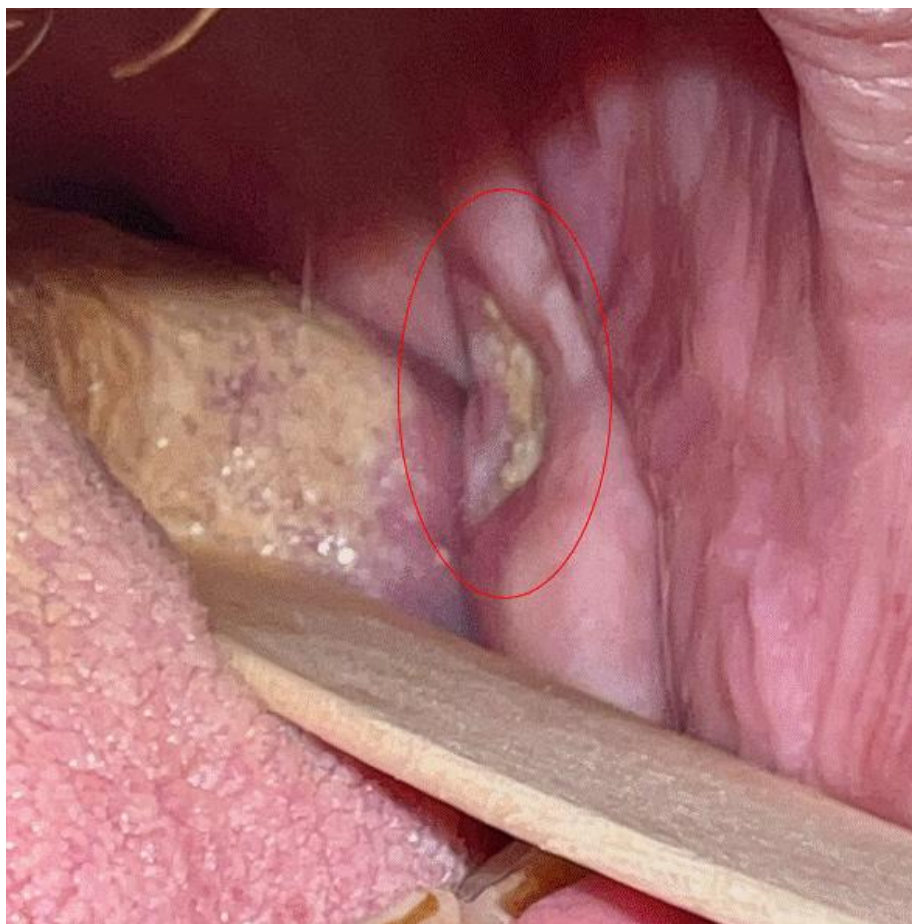


Figure 3: ORN of the posterior mandible with evidence of denuded bone and associated with pain.

Risk Factors

Radiation Risk Factors - Dosimetry

Radiotherapy parameters that influence development of ORN include total radiation dose to mandible, radiation technique and radiation volume. In a study including patients who received a total radiation dose greater than 40 Gy to the mandible, 11% of the patients developed ORN at an average of 13.5 months after radiotherapy; 89% of these patients had severe periodontal disease prior to radiotherapy [24]. Parotid gland sparing IMRT dosing protocols when combined with strict dental management led to zero cases of ORN in one study with a median follow up of 34 months.²⁵ When compared with 3D techniques, IMRT was linked to decreased rates of ORN [26]. Head and neck cancers are now also being managed in some cases with proton beam radiotherapy. Compared to photons, protons deposit an intermediate dose near the surface and deposit the maximum energy within the tumor target with negligible exit dose. The 3-year and 5-year rates of ORN after proton beam therapy have been reported to be 5.2% and 11.5%, respectively [27]. Essentially, proton beam therapy spares peripheral tissues due to its primarily surface targeting with minimal exit dose to non-tumor structures.

