Paradigm shifts in the management of osteoradionecrosis of the mandible

ARTICLE *in* ORAL ONCOLOGY · NOVEMBER 2010

Impact Factor: 3.61 · DOI: 10.1016/j.oraloncology.2010.08.007 · Source: PubMed

4 AUTHORS:

Adam S Jacobson
NYU Langone Medical Center
51 PUBLICATIONS **320** CITATIONS
SEE PROFILE

Daniel Buchbinder
Beth Israel Medical Center
83 PUBLICATIONS **2,134** CITATIONS
SEE PROFILE

Kaylie hu
University of Toronto
98 PUBLICATIONS **665** CITATIONS
SEE PROFILE

Mark L Urken
Beth Israel Medical Center
259 PUBLICATIONS **5,067** CITATIONS
SEE PROFILE

Oral Oncology 46 (2010) 795–801

211-268

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Paradigm shifts in the management of osteoradionecrosis of the mandible

Adam S. Jacobson, Daniel Buchbinder, Kenneth Hu, Mark L. Urken *

Department of Otolaryngology – Head and Neck Surgery, Beth Israel Medical Center, Albert Einstein College of Medicine, New York, NY, USA

ARTICLE INFO

Article history:
Received 17 August 2010
Accepted 18 August 2010
Available online 16 September 2010

Keywords:
Osteoradionecrosis
Microvascular surgery
Radiation therapy
Hyperbaric oxygen
Mandible reconstruction
Oral oncology

SUMMARY

Osteoradionecrosis (ORN) of the mandible is a significant complication of radiation therapy for head and neck cancer. In this condition, bone within the radiation field becomes devitalized and exposed through the overlying skin or mucosa, persisting as a non-healing wound for three months or more. In 1926, Ewing first recognized the bone changes associated with radiation therapy and described them as "radiation osteitis". In 1983, Marx proposed the first staging system for ORN that also served as a treatment protocol. This protocol advocated that patients whose disease progressed following conservative therapy (hyperbaric oxygen (HBO), local wound care, debridement) were advanced to a radical resection with a staged reconstruction utilizing a non-vascularized bone graft. Since the introduction of Marx's protocol, there have been advances in surgical techniques (i.e. microvascular surgery), as well as in imaging techniques, which have significantly impacted on the diagnosis and management of ORN. High resolution CT scans and orthopantamograms have become a key component in evaluating and staging ORN, prior to formulating a treatment plan. Patients can now be stratified based on imaging and clinical findings, and treatment can be determined based on the stage of disease, rather than determining the stage of disease based on a patient's response to a standardized treatment protocol. Reconstructions are now routinely performed immediately after resection of the diseased tissue rather than in a staged fashion. Furthermore, the transfer of well-vascularized hard and soft tissue using microvascular surgery have brought the utility of HBO treatment in advanced ORN into question.

Introduction

Radiation therapy plays a significant role in the contemporary management of head and neck malignancies. It is used in a variety of different treatment protocols, in combination with chemotherapy and surgery. Osteoradionecrosis (ORN) is usually a late complication of radiation exposure, occurring when irradiated bone becomes devitalized. It is classically defined as exposed bone through an opening in the overlying skin or mucosa, persisting as a non-healing wound for three months or more.[1] However, we have recently encountered a patient with a severe case of ORN, with a pathologic fracture but no evidence of bone exposure.

When ORN develops, it typically starts as a small area of mucosal breakdown with exposure of the underlying bone. As ORN progresses, patients often develop trismus, neuropathic pain, and chronic drainage. Additionally, these patients usually experience the full spectrum of collateral damage from radiation therapy (i.e. xerostomia, chronic trismus, dysgeusia, dysphagia, decreased tongue mobility). These extremely difficult problems, in combination with symptoms from ORN, often leave patients physically and emotionally disabled. Furthermore, the treatment of ORN can be frustrating for these already fragile patients because they often must endure repeated interventions without a clear end in sight (i.e. multiple debridements and HBO therapy).

Following an extensive review of the literature, there are a variety of issues which are called into question in determining the best staging and treatment for patients with ORN. There are a number of different staging systems which have been published, but few incorporate high resolution CT findings in determining the stage of disease. Marx's staging system is perhaps the most widely used and is predicated on staging ORN based on response to treatment.[1] Furthermore, there are few publications which address functional outcomes after treatment for ORN (i.e. type of diet, ability to wear dentures, resolution of trismus, and quality of life). Finally, most studies have short durations of follow-up and hence do not address the issue of disease progression over a patient's lifetime.

