DOI: 10.4274/gulhane.galenos.2020.1076
Gulhane Med J 2020;62:213-23

Osteoradionecrosis - a review of clinical features and management

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Date submitted:
04.04.2020
Date accepted:
16.04.2020
Online publication date:
15.12.2020

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Keywords: Osteoradionecrosis, mandible, radiotherapy

ABSTRACT

Radiotherapy is an important part of oral cancer management. A significant complication of radiotherapy to the head and neck is osteoradionecrosis (ORN). The present report reviews the risk factors, clinical features, and management of ORN affecting the maxilla and mandible. A "PubMed" database search was done to identify "case reports" of ORN that were published, using the keywords "osteoradionecrosis", "jaw"', "mandible" and "maxilla". Data on ORN published within the past 10 years from 2008 to 2018 were collected and analyzed. A total of 23 full text articles reporting 27 cases of ORN were identified. Males constituted 84% of the cases. The mandible was affected in 96% of cases with bilateral involvement in 26.9% of cases and posterior mandibular involvement in 53.8% of cases. The amount of radiation received ranged from 50 Gy to 77 Gy. ORN occurred in 3.87 years on average after radiotherapy. The highest risk of developing ORN was associated with extraction of mandibular teeth within the radiation field in patients who received a radiation dose greater than 60 Gy. ORN was managed using varied methods such as surgical therapy, reconstruction with free fibular graft, low level laser therapy, and platelet rich gel. The recurrence of ORN was reported in 22% cases ranging from three weeks to one year later. In conclusion, the present review highlights the clinical features and risk factors associated as well as the various methods used in the treatment of ORN. The use of preventive strategies and advanced methods of management can decrease the incidence of ORN.

Introduction

Osteoradionecrosis (ORN) is a severe complication of external beam radiotherapy (RT) for malignancies affecting the head and neck (1,2). It is defined as 'A potentially severe, delayed radiation-induced injury, characterized by bone tissue necrosis, failure to heal, and exposed bone for at least three months' (3). The incidence of ORN in the head and neck region varies from 2% to 22% in subjects with a history of radiotherapy (3).

Various mechanisms have been proposed to explain the occurrence of ORN. These include the most commonly accepted hypoxic-hypocellular-hypovascular concept where radiation causes hypoxia of the bone, death of bone cells and long term damage to vascular supply as a result of endothelial cell damage ultimately leading to bone death (4). Another theory suggests that radiotherapy results in decreased soft tissue matrix which gets replaced with fibrous tissue, thereby increasing the tendency to develop ORN (5). Another suggested cause is the suppression of osteoclast related bone turnover. Some authors have proposed that radiation leads to a local inflammatory process which causes osteoblastic cell death, thereby preventing the repopulation of cells (6). The most recent theory of ORN is the fibroatrophic theory. According to this theory, vascular changes in the bone lead to endothelial changes along with an inflammatory response. This is followed by abnormal fibroblastic activity and altered bone healing which is more susceptible to infection (6).

Among the various classifications, the one given by Notani et al. (7), which is based on the amount of bone involvement, is

simple and preferred by many authors (8). ORN is a progressive condition which is difficult to treat. Various management strategies include sequestrectomy, resection, segmental mandibulectomy, and hyperbaric oxygen (HBO) therapy with varied results. Recent methods include the use of Pentoxifylline, Tocopherol and Clodronate, "PENTOCLO" (8).

The present report reviewed the current literature of the demographic characters, clinical features, and latest management techniques employed in the treatment of ORN.

A "PubMed" database search was done to identify case reports on ORN, published using the keywords "osteoradionecrosis", "jaw", "mandible", and "maxilla". Data on ORN published within the past 10 years from 2008 to 2018 were collected and analyzed. Only those case reports for which full text was available were considered in the review. Demographic characters, clinical features, and management were tabulated. Descriptive statistics were calculated using means and percentages.

