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Predictive factors of osteoradionecrosis necessitating segmental mandibulectomy-A descriptive study

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Objective. The objective of this study was to assess characteristics of patients with mandibular osteoradionecrosis (ORN) of severity necessitating segmental mandibulectomy and osteocutaneous free flap reconstruction.
Study Design. This study is a retrospective review of patients who underwent free flap reconstruction of the mandible at the UCLA Medical Center between January 2016 and February 2020 secondary to ORN.
Results. Twenty-nine charts with detailed dental and medical records were identified. Hypertension was reported in 14 of 29 patients, diabetes in 2 of 29, osteoporosis in 2 of 29, antiresorptive use in 3 of 29, tobacco use in 15 of 29, and alcohol use in 19 of 29. Twenty-three patients initially had stage III-IV cancer. The median radiation dose was 68 Gy and median time to ORN was 5.2 years. Chemotherapy was given in 21 patients and 4 had previous mandibular surgery. Twelve of 29 patients had surgical procedures identified as the causative factor and 17 of 29 occurred spontaneously. Median decayed, missing, and filled teeth score was 17 and 17 of 29 patients had grade II-IV periodontitis. Periodontitis was present in 8 of 17 of spontaneous and 1 of 12 of surgery cases. Twenty-five of 29 cases occurred in the same oral sextant as the tumor.
Conclusion. Severe ORN occurred at doses >60 Gy in most cases. Location of the primary tumor was predictive of site of ORN and only molars were involved when precipitated by tooth extraction. Risk of ORN persists indefinitely. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;000:e1−e6)

Osteoradionecrosis of the jaw (ORN) after radiation therapy (RT) for head and neck cancer is a adverse effect of treatment that has varying degrees of severity. The pathogenesis is not clear, but Marx hypothesized it to be due to irradiated tissue becoming hypovascular, hypocellular, and hypoxic with subsequent tissue break down and nonhealing. The role of microorganisms and trauma was also questioned.[1] More recent findings of vascular and fibrotic changes after RT suggest that changes to tissue may be of prime importance.[2-4] Predictive factors of ORN development may include patient demographic characteristics, tumor staging, amount of prescribed radiation, tobacco and alcohol use, other systemic medical conditions, surgical trauma, dental disease, and denture-induced trauma. It may occur spontaneously or be precipitated by tooth extraction.[5-8]

The reported incidence of ORN varies widely, but there seems to be some agreement that it may be decreasing because of improvements in radiation delivery methods. Advanced treatment modalities allow for targeted dosing that results in sparing of surrounding tissues. Protocols to eliminate dental infection in high-risk areas as well as rigorous posttreatment oral hygiene also seems to have contributed to this improvement. Current estimates of occurrence range from 0% to 5%. Dental comorbidities include tooth extraction, periodontitis, and infection. Symptomatic ORN cases with exposed bone may require surgical intervention.[9-12]

Multiple authors have proposed grading systems based on extent of involved bone and response to conservative treatment.[13-15] Severity ranges from small self-limiting lesions to persistent pain and pathologic fracture. Treatment ranges from conservative with antibiotics to surgical resection. When segmental resection is done, bone containing free flaps are a reliable reconstruction that has acceptable survival and outcomes.[16-19] Given the high cost and complexity of such surgery, we reviewed the medical and dental records of patients who underwent free flap reconstruction secondary to ORN at the University of California, Los Angeles (UCLA) over 4 years. The purpose of this article is to identify risk factors for ORN necessitating composite resection.

Statement of Clinical Relevance

Severe osteoradionecrosis requiring composite resection occurs most often in the same mandibular third as the primary tumor radiated to >60 Gy. Molar extraction can be a causative event and preexisting periodontitis may be a risk factor for spontaneous development.

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METHODS

We conducted a retrospective study using the operating schedule of Head and Neck Surgery at the Ronald Reagan UCLA Medical Center from January 2016 to February 2020. Ethics approval was obtained from the UCLA review board. This time interval was selected because January 2016 was when an electronic medical record for dentistry became available and February 2020 was just before the coronavirus disease 2019 pandemic. A manual review of the operating room schedule identified 37 cases where composite resection followed by free flap reconstruction was performed secondary to ORN. Medical records reviewed included referral forms, history and physicals, computed tomography imaging, operating notes, progress notes, and discharge summaries. Dental records reviewed included clinical notes, charting, panoramic, and intraoral radiographs. Data extraction was performed for the following variables: age; sex; other medical conditions; surgical history; chemotherapy; cancer staging; radiation; time since radiation; decayed, missing, and filled teeth (DMFT); and periodontal status. Patient charts missing more than 1 of these factors were excluded. Twenty-nine patients met the inclusion criteria.