In this review article, we will discuss the etiology, epidemiology, and pathophysiology of ORN. Additionally, we will discuss our current management strategies for ORN as well as strategies to prevent the development of ORN.

Etiology and pathogenesis

The presentation of ORN ranges from superficial, slowly progressive bone erosion, to pathological fracture. Patients often

* Corresponding author. Address: Beth Israel Medical Center, Department of Otolaryngology – Head and Neck Surgery, Albert Einstein College of Medicine, 10 Union Square East, Suite 5B, New York, NY 10003, USA. Tel.: +1 212 844 8775; fax: +1 212 844 6975.
E-mail address: murken@chpnet.org (M.L. Urken).

1368-8375/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.oraloncology.2010.08.007

Table 1
Risk factors associated with the development of ORN.

Primary site of tumor[39]
– Posterior mandible is more commonly affected by ORN because of its compact and dense nature
Proximity of tumor to bone[4]
Extent of mandible included in primary radiation field[23]
State of dentition – odontogenic and periodontal disease[40]
Poor oral hygiene[40]
Radiation dose >60 Gy[23]
Use of brachytherapy[4,23]
Nutritional status[4]
Concomitant chemo-radiation
Ill-fitting tissue borne prosthesis resulting in chronic trauma[39]
Acute trauma from surgical procedures to the jaw[23]
Advanced stage tumors[38,39,41]

present with signs and symptoms of pain, drainage, fevers, and fistula formation. It rarely occurs in patients who have been exposed to a radiation dose less than 60 Gy and it is more common when brachytherapy is utilized.[1,2] Dental and periodontal disease, dental extractions, surgery, and trauma are frequently associated with the onset of ORN.[3] ORN has also been reported to occur spontaneously. There are a number of risk factors which contribute to, and are associated with, the development of ORN (Table 1). Although the risk of developing ORN is thought to be higher following treatment with combined chemo-radiation, to date there have been no studies which have conclusively shown an increase in the incidence of ORN in this patient population.[4]

There have been a variety of different theories to explain the pathogenesis of ORN. In 1926, Ewing first recognized and reported the bone changes associated with radiation therapy and described this disease state as "radiation osteitis".[5] Later, in 1938 Watson and Scarborough described "radiation osteitis" as being caused by radiation, trauma, and infection.[6] It was believed that trauma to the soft tissue overlying bone in the oral cavity permitted bacteria to enter into the underlying demineralized bone, leading to osteomyelitis. In 1972, Daly challenged the role of trauma in ORN.[7] More recently, it has become clear that micro-organisms only play a surface contaminant role and are not the true etiological cause of ORN.[7,8]

In the early 1980s Marx re-defined the pathophysiology of ORN by proposing that radiation therapy induces an endarteritis that results in tissue hypoxia, hypocellularity, and hypovascularity which in turn causes tissue breakdown and chronic non-healing wounds.[1] In 1990, Bras et al. reported their study in which sequestrectomy and resection specimens from mandibles diagnosed with ORN were compared with both non-irradiated and irradiated non-osteoradionecrotic mandible specimens.[9] The histopathologic findings suggested that the radiation induced obliteration of the inferior alveolar artery was the dominant factor leading to ischemic necrosis of the mandible.[9]

More recently, there has been a new theory proposed based on the concept that osteoclasts suffer radiation damage earlier than the development of vascular alterations. It is theorized that suppression of osteoclast related bone turnover is the initial event in development of ORN.[10–12] Interestingly, the entity known as bisphosphonate induced *osteonecrosis* of the mandible appears to support this theory. Bisphosphonates bind to bone mineral surrounding osteoclasts and are internalized by the osteoclasts. This internalization of bisphosphonate disrupts osteoclast mediated bone resorption, hence *osteonecrosis* develops.[10]

Lastly, the "Fibro-Atrophic Theory" proposes that fibroblast populations not only undergo total cellular depletion in response to radiation exposure, but also show a reduced ability to produce and secrete collagen into the surrounding tissue.[13]

Epidemiology

Although ORN can occur at any time after radiation therapy, it is most frequently noted (70–94%) in the first few years after completion of treatment.[14] "Early onset" ORN (<2 years after radiation therapy), is thought to be related to radiation doses higher than 70 Gy or surgical trauma, whereas "late onset" ORN, is thought to arise from trauma in a chronically hypoxic tissue environment.[14]