A total of 23 full text articles reporting 27 cases of ORN were identified. The age range of the subjects was from 18 years to 84 years with a mean of 49 years. Males constituted 84% of the cases while females accounted for 16%. In 96% of the cases, the mandible was affected while 4% involved both the maxilla and mandible. The right and left mandible were equally affected in 34.6% of cases; and ORN was present bilaterally in 26.9% of cases. The posterior mandible was the most common site in 53.8% of cases.

ORN occurred three months -13 years later following radiotherapy, with an average time of 3.87 years. Associated malignancies varied with maximum cases having received radiotherapy for tonsillar carcinoma (Figure 1).

Radiotherapy was the primary treatment given in 25.9% of cases; surgery and radiotherapy were given in 40.7% of cases; subjects received adjuvant chemotherapy in 25.9% of cases while a combination of surgery, chemotherapy and radiotherapy was given in 7.4% of cases (Figure 2).

The amount of radiation received ranged from 50 Gy to 77 Gy.

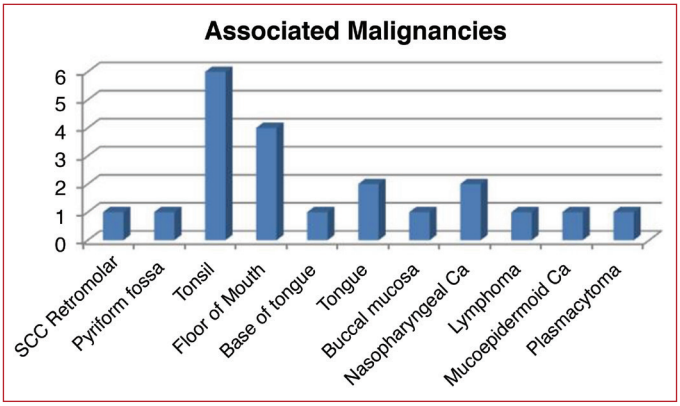

Figure 1. Graph showing the site of reported malignancies
SCC: Squamous cell carcinoma, Ca: Carcinoma

The presenting features of ORN included pain and discharge in 25.9% of cases, pathological fracture in 14.8% of cases, dysphagia and swelling in 7.4% of cases and anesthesia of the inferior alveolar nerve in 7.4% of cases.

Risk factors for ORN were tooth extraction, tobacco and alcohol abuse, and underlying medical conditions.

Management included surgical resection with fibular graft in 37% of cases, HBO therapy in 29.6% of cases, and segmental resection in 18.5% of cases. Other methods of ORN management included the use of leukocyte platelet-rich plasma (PRP), sequestrectomy, surgical debridement with Integra skin regeneration system and vacuum-assisted closure (VAC) system.

Recurrence of ORN was reported in 22% of cases, which ranged from three weeks to one year later. Table 1 (6,9-27) summarizes the details of subjects with ORN as reported by the various authors.

Discussion

Regaud first described post radiation ORN of the jaw in 1922 (13). Ewing, in 1926, reported the bone changes after radiotherapy as radiation osteitis (11).

Early bone changes after radiotherapy includes hyperemia, endarteritis, and cell death, while late changes include thrombosis, hypovascularization, and fibrosis (5).

ORN is a late effect of radiotherapy. RT for cancer in the head and neck has an increased chance of causing mandibular ORN. Recent reports suggest that the incidence of ORN has decreased from 20% to around 4-8%. This decrease is related to the elimination of all risk factors prior to radiotherapy and