RESULTS

Between January 2016 and February 2020, a total of 37 patients with osteoradionecrosis received segmental mandibulectomies at the Ronald Reagan UCLA Medical Center. Twenty-nine met the inclusion criteria. Patient characteristics are described in Table I. The median age of patients at time of ORN diagnosis was 64 years old (range, 42-85). Twenty were male (69%) and 9 were female (31%). Fourteen patients had hypertension (48%), 2 had diabetes (6.9%), and 2 had osteoporosis (6.9%). Two patients were on antiresorptive therapy for cancer control and 1 for osteoporosis. Fifteen (52%) had a history of tobacco use with 13 former smokers and 2 current. Nineteen (66%) had a history of alcohol use with 1 former and 18 current. Median radiation dose to the primary tumor site was 66 Gy, with a range of 54 to 70.2 Gy. Detailed RT records for 8 (28%) patient records could not be located. Five of these had treatment that occurred more than 15 years ago. Twenty patients were treated with intensity-modulated radiation therapy (IMRT) and 1 with both IMRT and brachytherapy, and 8 were pre-IMRT. Median time between radiation and diagnosis was 5.2 years (range, 0 months to 28.7 years). Twenty-one patients (72%) had adjuvant chemotherapy, and 4 (14%) had previous bony resection of the mandible. Hyperbaric oxygen therapy (HBOT) was attempted in 21 patients (72%). Medical management with pentoxifylline and tocopherol (PTXvE) was attempted in 5 patients (17%).

Table I. Patient characteristics (n = 29)

Characteristic	
Median age (range)	*64 years (42-85 years)*
Sex	
Male	20
Female	9
Hypertension	14
Diabetes	2
Osteoporosis	2
Antiresorptive medication	3
Smoking	
Current	2
Former	13
Never	14
Alcohol	
Current	18
Former	1
Never	10
Previous mandibular resection	4
Chemotherapy	21
Radiation delivery method	
IMRT	21
Pre-IMRT	8
Median radiation dose (range)	68 Gy (54-70.2 Gy)
Median time RT to ORN (range)	5.2 years (0-28.3 years)
HBOT	21
PTXvE	5

IMRT, intensity-modulated radiation therapy; *RT*, radiation therapy; *ORN*, osteoradionecrosis; *HBOT*, hyperbaric oxygen therapy; *PTXvE*, pentoxifylline and tocopherol.

Tumor details are described in Table II. Twenty-five (86%) were squamous cell carcinomas, 1 (3.4%) was adenocystic carcinoma, 1 was mucoepidermoid carcinoma (3.4%), and 2 (6.9%) patients had metastases from distant sites (colon cancer and adenocarcinoma of the prostate). Fourteen (48%) patients had stage IV disease, 9 (31%) had stage III disease, 2 (6.9%) had stage II disease, and 4 (13.8%) were missing information and could not be staged. The American Joint Committee on Cancer seventh edition TNM Staging Classification was used in the assessment. Eight (28%) primary tumors sites were of the tonsils; 5 of the base of the tongue (17%); 4 of the mandible/gingiva (14%), 2 of which were metastases from distant sites; 4 of the buccal mucosa (14%); 2 of the tongue body (6.9%); 2 of the floor of mouth (6.9%); 2 of the upper lip or maxilla (6.9%); 1 of the retromolar trigone (3.4%); and 1 of the esophagus (3.4%). All tumors had defined left or right laterality except for the upper lip case and 1 tonsil case, which were bilateral. Twenty-five of 29 instances of ORN were in the same sextant when separating the oral cavity (Figure 1).

Patients were divided into 2 groups: spontaneously occurring ORN (n = 17) and induced by dentoalveolar surgery (n = 12). Dental characteristics are reported in Table III. The median DMFT score of all patients was 17. DMFT for the spontaneous group was 19 and

Table II. Tumor characteristics (seventh edition AJCC staging)

Characteristic	
Histology	
Squamous cell carcinoma	25
Adenocystic carcinoma	1
Mucoepidermoid carcinoma	1
Adenocarcinoma	1
Unknown	1
Site	
Tonsil	8
Base of tongue	5
Mandible/gingiva	4
Buccal mucosa	4
Tongue body	2
Upper lip or maxilla	2
Floor of mouth	1
Retromolar trigone	1
Esophagus	1
Staging	
I	0
II	2
III	9
IVa	8
IVb	1
IVc	3
Distant site	2
Unknown	4

AJCC, American Joint Committee on Cancer.