Prevention

Prevention of ORN is an extremely important part of the comprehensive management of patients who undergo external beam radiation therapy to the head and neck. All patients should undergo prophylactic oral care prior to, during, and after the completion of radiation therapy. All diseased teeth should be extracted. The optimal time for extraction of teeth is 21 days prior to initiating radiation therapy (no less than two weeks before starting therapy).[15] Less optimally, extractions can be performed within four months of completion of therapy. All patients should be instructed on meticulous oral hygiene and fluoride should be applied to the dentition daily via custom molded trays. Patients should undergo weekly checkups during radiation therapy and monthly thereafter for the first six months. Following this early post-treatment period, the patients should see their dentist every four months. The reason behind this "close follow-up" schedule is to monitor the patient's compliance with meticulous oral hygiene and the daily application of topical fluoride. Cervical root caries, common in xerostomic patients, must be treated promptly in order to avoid involvement of the pulp chamber or undermining the structure of the clinical crown. Those who require dental extractions more than four months after radiation therapy should be treated with HBO. The Marx protocol of 20 dives at 2.4 atmospheres for 90 min per dive before extraction and 10 dives after extraction has become the de facto standard.[15]

Advances in the delivery of radiation therapy such as intensity modulated radiation therapy (IMRT) holds promise to decrease the incidence of osteoradionecrosis (ORN) by increasing the conformality of the high dose prescription to spare larger volumes of mandible and improve homogeneity of dose. The primary treatment factors that impact the probability of developing ORN include total dose of radiation (>60 Gy), volume of mandible receiving that dose, the part of the mandible that is irradiated and dose fractionation (fraction sizes >2 Gy).[15–17] Spontaneous ORN is associated with doses >60 Gy and can occur at a rate of 5–15% with older techniques while newer techniques with three-dimensional (3D) conformal therapy and IMRT have decreased the rate to 6% or less.[18,19] A study comparing 3D and IMRT approaches, showed that when constrained appropriately, the volume of mandible receiving more than 50, 55 and 60 Gy could be decreased in oral cancer patients undergoing IMRT. In addition, there were fewer hot spots in the mandible and lower maximum dose.[17] Several studies reporting the incidence of ORN after IMRT have been reported. The RTOG-0022 study reported an incidence of 6% ORN in oropharynx cancer patients treated at fraction size of 2.2–66 Gy without chemotherapy.[20] The University of Michigan reported on 176 patients treated with IMRT.[21] At a median follow-up of 34 months, no cases of ORN developed which they attribute not only to the conformality of IMRT, but also to meticulous dental hygiene as well as salivary gland sparing which may decrease the risk for dental caries. Similarly Studer reported a 1.3% incidence of ORN after parotid-sparing IMRT.[22] Thus, to date the best outcomes with IMRT with regard to ORN appear to be when the dose to organs at risk (mandible, oral cavity and parotid) are constrained, conventional fractionation is utilized, and meticulous dental hygiene is applied.

Staging

There have been several staging or scoring systems which have been proposed. These systems are based on response to HBO therapy, degree of bone damage, clinical–radiological findings, length of bone exposure through the overlying skin or mucosa, and treatment needed.[3,23] See Table 2.

Although there are a variety of different staging systems, none of these has been adopted as widely as the system proposed by Marx in 1983.[1] Marx's classification system, based on response to therapy, has three stages through which patients are advanced until the ORN is resolved. Stage I ORN treatment involves primary HBO therapy, regardless of prior treatment. The patient is given 30 HBO dives, followed by re-evaluation and restaging. If the wound shows clinical improvement (granulation tissue, re-mucosalization), the patient completes a full course of 60 dives with the goal of producing a full mucosal cover. If there is no clinical improvement by 30 dives, the patient is categorized as a non-responder to Stage I and is advanced to Stage II. Treatment in Stage II involves a combination of trans-oral debridement or sequestrectomy, with a primary mucosal repair, followed by additional HBO therapy. If healing progresses without complication, the patient completes a total of 60 dives. If the wound breaks down, with recurrent bone exposure, the patient is identified as a non-responder and is advanced to Stage III treatment. Stage III involves a definitive surgical extirpation of all the diseased bone, primary wound closure, and external fixation followed by additional HBO therapy (20 dives). Ten weeks after resection of diseased bone, a staged reconstruction is performed with autogenous cancellous bone packed into a freeze-dried allogenic bone carrier. Additional post-operative HBO (10 dives) is then administered for completion of this protocol. Maxillo-mandibular fixation is maintained for eight weeks. Patients who present with a pathologic fracture, oro-cutaneous fistula, or radiographic evidence of bony resorption of the lower border of the mandible are immediately classified as Stage III disease, bypassing the protocol for Stage I and II disease.