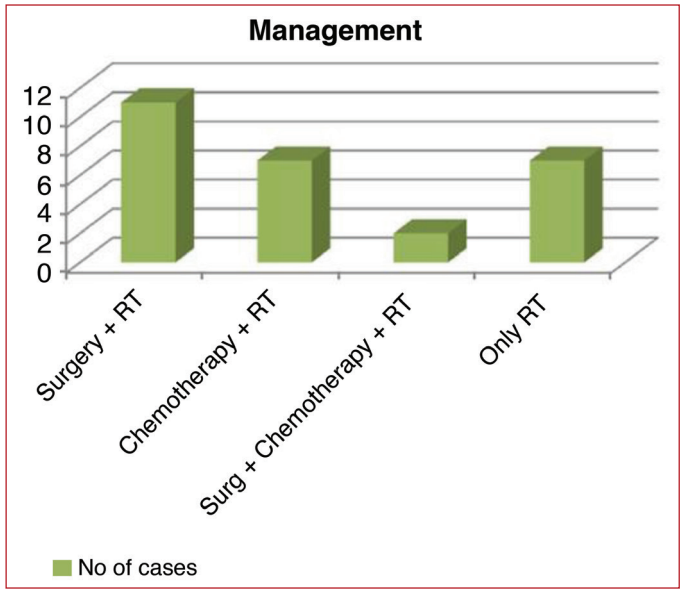

Figure 2. Graph showing the management strategies used in the reported cases
RT: Radiotherapy

recent advances in radiotherapy such as intensity modulated radiotherapy (IMRT) (28). The incidence of occurrence of ORN in the mandible is between 2% and 22% with most cases occurring in the mandibular body (9). This is in accordance with the present report where the mandible was the most affected, predominantly the posterior mandible. This increased predilection for the mandible is due to the richer vascularity in the maxilla and also because the mandible is irradiated more often. Also, since the mandibular bone is denser, the amount of radiation absorbed by the bone is more (6,29).

Around 70-90% of ORN cases are reported to occur within the first three years after radiotherapy. In the present report, ORN occurred from three months to 13 years following radiotherapy. However, the majority of cases occurred within the first five years. This variability could be because of the size and nature of the tumor, the type of radiotherapy used or individual patient risk factors (28).

The amount of radiation received ranged from 50 Gy to 77 Gy. The risk of developing ORN is medium at a radiation dosage of 40-60 Gy and high at a dose above 60 Gy (23). This is in conformity with our results.

The subjects may be asymptomatic in the initial stages. The main diagnostic feature is the presence of exposed bone in the mucosa or skin which can get secondarily infected. Other features include pain, dysesthesia, halitosis, and dysgeusia. Severe cases may lead to fistula formation from the oral mucosa or skin and pathological fractures (9). Diagnosis of ORN is made on the basis of patient history and the presence of exposed bone for more than three months. Radiological investigations such as panoramic radiographs and computed tomography are used to assess the extent of bone changes (17,23,30). This is similar to the clinical features reported by ORN cases in the present review.

Chemoradiotherapy (CRT) is linked to better locoregional control and overall survival and eradicates micrometastases. Although CRT is associated with an increase in early toxicity such as mucositis, the role of CRT in late toxicity is not clear. Recent studies have concluded that CRT does not increase the risk of ORN. In the present review, 25.9% of the cases received CRT. However, previous studies show difference in the incidence of ORN after RT and CRT (31).

Conventional management of ORN includes surgical debridement, sequestrectomy, oral hygiene maintenance with oral antiseptics, and the use of medications such as analgesics, antibiotics and corticosteroids (11). Segmental mandibulectomy is the next option followed by a complex reconstruction. In accordance with the fibro atrophic theory, a recent regimen for ORN recommends the use of vascular directed therapy using alpha – tocopherol (Vitamin E) and pentoxifylline (PENTO). Addition of clodronate to PENTO was found to be beneficial but carried the risk of bisphosphonate induced osteonecrosis (9,26). Delanian et al. (30,32) reported that PENTOCLO resulted in spontaneous sequestrectomy within the first six months of therapy leading to bone healing. PENTOCLO is not recommended in patients with recurrent or residual tumor. HBO therapy has been used along with surgery due to its ability to promote vascularity. HBO therapy includes the use of 100% oxygen for 90 mins at 2.4 atm pressure (24). However, recent trials have failed to demonstrate definite benefits. HBO is advised as an adjunct when resection or reconstruction surgery is needed (26). In the present report, HBO therapy was used in 29.6% of cases, usually in association with surgical debridement and resection with good results.