DMFT for the surgical group was 15. Periodontitis was graded according to the American Academy of Periodontology's 2017 classification system and was considered present at site if seen at or 1 tooth adjacent to the site of ORN. Dentition is graded from I to IV based on interdental attachment loss and residual bone level, with I being least severe and IV being the most severe. In the spontaneous group, 11 (61%) had periodontitis grade II-IV compared with 6 (55%) in the surgery group. Periodontitis was present at or immediately adjacent to the site of ORN in 8 patients (47%) in the spontaneous group and 1 (88%) in the surgery group.

DISCUSSION

Patients in our study had a combination of persistent pain, fistula, trismus, and pathologic fractures. Figures 2 and 3 are representative examples of clinical presentation at initial visit. Segmental mandibular resection with osteocutaneous free flap reconstruction was done in all cases. Twenty-eight flaps were harvested from the fibula and 1 from the scapula. Depending on insurance and urgency of treatment, implants were placed primarily or secondarily as seen in Figure 4. Twenty-one of 29 cases failed treatment with HBOT and 5 with PTXvE and required aggressive surgery for resolution. Epstein et al.[13] staged ORN from I to III with progressive cases that did not respond to conservative treatment as stage III. Notani et al.[14] and Schwartz and Kagan[15] graded cases based on size with grade III extensive involvement of the mandible. All cases we reviewed were considered Epstein III, Notani III, and Schwartz III.

The median patient age was 64 with a male:female ratio of approximately 2:1. Medically, 14 of 29 (48%) patients had a history of hypertension, and 2 of 29 (6.9%) had a history of diabetes. Twenty-two of 29 (76%) patients had a history of alcohol and/or tobacco use with 18 of 19 (95%) alcohol users still drinking and 2 of 15 (13%) still smoking. Age, sex, hypertension, diabetes, and tobacco and alcohol use prevalence were similar to those found in recent studies of ORN.[20,21] These systemic factors are not more prevalent in our subset of Grade III ORN.

Most authors report RT dose greater than 50 or 60 Gy as a risk factor for ORN.[5,6,8,10,12,20,21] Median radiation dose in our sample was 68 Gy, with all but 3 patients treated with over 60 Gy. For the 3 exceptions, 1 case occurred spontaneously with tumor dose 54 Gy. This patient had concurrent chemotherapy and had >14 alcoholic drinks per week. The second had a dose of 54 Gy that occurred after extraction of tooth #18. The patient also had induction and concurrent

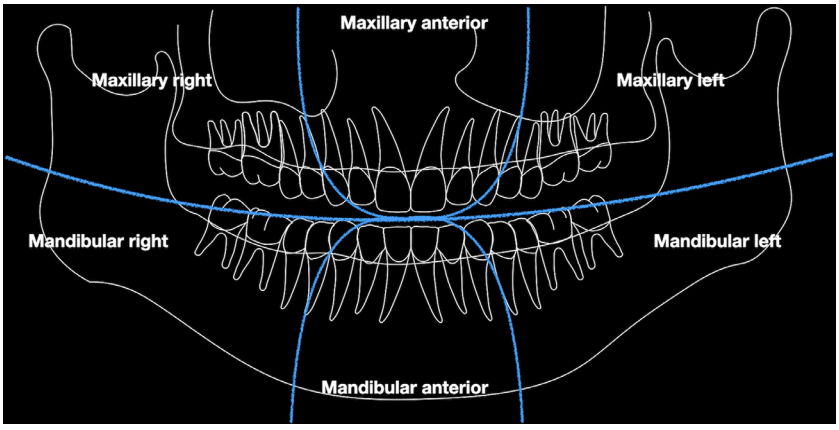

Fig. 1. Diagram separating the oral cavity into sextants.

Table III. Dental status of patients separated by occurrence spontaneously or after dentoalveolar surgery.