More recently, Kagan and Schwartz described a three stage clinical staging system.[23] This staging system differs significantly from the system created by Marx because the disease is classified based on clinical and radiologic findings and treatment is determined based on the stage, similar to the approach for malignancies of the head and neck. Stage I is defined as minimal soft tissue ulceration and limited exposed cortical bone. These patients are treated with conservative management. A small number of patients progress to Stage II. Stage II is defined as localized involvement of the mandibular cortex and underlying medullary bone. Stage II is divided into groups a and b. Stage IIa has minimal soft tissue ulceration. Stage IIb is defined based on the presence of an oro-cutaneous fistula and mild soft tissue necrosis. Again, the majority resolve with conservative management or minor surgical procedures. Stage III is classified based on full thickness involvement of the bone, including the inferior border. Pathological fracture may also be present. All require surgical intervention, including bone and/or soft-tissue replacement.

Table 2
ORN staging systems.

Author	Date	Stages	Basis of stage
Marx	1983	I–III	Response to HBO therapy
Kagan + Schwartz	2002	I–III	Imaging andclinical findings
Glanzmann and Gratz	1995	1–5	Length of bone exposure and treatment necessary
Store and Boysen	2000	0–3	Combination of radiological and clinical parameters
NCI common toxicity criteria	N/A	0–4	Bone damage
Epstein et al.	1987	3	Disease progression

Although Marx's treatment protocol provides a framework for managing ORN, the concept of determining a patient's disease stage based on their response to treatment is very different from how surgeons are conditioned to treat diseases of the head and neck. In the treatment of head and neck cancer we utilize physical examination findings and a variety of different imaging techniques to stage the disease prior to formulating a treatment plan. It is the stage of disease that dictates the treatment options for each patient. In the contemporary management of ORN, we now utilize imaging and physical exam findings to stage the disease and then formulate the best possible treatment plan for each individual patient. Hence, Marx's treatment protocol remains an important contribution to the treatment of ORN, but the current approach has shifted to staging the disease first and then developing a treatment plan.

HBO therapy

Hyperbaric oxygen has been utilized as an adjunctive treatment modality in the management of ORN since the 1960s. The basis for applying HBO to ORN is an extension of Marx's theory that ORN is the result of tissue hypoxia, hypocellularity and hypovascularity.[1] The purpose of HBO is to increase the blood-tissue oxygen gradient, which enhances the diffusion of oxygen into hypoxic tissues. The increased oxygen supply stimulates fibroblast proliferation, angiogenesis, and collagen formation.[8,15] Additionally, the increased oxygen tension is bactericidal and bacteriostatic.

Initially, HBO yielded favorable results in the treatment of ORN. In 1975 Mainous and Hart reported their use of HBO as adjunctive therapy to surgical treatment of refractory ORN in 14 patients and reported successful results.[24] In 1976 Mainous and Hart reported a larger series in which there were successful results in 69 patients treated with HBO as an adjunctive measure for ORN.[25] In 1979 Davis et al. reported that 19 out of 23 patients treated with adjunctive HBO remained in remission for 2 years of follow-up.[26] In 1981 Mansfield et al. reported that 11 of 12 patients with refractory ORN responded favorably to HBO.[27] In 1983, Marx reported that 58 patients with refractory ORN were successfully treated with his published protocol.[1] In 1985 Kraut reported three cases in which HBO was used successfully as a prophylactic measure before and after dental extraction to prevent the development of ORN.[28]

More recently, the utility of HBO in the treatment of ORN has been called into question by a number of authors. In 1993 Mounsey et al. reviewed their experience with 41 patients with ORN who were treated with HBO. These authors found that HBO was beneficial in the treatment of mild ORN but a combination of surgery and HBO is necessary for more advanced ORN.[29] In 2000, Maier et al. reviewed their experience in 41 patients with advanced ORN who were retrospectively analyzed in two groups, one treated with HBO and the other was not.[30] All patients had Marx Stage III disease by definition. HBO was utilized in the post-operative setting only. Their conclusion was that the patients with advanced ORN who were treated with debridement and antibiotics alone were just as likely to recover as those who were treated with debridement, antibiotics, and post-operative HBO.[30] In 2003, Gal et al. reported their experience with 30 patients with Marx Stage III ORN who were treated with a radical resection and an osteocutaneous free flap reconstruction without the use of peri-operative HBO. They reported a 97% overall success rate for the treatment of Stage III disease without the use of HBO therapy. They stated that in advanced disease, they felt that HBO will only delay more definitive therapy.[31] In 2004, Annane et al. reported the first prospective, ran-

domized, double-blind, placebo-controlled study which had enrolled 68 patients and was terminated early because it failed to demonstrate significant benefit of HBO over placebo controls in patients with overt ORN.[32]