ORN can be of two types-spontaneously occurring and trauma induced (5). Spontaneously occurring ORN depends on the radiation dose that is received while ORN after dental treatments is categorized as trauma-induced ORN (5,27). Around 5% of cases occur following dental extraction (8). This is reflected in the present results where only two cases of ORN were reported after tooth extraction.

Spontaneous ORN commonly occurs between 6 months and 2 years after radiotherapy while the possibility of trauma-induced ORN is for long term. Thus, the risk of trauma induced ORN is higher in the dentate subjects due to extraction or dental and periodontal infection (9). Other factors include the grade and site of tumor, amount of radiation, immune deficiencies and any comorbidities (14). Moon et al. (28) found that pre-radiotherapy extractions were an independent risk factor for ORN but mentioned that it might be a reflection of the poor oral hygiene of the subjects. The use of IMRT has decreased the incidence of ORN especially in combination with good oral hygiene measures and decreased radiation to the mandible and parotid salivary glands (8). Contributing factors noted in the present review included tobacco and alcohol abuse and underlying medical conditions.

Marx's staging of ORN as stage 1, stage 2 and stage 3 is still widely followed (21). Stage 3 ORN requires surgical intervention (23). Kraeima et al. (23) used a novel method of combining the chemotherapy with the radiotherapy isodose curves in order to accurately predict the areas of ORN risk, and plan exact resection of affected bone and screw locations for reconstruction plates which are outside high dose areas.

Management of ORN in the present review was done using various methods. Most management strategies involved surgical treatment with the debridement of non-viable tissue and subsequent reconstruction. Successful management strategies included the use of allogeneic platelet gel (1) and skin regeneration systems for the repair of minor to moderate intraoral defects (3). Schepers et al. (10) described successful prosthetic rehabilitation with fibular graft using virtual implant planning. PRP was used to regain mandibular integrity and continuity of bone following

Table 1. Table showing details of subjects with osteoradionecrosis

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Curi et al. (5) 2017	Bilateral posterior mandible	Retromolar trigone Ca (T2 N2 M0)	Postoperative fractionated RT (5 fractions/week; 2.0 Gy/fraction; 34 sessions total of 68 Gy)	Surgery right radical neck dissection (lymph nodes levels 2 to 4) without ligation of the external carotid artery	56/M	8 yrs
Piccin et al. (1) 2016	Right posterior mandible	Right piriform sinus poorly differentiated adenocarcinoma	RT 7,000 cGy were given over 35 sessions	Chemotherapy (cisplatin 100 mg/ m^2 intravenous)	61/M	9 yrs
Beech and Farrier (3) 2016	Right posterior mandible	Left-sided tonsillar carcinoma	RT	Surgical excision	54/M	5 yrs
Schepers et al. (10) 2013	Right anterior mandible	Squamous cell carcinoma of the anterior floor of the mouth	RT 66 Gy	Surgical excision	54/M	1 yr
Reiffel et al. (11) 2012	Left posterior mandible	Cancer of base of tongue stage 4	RT	Chemotherapy	55/M	2.5 yrs
Rao et al. (4) 2012	Right posterior mandible	Low grade mucoepidermoid carcinoma	RT	Surgical excision	38/F	5 yrs
Poglio et al. (12) 2011	Right posterior mandible	Unknown	RT		41/M	2 yrs
Man et al. (13) 2015	Right posterior mandible	Malignant lymphoma	RT 60 Gy	Chemotherapy	18/M	1 yr
Scala et al. (14) 2010	Bilateral anterior and posterior mandible	Squamous cell carcinoma of the left half of tongue PT1pN0	RT 33 visits, 5 visits per week; each consisted of a dose of 200 cGy with a total dose of 6,600 cGy with Lonidamine	Partial left glossectomy with conservative neck dissection (CND) and bilateral suprahyoid lymph node dissection	44/M	4 yrs
Khatami et al. (15) 2010	Bilateral anterior and posterior mandible	Cancer of unknown primary	RT		62/M	