	No. of patients	*DMFT (median)*	*Periodontitis Stage II-IV*	*Periodontitis at site*
All	29	17	17 (59%)	9 (31%)
Spontaneous	17	19	11 (64%)	8 (47%)
Surgical	12	15	6 (50%)	1 (8.3%)

DMFT, decayed, missing, and filled teeth.

Fig. 2. Clinical presentation of a patient with exposed bone for approximately 6 months that progressed to pathologic fracture and malocclusion.

Fig. 3. Panoramic radiograph of the same patient before resection and reconstruction. Tooth #30 self-exfoliated. Resection is anticipated to span from tooth #26 to the R angle.

Fig. 4. Endosseous implants were placed primarily at time of resection and reconstruction. The patient is planned for a removable implant assisted resection prosthesis.

chemotherapy. The third had an unknown dose of radiation with chemotherapy for esophageal cancer treated over 15 years ago. ORN occurred after extraction of teeth #17 and #18. We believe that 60 Gy may be the threshold value for Grade III ORN. Other factors previously established as risk factors for ORN such as chemotherapy or heavy ongoing tobacco or alcohol use may have an additive effect.

Hansen et al.[22] found that more advanced tumor stages led to higher doses and higher volumes to the entire mandible. Chronopoulos et al.[23] found an association between tumor stage and ORN severity. Consistent with these conclusions, the present study includes 26 of 29 tumors located in the oral cavity or oropharynx with 23 of 29 stage III or IV cancers. Twenty-eight of 29 cases of ORN originated in the posterior mandible. No patients had ORN of the maxilla. Poor dentition is a risk factor for ORN development, with dentoalveolar surgery as a possible initiating event.[7-10,20-23] Of the 12 cases occurring after dentoalveolar surgery, 11 were after extraction of a molar tooth. The remaining 1 was soft tissue revision of a preexisting osteocutaneous free flap. This is in agreement with Beumer et al.[6] and Thorn et al.,[8] who found that the majority of mandibular ORN occurred in the molar region. No patients wore removable tissue-borne dental prostheses, so tissue irritation could not be evaluated as a contributing factor.

The DMFT index is a measurement to assess the extent of dental disease in a population. A large survey by the Centers for Disease Control in 2004 found a mean DMFT of 15 in seniors aged 65+, with 59% of patients having periodontitis based on clinical attachment loss levels.[24] Our population does not differ greatly: we found a median DMFT of 17 and periodontitis in 59% of patients. A case series by Galler et al. in 1992 detailed 3 cases of ORN from sites of periodontal disease.[25] In 2018, Schuurhuis et al. found that patients with periodontitis are more prone to develop bone healing problems after radiation.[26] One interesting note made in the present study was that periodontitis was present at or immediately adjacent to the site of ORN in 9 cases. Of these 9, 8 were in patients where ORN occurred spontaneously and only 1 where ORN was precipitated by dental extraction.

Twenty-five of 29 cases (86%) occurred in the same sextant as the primary tumor as drawn in Figure 1. Attention must be focused on the exceptions. One patient had a tumor of the R molar gingiva resulting in

ORN of the anterior sextant. The patient was treated with composite resection, fibula free flap, and adjuvant chemoradiation 60 Gy. ORN occurred near the midline after debulking at a second surgery. A second patient had radiation treatment of a tumor in the upper lip resulting in necrosis of the mandibular right and anterior sextants. This patient had induction and concurrent chemotherapy with bilateral neck radiation 50.4 Gy. The third had a tumor in the left palate treated to 70 Gy pre-IMRT with previous marginal mandibulectomy for ORN. ORN throughout the entire mandible developed 18 years later. The fourth had a tumor in the esophagus treated with radiation pre-IMRT and chemotherapy that resulted in necrosis of the lower left sextant. There were 5 cases with ORN on both the same and contralateral sides of the mandible necessitating angle-to-angle resection. Two of these were treated pre-IMRT, with 1 having full mouth extraction; 2 included radiation to bilateral neck in addition to chemotherapy; and 1 had full mouth extraction after IMRT and brachytherapy.

Hyperbaric oxygen therapy was first proposed by Marx to prevent ORN because it enhances healing of the radiation-induced hypoxic wound.[27] In our sample, HBOT was previously attempted and was unsuccessful in 21 cases (72%). ORN was found 0 months to 28.3 years after RT with a median time of 5.2 years. Hao et al.[28] and Shaha et al.[29] treated small samples of patients with severe ORN and concluded that conservative management with long-term antibiotics and HBOT was ineffective. Published studies on HBOT vary greatly in quality and have conflicting results.[30] Because of the lack of evidence, some large institutions recommend against routine use.[31] Although a relationship cannot be drawn, HBOT may be less effective in cases that have already progressed beyond a certain stage.