After critically evaluating the literature, it appears clear that advanced ORN requires aggressive surgical therapy, and it has become increasingly evident that HBO alone has minimal if any benefit in the treatment of advanced ORN. Additionally, as some recent publications have suggested, HBO may not have a clear role in the treatment of advanced ORN when a vascularized reconstruction is used.[4,33] The use of HBO in early and intermediate ORN remains important because the benefit seems clear based on numerous retrospective studies. The morbidity of HBO is minimal including transient myopia, middle ear barotrauma and seizures.[34] Absolute contraindication for HBO include optic neuritis, history of bullous pulmonary disease (COPD) or congenital pulmonary blebs.[35]

Contemporary management

In the current management of ORN, panorex and CT imaging findings are used in conjunction with clinical findings to determine if a patient has early, intermediate, or advanced stage disease. Treatment is then administered as below:

Stage I disease

Stage I disease represents small, superficial, localized bone resorption with cutaneous or mucosal dehiscence. Early stage ORN is approached conservatively with local wound care (oral rinses), HBO therapy for 20 dives,[36] and antibiotic therapy to quell the super-infection that is often present. If patients show definitive improvement, an additional 10 dives of HBO is given to allow for additional healing of the surrounding soft tissue. Patients that do not show signs of healing undergo a trans-oral debridement and additional HBO therapy. This approach of 20/10 differs from Marx's protocol where a 30/10 protocol is recommended.

Stage II disease

Stage II disease represents larger and deeper areas of bone resorption. Cortical and medullary bone are involved and the mucosal or cutaneous areas of breakdown are moderate in size. This stage of ORN is approached with antibiotics, trans-oral debridement or sequestrectomy, and HBO therapy (20 dives pre-operatively and 10 post-operative dives). All necrotic bone is debrided to a base of bleeding bone and a primary mucosal closure is performed. If the mucosa is unable to be closed primarily, a soft tissue flap can be utilized for coverage. All patients receive an additional 10 dives of HBO post-operatively. Patients that develop wound problems or repeat bone exposure are then treated with an aggressive surgical extirpation of all diseased hard and soft tissue and an immediate reconstruction with a well-vascularized free tissue transfer. Again, this approach differs from Marx's protocol in that only 20 pre-operative dives are performed prior to surgical debridement. Marx's Stage II protocol utilizes up to 60 total dives pre- and post-operatively.

Stage III disease

Stage III ORN is defined by full thickness devitalization of bone, resorption of the inferior border of the mandible, fistula or a pathological fracture. These patients are treated with an aggressive surgical extirpation of all diseased hard and soft tissue, and then immediate reconstruction is performed using a free tissue transfer. The ability to transplant tissue allows the extirpative surgeon to more aggressively resect the diseased hard and soft tissue rather than leaving residual areas of unhealthy tissue. Bony continuity is re-established immediately and patients can undergo a functional dental rehabilitation in a timely manner (implants are placed in the primary setting in non-irradiated well-vascularized bone, reducing the need for multiple surgeries and a prolonged period of functional impairment). This aggressive surgical treatment is often performed without using HBO therapy (pre- or post-operatively) or debridement. It has been our experience, and that of others, that patients who present with advanced disease do not benefit from HBO.[31] It has been speculated that this method of reconstruction enhances the viability of the remaining bone even in residual areas partially involved with ORN.[33,37] This approach markedly differs from Marx's treatment protocol in that he advocates for HBO therapy pre- and post-operatively, the reconstruction is staged and does not involve the use of vascularized bone flaps.

Discussion

In the critical evaluation of treatment of ORN it is difficult to find prospective, randomized, controlled studies. As can be seen in Table 3, there have been many published series involving various approaches to the management of ORN. However, most of these studies represent nothing more than a particular surgeon's experience or an institutional experience with the management of ORN. These studies are plagued by small patient cohorts. The largest is a series of 114 patients which was recently published in 2009 by Oh et al.[38] The small number of patients enrolled in each study makes it difficult to reach statistical significance. Additionally, almost all of the published literature is based on retrospective chart reviews rather than prospective design. Retrospective reviews are useful, but they often contain bias within the study. Finally, the majority of the studies listed in Table 3 do not mention the length of follow-up of the patients enrolled and hence do not address the issue of disease progression. We know from our own experience that ORN can progress in the proximal or distal mandibular segments following segmental resection of the involved bone. These studies help us to better understand the experiences that surgeons have encountered while managing ORN but they do not provide strong scientific evidence for management decisions when dealing with ORN.