Clinical features	Management	Any other	Risk factor
Dysphagia caused by a painful, swollen, and discolored tongue	Hyperbaric oxygen therapy (30 sessions: 20 sessions before surgery and 10 sessions after surgery; 2.4 ATA; 90-minute session in a monoplace chamber. Bilateral marginal bone resections	Associated tongue necrosis	Tooth extraction under local anesthesia using vasoconstrictor
Severe dysphagia, fever >38 °C, rigor swelling of the right jaw and right sternocleidomastoid muscle	Leukocyte platelet-rich plasma (PRP) every 3 days for a total of 7 weeks (22 applications in total)		Alcohol abuse
Pain, difficulty eating, foul taste. Anesthesia of right inferior dental nerve; pathological fracture	Surgical debridement and Integra skin regeneration system		
Oral dehiscence and necrotic mandibular bone	Surgical resection followed by reconstruction with a free osseous flap with the planning of an implant-based prosthesis		
Necrotic left mandibular body	Segmental mandibulectomy followed by free fibular graft		
Pain, restricted mouth opening and discharge from ear; discoloration of overlying skin	Hyperbaric oxygen therapy	Mastoiditis	
Lower jaw defect involving the oral mucosa, mandibular bone, external skin, and soft tissue, communication between the oral cavity and the exterior	Subtotal mandibulectomy, fibular graft and vacuum-assisted closure system		
	Hemimandibulectomy, debridement of necrotic soft tissue, repair of the orocutaneous defects with thigh flap	Recurrent ORN 2 yrs later repaired using stereolithographic 3-Dimensional Printing modeling technology osteomyocutaneous flap	
Stomatitis, purulent abscesses and exposed alveolar process H/o tooth exfoliation	Moxifloxacin hydrochloride 600 mg daily dose for 20 days, regenerative surgery with autologous platelet rich plasma		
	Mandibulectomy and reconstruction with vascularized fibula flap		

Table 1. Continued

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Mendonça and Juiz-Lopez (16) 2010	Mandibular and maxillary anterior and posterior	Tonsillar cancer	RT		63/M	
Pautke et al. (17) 2010	Right anterior and posterior mandible	Extramedullary plasmocytoma	RT chest at 50 Gy	Adenectomy and lobectomy of the right lower lobe Bisphosphonate therapy	72/M	11 yrs
Pautke et al. (17) 2010	Left anterior and posterior mandible	Carcinoma of the left margin of the tongue pT1, pN1, Mx	RT 68.7 Gy; brachytherapy 62.5 Gy 9 yrs later	Bilateral neck dissection and partial glossectomy; chemotherapy (cisplatin and 5-fluorouracil) 9 yrs later	68/M	11 yrs
Le Stanc et al. (18) 2009	Left posterior mandible	Left tonsil squamous cell carcinoma extending to tongue and skull base cT4N1M0	RT 70 Gy	Chemotherapy (Carboplatin-Paclitaxel)	48/M	2 yrs
Jacobson et al. (19) 2010	Bilateral posterior mandible	Cancer of the tonsil	Opposing fields of external beam RT		72/M	4 yrs
Tursun and Green (20) 2017	Bilateral posterior mandible	Base-of the-tongue squamous cell carcinoma	7,000 cGy of radiation		72/M	13 yrs
Kakarala et al. (21) 2011	Bilateral mandible	Squamous cell carcinoma of the anterior floor of the mouth	RT	Resection and neck dissection	36/F	
Horta et al. (22) 2014	Mandible		RT		41/F	
Kraeima et al. (23) 2018	Left hemimandible	Squamous cell carcinoma in the floor of the mouth stage pT4N0	RT 56 Gy	Marginal mandibular resection.		3 months