The threshold dose for ORN of the mandible has been reported to be 65 Gy and when 75% or more of the body of the mandible was within the radiation treatment volume [28]. Mean dose to the mandible was also a predictor of ORN with cases occurring with Dmean between 30 Gy and 60 Gy [22,29]. Well established and standard mandibular constraints include the mean dose, volume receiving 40 Gy (V40), volume receiving 60 Gy (V60) and especially the volume receiving 50 Gy (V50) have been shown to be associated higher rates of ORN [30-32]. Other constraints, although used less often have also been validated such as mandibular doses V44 Gy < 42% (% volume of mandible receiving 44 Gy) and V58 < 25% (% volume of mandible receiving 58%) [22,33]. The max dose to the mandible although often recorded does not seem to be a reliable predictor of ORN as larger volumes of intermediate to high doses lead microvascular damage and ORN complications [34]. It is important to note that the above dosimetric constraints only apply to conventionally fractionated radiotherapy (when given at 2Gy/day). When radiotherapy is given in accelerated or hypo-fractionated regimens the dosimetric models would be expected to be different [35].

With semi-automated tooth delineation tools to assess mandibular and maxillary dental regions, personalized dosimetric evaluation of ORN risks are now possible to implement [36]. Artificial intelligence has also been applied to predicting estimated pre-radiotherapy dental doses [37]. With the advancement of the computational and automated capabilities that can be integrated with radiation treatment planning systems, the hope is that individualized pre-radiotherapy and post-radiotherapy dosimetric reports will be available for all head and neck cancer patients.

Dental Risk Factors

Dental risk factors for development of ORN include periodontal disease (pockets ≥ 6 mm), extractions, implantation, active alcohol use and smoking [21,24,26,38-40]. It is also important to note that extraction(s) for compromised teeth prior to RT is not consistently reported as indicative of poor outcome. In a study where dental extractions before radiotherapy were performed and with half of the extraction involving five or more teeth, there were higher rates of ORN compared to those who did not have any pre-radiotherapy mandibular surgeries and/or tooth extractions [29]. However, it is not clear whether the risk of ORN is truly changed by performing pre-RT vs. post-RT extractions [38,41-43]. However, in the IMRT era, pre-radiotherapy dental extractions seem to have reduced risks of ORN [38]. Pre-radiotherapy implant placement is also a risk factor for ORN development and the incidence rate of around 1-3 % has been reported [39].

Medical Risk Factors

There is evidence that the oral microbiome is also related with ORN [44]. For resected oral cavity resections there does not seem to be a difference in ORN risks after different types of reconstruction [45]. Low pretreatment hemoglobin-to-platelet ratios were associated with increased risk of ORN [46].

Staging and Grading

Although the definite pathophysiology of Osteoradionecrosis (ORN) is not known, there is some consensus regarding the clinical definition of ORN [47]. ORN is defined as overlying skin breakdown or mucosal damage secondary to underlying bone necrosis in an irradiated area not explained by tumor growth without resolution for a period of 3-6 months [29,34]. The American Head and Neck Society describes the initial presentation of ORN as an ulcerating lesion typically associated with a significant amount of pain and swelling. Diagnostically, MRI and CT imaging modalities may be used to confirm cases of suspected ORN. There are many ways to report severity of ORN (Table 1), one proposed methodology for ORN staging supports the utilization of both clinical presentation and radiographic evidence [48]. The authors of this study acknowledge more sophisticated imaging modalities may provide additional objective assessment details but counter this notion by remarking upon the worldwide availability of radiographs as opposed to CT or PET (Table 2-4) [48].