Delanian and Lefaix[3] and Delanian et al.[4] advocated a concept of ORN starting with radiation induced fibrosis leading to dysfunction of tissue synthesis and degradation. They suggested management through the antioxidant pathway to arrest or reverse progression. Pentoxifylline decreases blood viscosity, promotes vasodilation, inhibits inflammation, and has some antioxidant properties. Tocopherol is a potent antioxidant. Used in combination, they have a synergistic effect and have shown some success in reversing ORN after radiotherapy for head and neck cancer.[4,31,32] Hayashi et al. found a cure rate of 85% in 13 patients but did not detail severity of initial ORN.[32] Delanian et al. reported some improvement of ORN in 54/54 patients with a third severity Epstein II and the remainder Epstein III.[33] D'Souza et al. found reasonable response in cases of Notani I and II with less success in Notani III.[34] Most recently, Patel et al. found a 54% cure rate where ORN occurred a median 3 years after RT with greatest success in cases Notani I.[35] In the current sample, PTXvE failed in 5 cases with ORN diagnosed 1 year to 18.4 years after radiation with a median time of 5.4 years. PTXvE was started after referral to our center by the outside provider for management of refractory ORN. Our few cases cannot be used to imply that medical management of stage III ORN is ineffective but rather that it may be more successful if attempted sooner in the process.

There are multiple weaknesses of the present study. Some of these weaknesses include those inherent to a retrospective study of a rare disease. Our sample size is relatively small, some data are missing, and there is no control group. Dental care before and after radiotherapy was also not detailed. Periodontitis was staged primarily using panoramic images, so more precise staging and pocket depths could not be assessed. The exact treatment regimen with HBOT and PTXvE was not collected and there is bias regarding efficacy because only failed cases were reviewed. Medication-related osteonecrosis of the jaw is another concern prominent in the literature with a similar clinical presentation.[36] Of the 3 patients on antiresorptive therapy, 1 was on zoledronic acid and 1 was on denosumab and both stopped more than 5 years before ORN diagnosis. Another patient was taking alendronate for osteoporosis. All 3 were irradiated to over 60 Gy in the relevant region of the jaw. Therefore, the potential contributions or additive effects of antiresorptive therapies could not be assessed in the present sample. Future prospective studies should seek to address these issues.

CONCLUSIONS

Stage III osteoradionecrosis occurred in the same sextant as the primary tumor when treated to >60 Gy. Other factors to consider are chemotherapy, heavy tobacco/alcohol use, irradiation of neck lymph nodes, and treatment before IMRT. The risk of developing osteonecrosis persists for many years and periodontitis may contribute to spontaneous development.

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REFERENCES

1. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg*. 1983;41:283-288.
2. Weintraub NL, Jones WS, Manka D. Understanding radiation-induced vascular disease. *J Am Coll Cardiol*. 2010;55:1237-1239.
3. Delanian S, Lefaix JL. The radiation induced fibro-atrophic process: therapeutic perspective via the antioxidant pathway. *Radiat Oncol J*. 2004;73:119-131.
4. Delanian S, Depondt J, Lefaix J. Major healing of refractory mandible osteoradionecrosis after treatment combining

pentoxifylline and tocopherol: a phase II trial. *Head Neck*. 2005;27:114-123.