In the contemporary management of ORN, there are well defined and effective treatment strategies for early and advanced disease. Early disease (Stage I) is managed conservatively (local wound care, HBO, and antibiotics). Advanced disease (Stage III) is managed surgically with a wide extirpation and immediate microvascular reconstruction. It is the intermediate stage disease (Stage II) for which it remains difficult to recommend a definitive treatment course. Unquestionably, there are intermediate stage patients who will respond to trans-oral debridement, HBO, and antibiotics. There is also a subset of intermediate stage patients who do not respond to this treatment plan and ultimately require a segmental resection and reconstruction. Since we currently do not have any pre-operative radiological or clinical criteria which can differentiate these patients, our current philosophy is to bring these patients to the operating room with the plan for a trans-oral debridement and primary closure. If mucosal closure is not feasible a vascularized soft tissue flap is utilized. Furthermore, we prepare these patients for the possibility that it may not be possible to effectively debride back to healthy bleeding bone without the creation of a segmental defect and therefore require conversion of the procedure to a radical resection and free flap reconstruction. It is the intra-operative finding of bleeding bone edges, without com-

Table 3
Compilation of published series on approaches to management ORN.

Author (year)	Design	# of Pts	Treatment	Mean follow-up	Complications	Success (%)	Author's conclusions
Freiberger et al. (2009)	Retro	65	Multi-modality (HBO + surgery)	86.1 months	N/A	88	Multi-modality therapy is effective for ORN when less intensive therapies have failed
Wang et al. (2009)	Prospective	15	Resection and fibula free flap reconstruction	27.6 months	N/A	73% improved QOL	Mandible reconstruction with fibula free flap eliminates pain and controls local infection although radiation therapy induced complications still influence patients QOL
Oh et al. (2009)	Retro	114	Multi-modality	40 months	5/27 flaps had major complications	42/97 43% had complete resolution	Radical resection is a useful method for treating mandibular ORN that does not respond to conservative treatment. Signs of ORN are related to progression of ORN
Hirsch et al. (2008)	Retro	21	Radical Rsxn and immediate free flap reconstruction	N/A	12% flap loss 14.7% infection 7.4% fistula 8.8% hematoma 2.9% carotid blowout	100% successful reconstruction	Free tissue transfer is a viable option for advanced ORN
D'Souza et al. (2007)	Retro	23	HBO vs no HBO	30 months	N/A	12.5% cure rate in HBO group 86% cure rate in non-HBO group	Little benefit from HBO
Curi et al. (2007)	Retro	5	Radical resection with immediate microvascular reconstruction	25 months	20% flap loss	N/A	Radical resection + immediate microvascular recon is reliable and effective
Militsakh et al. (2005)	Retro	9	Osteocutaneous radial forearm flap	36 months	None	100%	Osteocutaneous radial forearm flap is an excellent reconstructive option for advanced mandibular ORN
Annane et al. (2004)	Prospective, randomized, double-blind, placebo-controlled	68	HBO vs placebo	Terminated early	None	N/A	Overt mandibular ORN does not benefit from HBO. Study was terminated early due to worse outcome in HBO arm
Gal et al. (2003)	Retro	30	Radical resection with immediate microvascular reconstruction	N/A	43% overall	97% complete resolution	Radical resection + immediate microvascular recon is reliable and effective
Ang et al. (2003)	Retro	21	Wide resection and free flap reconstruction	26.9 months	4.8% flap loss	100%	Free tissue transfer is a valuable option for advanced ORN
Celik et al. (2002)	Retro	27	Segmental resection and fibular free flap reconstruction	N/A	1 flap loss	N/A	Resection of non-viable bone and microvascular reconstruction is inevitable and a composite osteocutaneous free flap is a good option
Chang et al. (2001)	Retro	29	Radical resection with immediate microvascular reconstruction	33 months	21% overall 14% flap loss	100%	Radical resection + immediate microvascular recon is reliable and effective
Curi et al. (2000)	Retro	18	Surgery + HBO	24.8 months	N/A	14/18 had complete healing	In advanced ORN, Radical Rsxn + HBO has acceptable results
Shaha et al. (1997)	Retro	6	Wide resection and immediate microvascular reconstruction for advanced ORN	33 months	N/A	100%	Immediate free flap reconstruction for advanced ORN is an effective option
Wong et al. (1997)	Retro	32	Non-surgical/HBO management	N/A	N/A	63% improved, resolved, or stabilized	

(*continued on next page*)