CTCAE v5.0 ⁴⁹	Schwartz Clinical Staging ²⁶	VU University Medical Center Staging ⁴⁸	Notani grade ⁵⁰	Marx Grading ⁵¹	MDACC Grading ⁵²	Cancer Control Agency of British Columbia ⁵³
Grade I: Asymptomatic, no intervention	Stage I: superficial involvement of the mandible only (the majority resolve with minimal conservative management)	Stage 0: Exposure of mandibular bone for less than one month; no distinct changes on plain radiographs (panoramic radiograph or periapical film).	Grade I: Confined to alveolar bone	Grade I: exposed alveolar bone	Grade I: Minimal bone exposure with conservative management only	Stage I: Healed, resolved Stage Ib: Pathologic fracture reconstructed to provide continuity of jaw
Grade II: Symptomatic; medical intervention, limiting instrumental	Stage II: localized involvement of the mandible, exposed cortical bone and also a	Stage I: Exposure of mandibular bone for at least one month; no distinct changes on plain radiographs (panoramic	Grade II: Limited to the alveolar bone and/or mandible	Grade II: exposed alveolar bone that does not respond to	Grade II: Minor debridement received	Stage II: Chronic (>3 months), persistent. Lesion is not tender, remains stable in size and neurologic

ADL	portion of the underlying medullary bone are necrotic (the majority resolve with conservative management or minor surgical procedures)	radiograph or periapical film). Asymptomatic otherwise, e.g. no pain or presence of cutaneous fistulas (I A), or symptomatic, e.g. pain or presence of cutaneous fistulas (I B)	above the level of the mandibular alveolar canal	HBOT		symptoms of paresthesia and anesthesia are not progressive. IIb: Pathologic fracture with jaw dysfunction
Grade III: Severe symptoms, limiting self-care ADL; elective operative intervention	Stage III: diffuse involvement of the mandible, full thickness of a segment of bone is involved including the lower border (all require surgical intervention including bone and/or soft-tissue replacement)	Stage II: Exposure of mandibular bone for at least one month; distinct changes present on plain radiographs (panoramic radiograph or periapical film), but not involving the lower border of the mandible. Asymptomatic otherwise, e.g. no pain or presence of cutaneous fistulas (II A), or symptomatic, e.g. pain or presence of cutaneous fistulas (II B).	Grade III: Extended to the mandible under the level of the mandibular alveolar canal and with skin fistula and/or pathologic fracture	Grade III: full-thickness involvement and/or pathologic fracture, or draining tract to the overlying skin	Grade III: HBOT needed	Stage III: Active and progressive symptoms IIIb: Pathologic fracture with jaw dysfunction
Grade IV: Life threatening, urgent intervention		Stage III: Exposure of mandibular bone for at least one month; distinct changes on plain radiographs (panoramic radiograph or periapical film), involving the lower border of the mandible, irrespective of any other signs and symptoms.			Grade IV: Major surgery required	
CTCAE v5.0 = Common Terminology Criteria for Adverse Events version 5.0 ADL = activities of daily living HBOT – hyperbaric oxygen therapy						

Table 2: Grading and staging systems for severity of ORN based on clinical and imaging findings, as well as required treatment or treatment response.