5. Wahl MJ. Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys*. 2006;64:661-669.
6. Beumer J, Harrison R, Sanders B, Kurrasch M. Osteoradionecrosis: predisposing factors and outcomes of therapy. *Head Neck Surg*. 1984;6:819-827.
7. Kluth EV, Jain PR, Stuchell RN, Frich JC. A study of factors contributing to the development of osteoradionecrosis of the jaws. *J Prosthet Dent*. 1988;59:194-201.
8. Thorn JJ, Hansen HS, Specht L, Bastholt L. Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. *J Oral Maxillofac Surg*. 2000;58:1088-1093.
9. Ben-David MA, Diamante M, Radawski JD. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys*. 2006;68:396-402.
10. Owosho AA, Tsai JC, Lee RS, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): the Memorial Sloan Kettering Cancer Center experience. *Oral Oncol*. 2017;64:44-51.
11. Nguyen NP, Vock J, Chi A. Effectiveness of intensity-modulated and image-guided radiotherapy to spare the mandible from excessive radiation. *Oral Oncol*. 2012;48:653-657.
12. Tsai J, Hofstede TM, Sturgis EM, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2013;85:415-420.
13. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis: clinical experience and a proposal for classification. *J Oral Maxillofac Surg*. 1987;45:104-110.
14. Notani K, Yamazaki Y, Kitada H, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck*. 2003;25:181-186.
15. Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible—scientific basis for clinical staging. *Am J Clin Oncol*. 2002;25:168-171.
16. Zaghi S, Danes J, Hendizadeh L, et al. Changing indications for maxillomandibular reconstruction with osseous free flaps: a 17-year experience with 620 consecutive cases at UCLA and the impact of osteoradionecrosis. *Laryngoscope*. 2014;124:1329-1335.
17. Hidalgo DA, Pusic AL. Free-flap mandibular reconstruction: a 10-year follow-up study. *Plast Reconstr Surg*. 2002;110:438-449.
18. Cordeiro PG, Disa JJ, Hidalgo DA, Hu QY. Reconstruction of the mandible with osseous free flaps: a 10-year experience with 150 consecutive patients. *Plast Reconstr Surg*. 1999;104:1314-1320.
19. Urken ML, Buchbinder D, Costantino PD, et al. Oromandibular reconstruction using microvascular composite flaps: report of 210 cases. *Arch Otolaryngol Head Neck Surg*. 1998;124:46-55.
20. Kubota H, Miyawaki D, Mukumoto N, et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. *Radiat Oncol*. 2021;16:1.
21. Sathasivam H, Davies G, Boyd N. Predictive factors for osteoradionecrosis of the jaws: a retrospective study. *Head Neck*. 2018;40:46-54.
22. Hansen HJ, Maritim B, Bohle GC III, et al. Dosimetric distribution to the tooth-bearing regions of the mandible following intensity-modulated radiation therapy for base of tongue cancer. . Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114:e50-e54.
23. Chronopoulos A, Zarra T, Troltzsch M, et al. Osteoradionecrosis of the mandible: a ten year single-center retrospective study. *J Craniomaxillofac Surg*. 2015;43:837-846.
24. Dye BA, Tan S, Smith V, Lewis BG, et al. Trends in oral health status: United States, 1988-1994 and 1999-2004. National Center for Health Statistics. *Vital Health Stat 11*. 2007:1-92.
25. Galler C, Epstein JB, Guze KA, et al. The development of osteoradionecrosis from sites of periodontal disease activity: report of 3 cases. *J Periodontol*. 1992;63:310-316.
26. Schuurhuis JM, Stokman MA, Witjes MJH, et al. Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study. *Support Care Cancer*. 2018;26:1133-1142.
27. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc*. 1985;111:49-54.
28. Hao SP, Chen HC, Wei FC, et al. Systematic management of osteoradionecrosis in the head and neck. *Laryngoscope*. 1999;109:1324-1327.
29. Shaha AR, Cordeiro PG, Hidalgo DA, et al. Resection and immediate microvascular reconstruction in the management of osteoradionecrosis of the mandible. *Head Neck*. 1997;19:406-411.
30. Shaw RJ, Dhanda J. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: treatment. *Br J Oral Maxillofac Surg*. 2011;49:2-8.
31. Sultan A, Hanna GJ, Margalit DN, et al. The use of hyperbaric oxygen for the prevention and management of osteoradionecrosis of the jaw: a Dana-Farber/Brigham and Women's Cancer Center multidisciplinary guideline. *Oncologist*. 2017;22:343-350.
32. Hayashi M, Pellecer M, Chung E, et al. *The efficacy of pentoxifylline/tocopherol combination in the treatment of osteoradionecrosis.* Spec Care Dent. 2015;35:268-271.
33. Delanian S, Chatel C, Porcher R, et al. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Biol Phys*. 2011;80:832-839.
34. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: experience from a regional head and neck unit. *Br J Oral Maxillofac Surg*. 2014;52:356-362.
35. Patel S, Patel N, Sassoon I, et al. The use of pentoxifylline, tocopherol and clodronate in the management of osteoradionecrosis of the jaws. *Radiother Oncol*. 2021;156:209-216.
36. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.

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