Table 3 (*continued*)

Author (year)	Design	# of Pts	Treatment	Mean follow-up	Complications	Success (%)	Author's conclusions
Van Merkesteyn et al. (1995)	Retro	29	Multimodality (surgery + HBO + Abx)	16 months	N/A	20/29 pts had complete resolution	Multimodality therapy has acceptable results for larger lesions and patients that do not respond to conservative therapy
McKenzie et al. (1993)	Retro	26	HBO with or without hemi-mandibulectomy	24 months	N/A	50% had complete resolution	HBO with or without surgery appears to be effective
Mounsey et al. (1993)	Retro	41	Role of HBO in ORN	N/A	N/A	83% had significant improvement	HBO is of benefit in management of mild ORN but surgery and HBO is necessary for severe ORN
Koka et al. (1990)	Retro	104	Segmental mandibulectomy	N/A	8.6% minor sepsis 2.9% major sepsis 3.8% fistula 2.9% hematoma	100%	Radical surgery resolved chronic pain, trismus, and swallowing dysfunction
Marx et al. (1983)	Retro	58	Marx's HBO treatment and staging protocol	N/A	N/A	N/A	Refractory ORN successfully treated with this protocol
Mansfield (1981)	Retro	12	HBO as an adjunct in the treatment of ORN	N/A	N/A	N/A	HBO was used to successfully treat 11 of 12 patients
Hart and Mainous (1976)	Retro	69	Multimodality therapy including HBO	N/A	N/A	N/A	Multimodality therapy resulted in improvement in all cases
Mainous and Hart (1975)	Retro	14	Use of HBO for intractable ORN	N/A	N/A	N/A	HBO resulted in resolution of pain, draining fistula, and healing of pathological fracture

promise to the structural integrity of the mandible, that we use to try to differentiate between the patients that will respond to a trans-oral debridement and the patients that will not. We believe that the patients who do not have adequate bleeding from the cut bone edges at the time of debridement are at high risk for failure. The assessment of bone viability via the intra-operative finding of bleeding bone edges is admittedly a very crude technique for determining adequacy of debridement but currently there is no other scientific measure which can be utilized. It is hoped that in the future there will be a more objective means to assess bone viability.

Conclusion

The management of ORN has become similar to the approach used for treating malignancies of the head and neck. The workup of ORN should include imaging studies, i.e. high resolution CT and panorex films, and a meticulous physical examination. The patient's disease is staged based on symptomatology, imaging, and physical examination findings. Currently, the published literature does not provide us with a definitive treatment strategy for each stage of disease. We are currently working on developing a new staging system based on the aforementioned parameters which we feel will help us develop a more effective treatment algorithm.

What can be distilled from the current literature is that early disease frequently responds well to conservative management and advanced disease commonly requires a radical resection and reconstruction. Microvascular free tissue transfer plays an important role in the management of advanced stage ORN. It is the intermediate stage patients who often undergo multiple debridements combined with HBO therapy, unfortunately, a subset will ultimately require a radical resection and reconstruction.

Additionally, throughout the literature, there is little consideration given to the wide range of complications that patients' endure from radiation therapy such as trismus, loss of taste, xerostomia, etc. It is clear that the treatment of ORN will not result in significant improvement in these additional conditions, hence, quality of life for a patient with ORN can be difficult to improve even with the successful treatment of ORN. Future studies should address the problem of disease progression and functional outcomes should be assessed with respect to dental rehabilitation, relief of trismus, improvement in oral intake, and pain relief.

Conflicts of interest statement

None declared.

References

1. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;**41**:351–7.
2. 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**:1088–93. discussion 93–5.
3. Store G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. *Clin Otolaryngol Allied Sci* 2000;**25**:378–84.
4. Teng MS, Futran ND. Osteoradionecrosis of the mandible. *Curr Opin Otolaryngol Head Neck Surg* 2005;**13**:217–21.
5. Ewing J. Radiation osteitis. *Acta Radiol* 1926;**6**:399–412.
6. Watson WL, Scarborough JE. Osteoradionecrosis in intra-oral cancer. *Am J Roentgenol Radiat Ther* 1938;**40**:524–34.
7. Daly TE, Drane JB, MacComb WS. Management of problems of the teeth and jaw in patients undergoing irradiation. *Am J Surg* 1972;**124**:539–42.
8. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg* 1983;**41**:283–8.
9. Bras J, de Jonge HK, van Merkesteyn JP. Osteoradionecrosis of the mandible: pathogenesis. *Am J Otolaryngol* 1990;**11**:244–50.
10. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;**62**:527–34.
11. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;**61**:1115–7.