	Osteoradionecrosis (ORN)	Gingival Recession (GR)	Radiation Induced Oral mucositis (RIOM)	Caries, extractions and tooth loss
Dosimetric thresholds	Mandible Dmax >60 Gy Dmean 30-60 Gy V44 Gy > 42% V58 Gy > 25% V59.8 Gy > 36% V60 Gy > 14% D2% > 65 Gy D30% > 42 Gy (w/o tooth extraction) D30% > 35 Gy (w/ tooth extraction)	1. Mean radiation dose to the mandible and for every additional 10 Gy of radiation, the percentage of mandibular sites with recession increased by 2% ⁸² 2. Prescribed dose > 60Gy (0.45 mm/yr) shown to have more GR than <50Gy (0.16 mm/yr) ⁸⁰	1. Radiation induced oral mucositis usually presents after the first 10-20 Gy of dose 2. Cumulative radiation dose > 60 Gy increases risk of RIOM 3. Cumulative dose > 65 Gy greatly increases risk of RIOM 4. < 32 Gy associated with mild severity (Grade 1) and short duration (<1 week) 5. >39 Gy associated with longer duration ⁸⁹	1. A mean parotid dose of > 26 Gy was associated with development of dental caries. 2. Doses of Dmax > 70 Gy and Dmean > 40 to the mandible was predictive of a dental extraction after radiation therapy. 3. Teeth exposed to 30-60 Gy were 2-3 times more likely to develop moderate/severe damage ⁹⁹ 4. Teeth exposed to > 60 Gy were 10 times more likely to have moderate/severe tooth damage ⁹⁹
Incidence	7-11% after extraction in irradiated patients ^{18,100}	~85% with a 0.2-0.87 mm decrease in distance from CEJ junction to the free gingival margin ⁷⁸	1. Grade 3 mucositis/confluent mucositis on clinical trials: 21-27% ^{89,101,102} 2. Any grade 69-98% ^{79,103}	1. 20.6% dental caries ⁷⁹ 2. 1 in 3 patients develop caries within 2 years of radiotherapy ¹⁰⁴ 3. 2-year rate of tooth failure 18% ⁸⁶
Onset	Median 3-31 months ²⁴	1. For > 60 Gy group, GR continues from year 1-5 2. For < 50 Gy group, GR occurs between year 1-3 and plateaus thereafter ⁸⁰ 3. Around ~47% of patients have periodontal disease at the start of RT ¹⁰⁵	1. Can start emerging after 1 week of conventionally fractionated radiotherapy – 2. Most develop severe OM between weeks 2 and 3 of treatment 3. ~98% develop some degree of mouth and throat soreness by the last day of radiotherapy 4. Can continue up to 2-3 weeks after treatment completion	1. Patients commonly (~37%) begin radiotherapy with untreated carious teeth
Treatment	1. PENTO, a combination of pentoxifylline 400 mg twice daily plus vitamin E 1000 IU once daily 2. PENTOCLO, a	Optimize oral hygiene status through professional dental care ⁷⁹	1. Mouthwashes (baking soda, elixir of diphenhydramine, xylocaine, antacid in a 1:1:1 ratio, Ayurvedic	1. Topical fluoride gel with custom tray or brush on ^{99,111,112} 2. Fluoride toothpaste 3. Oral hygiene (brushing

	combination of pentoxifylline (phosphodiesterase inhibitor), tocopherol (vitamin E) and clodronate (bisphosphonate) 3. HBOT 4. Surgery		medicines ⁹⁷ , dexamethasone- lidocaine-vitamin B12 ¹⁰⁶ 2. Intravenous L-alanyl- L-glutamine ¹⁰⁷ 3. Various Supplements (ie. beta-hydroxy-beta- methylbutyrate (HMB), arginine (Arg) and glutamine (Gln) (HMB/Arg/Gln) mixture ⁹⁴ 4. Bioadhesives ^{108,109} 5. Probiotics ¹¹⁰	teeth twice daily, floss or interdental cleaner daily, alcohol-free mouthwash twice daily) 4. Diet counseling 5. Dry mouth strategies (increased hydration, minimize ingestion of caffeinated products and alcohol, salivary substitutes, alcohol-free mouthwash, salivary stimulants)
CEJ – cemento-enamel junction GR – gingival recession, distance from the CEJ junction to the free gingival margin when the gingival margin was located on the root (for sites where the gingival margin as on the crown, GR was scored as zero) Dmax = Maximum dose within specified volume Dmean = Mean dose of specified volume V44 > 42% = More than 42% of the specified volume received at least 44 Gy V58 Gy > 25% = More than 25% of the specified volume received at least 58 Gy V59.8 Gy > 36% = More than 36% of the specified volume received at least 59.8 Gy V60 Gy > 14% = More than 14% of the specified volume received at least 60 Gy D2% > 65 Gy = Dose received by 2% of specified volume received more than 65 Gy D30% > 42 Gy = Dose received by 30% of specified volume received more than 42 Gy D30% > 35 Gy = Dose received by 30% of specified volume received more than 35 Gy				

Table 3: Summarizes the dosimetric parameters, incidence, onset and treatment options for the dental issues that are related to head and neck radiotherapy.