Clinical features	Management	Any other	Risk factor
Tooth extraction, pathologic fracture, life-threatening infection, prolonged hospitalization, and severe chronic pain	Surgical debridement, 45 dives in hyperbaric oxygen, antibiotic therapy	Recurrent ORN after 1 year, suppuration from two fistulas, severe trismus, total lip anesthesia, treated with cultures stem and progenitor cells using bone marrow aspirate	
Submental abscess and an extraoral fistula in the anterior right chin region	Abscess was incised, extraction from the left lower first incisor to the right lower canine	Recurrence occurred twice mandibulectomy was done	Peripheral artery disease, coronary artery disease, arterial hypertension, diabetes mellitus, and a smoking habit
Exposed bone in the left lower jaw, fetor ex ore, and intensive, therapy-resistant pain	Partial resection of the left mandible and immediate reconstruction with fibular graft		Hypertension, glaucoma, and hyperthyroidism
Left submandibular fistula and pain; later pathological fracture	Surgical treatment	ORN with recurrent tumor	Alcohol and tobacco consumption
Bone exposure	Hyperbaric oxygen, antibiotics, and local debridements	Marx stage 3 ORN 6 months later; segmental mandibulectomies, with preservation of the native symphysis, and a reconstruction using a single fibular free flap	
Exposed bone in the right mandible with pain, purulent discharge, and severe hypoesthesia in the distribution of the inferior alveolar nerve	Antibiotics in addition to chlorhexidine mouth rinses 3 times daily to control the localized infection. The patient underwent hyperbaric oxygen therapy; ultimately surgical resection and fibular graft		
ORN	Resection and fibular graft	Wound infection and free flap loss; revision fibular free flap reconstruction was done with VAC	
	Resection and fibular graft	Chimeric anterolateral thigh flap	
Intraoral exposed necrotic bone (ORN) and a fractured mandible with an orocutaneous fistula	HBO treatment; reconstruction with iliac graft (30 sessions)	Repeat ORN in three weeks; reconstruction with fibular graft	

Table 1. Continued

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Kraeima et al. (23) 2018	Bilateral mandible	Squamous cell carcinoma floor of the mouth	RT 56 Gy	Surgical resection including a marginal resection of the mandible		11 months
Kraeima et al. (23) 2018	Left mandible	Squamous cell carcinoma in the buccal mucosa of the left mandible (pT4N1)	RT 66 Gy	3D guided surgical resection, including neck dissection, and the defect was reconstructed with a free vascularized fibula flap	84/M	20 months
Jeyaraj and Bandyopadhyay (24) 2016	Left mandible	Carcinoma of the left tonsil and faucial pillar and the left lateral and posterior pharyngeal wall	RT 76.8 Gy		60/M	10 months; One month after tooth extraction
Badeau and Deleyiannis (25) 2013	Left mandible	Left basaloid squamous cell carcinoma with recurrence	RT	Chemotherapy	59/M	3 yrs
Rathy et al. (9) 2013	Right mandible	Squamous cell carcinoma	RT	Surgery	65/M	4 yrs
Etezadi et al. (26) 2013	Left mandible	Left tonsillar squamous cell carcinoma stage T4bN3	RT 7,000 cGy	Radical tonsillectomy and modified neck dissection; chemotherapy	46/F	
Shimizu et al. (27) 2012	Right mandible	Nasopharyngeal cancer	RT 60 Gy to bilateral mandible	Chemotherapy	74/M	5 yrs
Shimizu et al. (27) 2012	Left mandible	Nasopharyngeal cancer	RT 66 Gy to bilateral mandible	Chemotherapy	69/M	3 yrs