12. Wang J, Goodger NM, Pogrel MA. Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg* 2003;**61**:1104–7.
13. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. *Radiother Oncol* 2004; **73**:119–31.
14. Reuther T, Schuster T, Mende U, Kubler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients – a report of a thirty year retrospective review. *Int J Oral Maxillofac Surg* 2003;**32**:289–95.
15. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987;**64**:379–90.
16. Glanzmann C, Gratz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. *Radiother Oncol* 1995;**36**: 94–100.
17. Ahmed M, Hansen VN, Harrington KJ, Nutting CM. Reducing the risk of xerostomia and mandibular osteoradionecrosis: the potential benefits of intensity modulated radiotherapy in advanced oral cavity carcinoma. *Med Dosim* 2009;**34**:217–24.
18. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;**14**:199–212.
19. Studer G, Gratz KW, Glanzmann C. Osteoradionecrosis of the mandibula in patients treated with different fractionations. *Strahlenther Onkol* 2004;**180**: 233–240.
20. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys* 2009;**76**: 1333–8.
21. Ben-David MA, Diamante M, Radawski JD, et al. 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* 2007;**68**:396–402.
22. Studer G, Studer SP, Zwahlen RA, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). *Strahlenther Onkol* 2006;**182**:283–8.
23. Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible: scientific basis for clinical staging. *Am J Clin Oncol* 2002;**25**:168–71.
24. Mainous EG, Hart GB. Osteoradionecrosis of the mandible. Treatment with hyperbaric oxygen. *Arch Otolaryngol* 1975;**101**:173–7.
25. Hart GB, Mainous EG. The treatment of radiation necrosis with hyperbaric oxygen (OHP). *Cancer* 1976;**37**:2580–5.
26. Davis JC, Dunn JM, Gates GA, Heimbach RD. Hyperbaric oxygen. A new adjunct in the management of radiation necrosis. *Arch Otolaryngol* 1979;**105**: 58–61.
27. Mansfield MJ, Sanders DW, Heimbach RD, Marx RE. Hyperbaric oxygen as an adjunct in the treatment of osteoradionecrosis of the mandible. *J Oral Surg* 1981;**39**:585–9.
28. Kraut RA. Prophylactic hyperbaric oxygen to avoid osteoradionecrosis when extractions follow radiation therapy. *Clin Prev Dent* 1985;**7**:17–20.
29. Mounsey RA, Brown DH, O'Dwyer TP, Gullane PJ, Koch GH. Role of hyperbaric oxygen therapy in the management of mandibular osteoradionecrosis. *Laryngoscope* 1993;**103**:605–8.
30. Maier A, Gaggl A, Klemen H, et al. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. *Br J Oral Maxillofac Surg* 2000;**38**:173–6.
31. Gal TJ, Yueh B, Futran ND. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Arch Otolaryngol Head Neck Surg* 2003;**129**:72–6.
32. Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;**22**:4893–900.
33. Mirante JP, Urken ML, Aviv JE, Brandwein M, Buchbinder D, Biller HF. Resistance to osteoradionecrosis in neovascularized bone. *Laryngoscope* 1993;**103**: 1168–73.
34. Vudiniabola S, Pirone C, Williamson J, Goss AN. Hyperbaric oxygen in the prevention of osteoradionecrosis of the jaws. *Aust Dent J* 1999;**44**:243–7.
35. Giebfried JW, Lawson W, Biller HF. Complications of hyperbaric oxygen in the treatment of head and neck disease. *Otolaryngol Head Neck Surg* 1986;**94**:508–12.
36. 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.
37. Baker SR. Management of osteoradionecrosis of the mandible with myocutaneous flaps. *J Surg Oncol* 1983;**24**:282–9.
38. Oh HK, Chambers MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the mandible: treatment outcomes and factors influencing the progress of osteoradionecrosis. *J Oral Maxillofac Surg* 2009;**67**:1378–86.
39. Kluth EV, Jain PR, Stuchell RN, Frich Jr JC. A study of factors contributing to the development of osteoradionecrosis of the jaws. *J Prosthet Dent* 1988;**59**: 194–201.
40. Murray CG, Daly TE, Zimmerman SO. The relationship between dental disease and radiation necrosis of the mandible. *Oral Surg Oral Med Oral Pathol* 1980;**49**:99–104.
41. Bedwinek JM, Shukovsky LJ, Fletcher GH, Daley TE. Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinomas of the oral cavity and naso- and oropharynx. *Radiology* 1976;**119**:665–7.