	Pre-Radiotherapy Recommendations	During Radiotherapy Recommendations	Post-Cancer Radiotherapy
NCCN ⁸³	1. Patient education, both oral and written, regarding oral and dental complications of RT and need for adherence with preventive protocols. 2. Discuss radiotherapy effects on salivary glands and bone in irradiated field. 3. Examination and assessment of patient with treatment plan • Complete oral and head and neck examination, including radiographs of all teeth • Risk assessment for caries and periodontal disease • Treatment plan ○ Eliminate potential sources of infection ○ Perform extractions at least 2 weeks before start of RT ○ Treat active dental caries,	1. Manage xerostomia 2. Prevent trismus of masticatory muscles 3. Evaluate for oral candidiasis and treat as clinically indicated	1. Manage xerostomia 2. Prevent and minimize trismus 3. Prevent and treat dental caries 4. Prevent and manage post-radiation osteonecrosis - Stabilized 0.1% chlorine dioxide oral rinse 5. Prevent and manage oral candidiasis 6. Consultation with treating radiation oncologist is recommended before considering implants or extraction. 7. Dental recall visit interval based on risk, at least once every 6 months, or more frequently for those with xerostomia, or for those with new caries or lesions

	periodontal disease ○ Use silicone guards to minimize radiation backscatter, if patients have metal restorations ○ Prescribe potent topical fluoride for daily use. Duration of use to be determined by periodic caries risk assessment over time ○ Schedule return visit for re-evaluation and reinforcement of preventive protocol for 6–12 weeks after completion of RT ○ Evaluate for oral candidiasis and treat appropriately with antifungal agents		following radiotherapy
Saudi ¹¹³	1. Elimination of oral infection and potential risk of oral disease or discomfort such as sharp teeth or ill-fitting dentures. 2. Achieving optimal healing after any tooth extraction. 3. Oral hygiene instructions. 4. Impressions of the mouth are taken for study casts to construct applicator trays and where appropriate for obturators planning.	1. Recommendations to use an alcohol-free chlorhexidine mouthwash. 2. Reducing the side-effects such as xerostomia and mucositis. 3. If the mouth is too painful for cleaning with a soft toothbrush, the tissues can be cleaned with oral sponges or gauze moistened with alcohol-free mouthwash.	1. Regular radiographs, oral health advice and preventive regime reinforcement. 2. Strategies for dealing with xerostomia continue. 3. High fluoride toothpaste should be used. 4. Jaw exercises are implemented in the event of trismus.
Australia ⁶⁸	1. Dental assessment with thorough clinical and radiographic examination 2. Appropriate preventive care and any required immediate treatment 3. Risk factor modifications, smoking and alcohol cessation 4. Unrestorable or periodontally hopeless teeth are extracted with minimal trauma before radiotherapy; prophylactic extraction of healthy teeth based on location within the radiation field appear to be unjustified; if extractions are performed, a 2-3 week waiting period for mucosal healing is acceptable before radiotherapy commencement 5. Perform scaling and fluoride application 6. Amalgams generally avoided due to backscatter and subsequent local mucositis 7. Any sharp cusps or restorations should be smoothed or repaired to avoid trauma to the vulnerable irradiated soft tissue 8. Dentures should be checked to ensure good fit to avoid ulceration; advised to avoid using	1. Management of xerostomia – salivary substitutes, sialogogues, oral rinses 2. Management of mucositis – adequate hydration, avoidance of irritants, topical barrier gels, analgesia, dietitian assessment 3. Management of trismus – early physical therapy, including jaw massage and exercises, maintain good oral hygiene 4. In the case of a dental emergency, keep in mind radiotherapy interruptions should be avoided, as delays reduce treatment efficacy and thus survival	1. Prevention of caries – regular oral hygiene including gentle and thorough brushing and flossing and non-acidic fluoride or bicarbonate mouth rinses 2. Daily topical fluoride in custom trays is recommended 3. resin-modified (RMGIC) and conventional glass ionomer (GIC) restorations may be more suitable in high-caries-risk situations as they offer simpler bonding procedures, chemical adhesion and fluoride release 4. Endodontic treatment for pulpally involved teeth preferred to extraction 5. Denture provision within 6 months or after 1 year are unlikely to differ in complication rates 6. Expect implant failure to be