Yrs: Years, Yr: Year, ORN: Osteoradionecrosis, HBO: Hyperbaric oxygen, RT: Radiotherapy

ORN (14). The most commonly reported treatment in large defects involved mandibular resection followed by free fibular graft and implant supported prosthesis (15). Tursun and Green (20) reported the use of processed allogeneic nerve allograft during surgical treatment for regaining neurosensory function in patients with ORN. Iliac marrow aspirate was used successfully for bone regeneration in one case (16). Kakarala et al. (21) used VAC dressing over free flap muscle to assist the closure of cutaneous defects in ORN. Horta et al. (22) reported a case where the failure of fibular graft was managed using chimeric anterolateral thigh flap and a dural substitute membrane with acceptable results.

Based on the fibroatrophic theory of ORN, a combination of pentoxifylline, tocopherol and clodronate is being tried as medical management in ORN cases refractory to surgery and HBO therapy. This protocol included antibiotic and corticosteroid treatment for one month to control infection followed by pentoxifylline, tocopherol and clodronate for at least six months. The authors reported a resolution rate of around 89% (33,34). In the present review, Garg et al. (6) was able to achieve good results with a combination of PENTOCLO therapy and sequestrectomy. An additional finding in the study was the incidence of ORN recurrence. As much as 22% of cases reported the recurrence ranging from

Clinical features	Management	Any other	Risk factor
	Reconstruction using isodose curves		
An intraoral fistula with exposed bone	HBO with soft tissue nasolabial flap; reconstruction using isodose curves		
Inability to open his mouth, difficulty in consuming even semisolid food and a persistent dull aching pain in the left side of his lower jaw	Segmental mandibular resection followed by Titanium reconstruction plate		Smoker, microvascular thrombosis, bronchiectasis of lung
Anterior submental draining sinus tract extending to the bone	Antibiotics and hyperbaric oxygen; surgical resection with fibular free flap		
Sharp bony projection in the mouth and pus discharge on right cheek	Sequestrectomy		
Exposed bone pain, trismus, and intraoral drainage	HBO; Segmental resection of the affected bone of the mandibular body, bilateral coronoidectomies, and placement of an external pin fixator	Dehiscence of the skin at the incision site with orocutaneous fistula after three months. Reconstruction with fibular flap	
Cheek skin was stiff, orocutaneous fistula, limited mouth opening	Surgical resection with fibular osteoseptocutaneous flap	ORN of left mandible occurred 3 yrs later; treated similarly	
Cheek skin was stiff, orocutaneous fistula, limited mouth opening	Surgical resection with fibular osteoseptocutaneous flap	ORN of right mandible occurred 2 yrs later; treated similarly	Extraction of left mandibular molar

three weeks to one year later; thus highlighting the recalcitrant nature of ORN.

The present review has certain limitations. In the reviewed case reports, data regarding newer methods of surgical management are highlighted. Pharmacologic management using pentoxifylline, tocopherol, and clodronate “PENTOCLO” has shown promise in treating patients with ORN. However, none of the reviewed case reports had data regarding the pharmacologic management of ORN. The incidence of ORN can be decreased through the use of new RT protocols such as 3D conformational radiotherapy and IMRT, which are able to deliver maximum radiation to the affected area while sparing the normal surrounding tissue as far as possible. However, data regarding the use of these methods were not available in the reviewed articles.

Conclusion

ORN is an important late complication of RT for head and neck cancer. The present review highlights the predilection of ORN to occur in the posterior mandible in subjects who have received radiation doses greater than 60 Gy. Tooth extraction, tobacco and alcohol use, and patient comorbidities are the risk factors for the development of ORN. All patients should undergo prophylactic oral care before, during and after the completion of radiotherapy.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.A., S.H., Design: V.A., S.H., Data Collection or Processing: V.A., Analysis or Interpretation: V.A., S.H., Literature Search: V.A., Writing: V.A., S.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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