	until radiotherapy is completed 9. Impressions taken for study models	- acute toothaches may be managed with standard restorative or endodontic techniques - extractions, where unavoidable, should have a low threshold for tertiary referral, especially for teeth in the radiation field	twice as likely in irradiated bone (Khadembaschi 2020 and Chrcanovic 2016) 7. Use of HBOT and antibiotics for prevention and treatment of ORN are controversial 8. General recalls every three months
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Table 4: This table provides a summary of the recent recommendations from national guidelines from the United States, Saudi and Australia regarding dental management for patients receiving head and neck radiotherapy.

Prevention, Treatment and Management

Prophylaxis

Currently, the routine use of Hyperbaric Oxygen Therapy (HBOT) for prevention for ORN is not recommended. There is weak evidence to support other preventative measures that have been studied such as pentoxifylline/tocopherol, growth factors and perioperative antibiotic therapy [49-56]. However, the best prevention of ORN is optimization of pre-radiotherapy dental health and maintaining good dental health during and after radiotherapy. Anatolian propolis, a natural substance produced by honeybees, showed promising pre-clinical data for prevention of ORN [57].

Hyperbaric Oxygen Therapy (HBOT)

HBOT is one of the most well-known treatment modalities for ORN as well as for other late radiation tissue injuries. HBOT is delivered in an airtight vessel with 30 to 60 administrations of 100% oxygen typically between pressures of 2.0 and 2.5 Atmosphere Absolute (ATA). This therapy is done for 60 to 120 minutes once or twice daily [58]. Contraindications to HBOT include emphysema, uncontrolled asthma or epilepsy, and/or previous optic neuritis [59]. Risks to HBOT include reduction in visual acuity and otic barotrauma [60]. HBOT works by increasing the number of blood vessels and improves white cell and fibroblast function, which enhances wound healing [61,62]. The UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis) was a phase 3 controlled trial that randomized patients who required dental extractions or implant placement in the mandible with prior radiotherapy > 50 Gy. These randomized patient groups either received or did not receive prophylactic HBOT. Results showed no statistical difference between the two groups, 6.4% and 5.7% [63]. An older study published in 1985 demonstrated a great benefit from HBOT compared to antibiotics alone after extraction(s) in patients who had received > 60 Gy; the difference in ORN development was 5.4% versus 29.9% [64]. In patients receiving prophylactic HBOT, the development of ORN can be exacerbated by active alcohol consumption and age > 65 [65]. Using HBOT for ORN treatment after its development did not show improvement in ORN resolution at 1 year after treatment in a randomized, sequential, double-blind, placebo-controlled trial [59]. A pooled analysis of two studies with poor accrual showed that there was no difference in HBOT + surgery versus surgery alone despite an absolute difference of 19% [66]. In the most recent Cochrane review of HBOT published in 2023, there remains to be low evidence for use of HBOT to improve wound dehiscence and ORN, although there is moderate support for improving pain scores at 12 months [60]. Despite the wide use of HBOT for ORN there is overall confounding evidence.

Medical Management

Although there is uncertainty and paucity of studies regarding strategies for prevention, there are numerous studies that have shown effective treatment and management after ORN development. A phase II trial found that PENTOCLO, a combination of pentoxifylline (phosphodiesterase inhibitor), tocopherol (vitamin E) and clodronate (bisphosphonate), to be effective for refractory cases of ORN that have failed previous treatments such as antibiotics, HBOT, and/or surgical procedures [67,68]. PENTOCLO was deemed safe and had a response rate of 59% [69]. PENTO, a combination of pentoxifylline 400 mg twice daily plus vitamin E 1000 IU once daily, had superior rates of healing compared to PENTOCLO in a registry study and would also be an acceptable medical management strategy [70]. Upfront medical management with pentoxifylline 400 mg twice daily, tocopherol 1000 IU/mg/day and doxycycline 100 mg daily decreased the rates of patients requiring resection a free flap reconstruction by half in an observational study [71].

Surgery

For severe mandibular defects caused by ORN, surgical reconstruction is often required and flaps harvested from fibular, iliac crest, scapular and radial forearm can be used [15]. ORN of the maxilla are often managed with sequestrectomy and segmental osteotomy followed by flap reconstruction derived from radial forearm, pectoralis major myocutaneous flap and submental island flap [72].

Gingival Recession

The worsening or periodontal disease in head and neck cancer patients is purported to be caused by an increase in the local levels of proinflammatory cytokines and collagenase enzymes [73-75]. Gingival recession following RT is a multifactorial process and may be the result of changes to the microbiome of the oral cavity, loss of supporting structures, changes in vascularity and salivary flow (Fig. 4) [76,77]. After radiotherapy, periodontal disease can be identified by bleeding on probing, periodontal pocket depth changes, clinical attachment level, plaque index and measuring gingival recession [78-80]. While the risk of periodontal complications can be mitigated with pre-radiation multidisciplinary collaboration, patient cooperation is a strong determinant in periodontal outcomes. Aside from the inherent changes induced by radiation therapy, it is important to elucidate that good oral hygiene, established via patient education, may reduce the risk of gingival recession. The OraRad trial tracked gingival recession by measuring the distance from the Cemento-Enamel Junction (CEJ) to the Gingival Margin (GM) [81]. There was a statistically significant decrease in the distance from the CEJ to the GM following RT for the treatment of head and neck cancer at all measured time points (baseline, 6, 12, 18, 24 months after start of RT) [82]. The percentage of sites with measurable gingival recession positively correlated with mean radiation dose to the mandible and for every additional 10 Gy of radiation, the percentage of mandibular sites with recession increased by 2% [82]. Greater gingival recession was associated with higher rates of whole mouth proportion of Decayed, Missing or Filled Surfaces (DMFS) [82]. Over the entire 2-year study period, the mean CEF-GM distance decreased by 74% [82].



Figure 4: Gingival regression on the lingual surface of the gingiva after oral cavity RT.

Caries, Extractions and Tooth Loss

Dental caries related to radiotherapy generally occur on atypical locations such as cusp tips or in the cervical area on the facial/buccal or lingual surfaces of teeth [82].

Hyposalivation increases the rate of dental caries after radiotherapy due to dysfunction of the salivary glands, changes in salivary pH, changes in diet and oral hygiene, immunoprotein deficiency and reduced oral clearance. A mean parotid dose of > 26 Gy was associated with development of dental caries. Doses of Dmax > 70 Gy and Dmean > 40 to the mandible was predictive of a dental extraction after radiation therapy [17]. Strategies to treat dry mouth include increased hydration, minimize ingestion of caffeinated products and alcohol, salivary substitutes (eg, gels containing lysozyme, lactoferrin, peroxidase and supersaturated calcium phosphate solutions), alcohol-free mouthwash (stabilized 0.1% chlorine dioxide oral rinse preferred), salivary stimulation with gustatory stimulants (eg, xylitol chewing gum, sorbitol/malic acid lozenges, xylitol lozenges) or cholinergic agonists (eg, pilocarpine, cevimeline) [83].

Although dental extractions are commonly due to dental caries, they can also be due to periodontal disease, root lesions and compromised mandibular tissue. Patients who have had a history of dental caries and poor oral hygiene before radiotherapy are at high risk of tooth failure in general [17]. Preventative measures include diet counseling, meticulous oral hygiene (brushing twice daily, floss or interdental cleaning daily, alcohol-free mouthwash twice daily), high potency topical fluoride (daily 1.1% NaF gel or SNF2 gel, brush on or in custom dental trays; or daily 1.1% NaF dentifrice; or fluoride varnish application, three times per year) (NCCN). Teeth with caries that are at low risk of post-RT complications include location with low risk of infection, good oral health and poor-long term prognosis [84]. Management of dental caries following RT includes, fluoride treatments, chlorhexidine. 12-.2% mouth rinse 1-2x daily and composite resin fillings for fluoride compliant patients [85]. Additionally, the ORAD study found that individuals with dental caries have 2x higher risk of primary tooth failure following head and neck radiotherapy [86]. Rate of tooth failure for the 520 applicable patients, constituting either complete evacuation of the tooth or unredeemable status, was 17.7% at two years. The mandible was statistically more likely to experience tooth loss. Furthermore, low baseline number of teeth at the onset of RT was noted to be statistically associated with primary tooth loss where baseline tooth number is assumed to be a placeholder for periodontal disease [86]. Indeed, it has also been found that there is an increased two-year risk of tooth loss following radiation therapy for patients who meet the following individual tooth parameters: untreated caries, periodontal pockets greater than or equal to 6mm, recession greater than 2 mm, furcation defect score of 2, any mobility or the presence of a 'hopeless' tooth deemed unrestorable [87].

Oral Mucositis

Patients undergoing any head and neck radiotherapy may experience oral mucositis, but the incidence and severity is highest among patients receiving treatment for oral cavity or oropharyngeal cancers. Numerous factors affect severity including tumor location, radiation dose and regimen, neutropenia and concurrent chemotherapy. There are multiple grading systems available for radiation-induced oral mucositis.

The pathogenesis of Radiation Induced Oral Mucositis (RIOM) is multifactorial and can be broken down into 5 stages: initiation of tissue damage, the primary damage response, signal amplification of pro-inflammatory response, ulceration and healing. Onset of RIOM usually occurs 2.5 weeks after initiation of radiotherapy and spontaneous healing usually occurs 4-12 weeks after completion of treatments [89,90].

In patients receiving IMRT, the rate of persistence oral mucositis and oral ulceration is around 8.1% and 3.8% at 6 months, respectively [91]. Cumulative radiation dosing greater than 50 Gy and concurrent chemotherapy are associated with oral mucositis [92]. Although interplay between the oral microbiome and formation of radiation-induced oral mucositis is unclear, the use of probiotic lozenges has been associated with lower rates of mucositis in patients receiving concurrent chemotherapy and radiotherapy [93]. Indeed, there is speculation that the changes to the oral microbiome induced by RT is likely due to upregulation of pro-inflammatory cytokines (TH17) downregulation of anti-inflammatory markers and direct damage to epithelial DNA/RNA. More intuitively, there is decreased risk of oral mucositis in patients who engage in rigorous oral hygiene routines. Regular brushing, flossing, maintenance of oral cavity moisture and rinsing with alkaline mouth wash has been associated with favorable outcomes [89]. Preventative measures such as oral administration of a beta-Hydroxy-Beta-Methylbutyrate (HMB), arginine (Arg) and Glutamine (Gln) (HMB/Arg/Gln) mixture has shown to decrease severe mucositis

from 64.6% to 25% [94]. Topical Omega-3 nanoemulgel has been shown to significantly lower mucositis grades at 3 and 6 weeks after treatment compared to the control arm. Ayurvedic mouthwashes have been shown to be effective in preventing RIOM [95-113].

Conclusion

The importance of collaboration between radiation oncologists and dentists is critical to ensure all patients have optimal dental and cancer outcomes. Collaboration enhances care before, during and after cancer treatment. Prevention is key and working together to develop a dental and radiation plan that minimizes the risks to the patients is essential. For dentists, understanding some of the key oncologic principles, basics of radiation therapy and how to manage common RT-related dental/oral complication can improve collaboration efforts.

Conflict of Interest

There are no potential conflicts of interest to declare in this paper.

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Author Contributions

All authors contributed equally for this paper.

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