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Management of Pathologic Fractures of the Mandible Secondary to Osteoradionecrosis

Raja Sawhney, MD[1], and Yadranko Ducic, MD, FRCS[2,3,4]

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Abstract

Objective. To review our experience with late Marx stage III osteoradionecrosis (ORN) of the mandible in patients who present with pathologic fracture.

Study Design. Case series with chart review.

Setting. Tertiary care center.

Subjects and Methods. Thirty-seven patients were identified from June 1998 to August 2010 who underwent treatment of Marx grade III osteoradionecrosis with pathologic fracture of the mandible. All patients underwent reconstruction with osteocutaneous free tissue transfer and when possible underwent hyperbaric oxygen therapy Marx protocol.

Results. The average time between completion of radiation therapy and presentation of ORN-induced pathologic fracture was 3.2 years. Sixteen patients developed ORN following tooth extraction. Sixteen patients had no previous documented ORN prior to presenting with pathologic fracture. Follow-up after surgery averaged 4.5 years with no recurrence of disease. The overall complication rate was 24% with no total flap loss. Of the patients, 95% returned to prefracture dietary intake. Twenty-six patients underwent a staged protocol, in which after resection and plate reconstruction, they underwent 20 hyperbaric oxygen (HBO) dives. They then underwent free tissue transfer followed by a further 10 HBO dives. There were no flaps lost or nonbony unions. Eleven patients did not receive HBO therapy as part of their surgical treatment plan. Again, there was no total flap loss, but 2 skin paddles were lost and 4 bony nonunions occurred.

Conclusions. Pathologic fracture in conjunction with ORN has a relatively high treatment complication rate. Free tissue transfer and HBO are the treatment of choice for this population.

Keywords

osteoradionecrosis, pathologic fracture, free tissue transfer, fibula free tissue transfer, hyperbaric oxygen therapy, HBO therapy, Marx protocol, mandible fracture, mandible reconstruction

Radiation therapy is a tremendous boon to the armamentarium of head and neck cancer treatment. Unfortunately, it has brought with it a number of sequelae, including osteoradionecrosis (ORN), which, when occurring in the mandible, is one of the most difficult complications to treat.[1] A number of theories have been proposed as to the pathogenesis of ORN. It was originally thought that a combination of radiation, trauma, and infection led to its development, but this belief has now been all but abandoned. In the early 1980s, Marx developed the most widely accepted theory of ORN pathogenesis.[2] He felt that ORN occurred when radiation-induced endoarteritis led to areas of poor vascularity and hypoxia, in turn causing chronic inflammation and eventually wound breakdown.[3] More recently, however, osteonecrosis in the setting of bisphosponates exposure introduces the idea of osteoclast dysfunction and poor bone regeneration in a hypoxic, hypovascular environment as the inciting event.[4,5]

Once the initial radiation insult occurs, ORN can present itself months to years later. It can be instigated by a number of causes, although dental disease and associated tooth extractions are the most often cited nidus.[2,6,7] There are a number of staging systems for the disease process, with Marx's system still the most widely used (**Figure 1**). This system is based on a linear treatment protocol with a patient progressing through each stage after failing more conservative therapy.[8] Stage III disease is based on ORN that is recalcitrant to both hyperbaric oxygen (HBO) therapy and local debridement. Included in this group are those patients who initially present with pathologic fracture or fistula.[8] Surgical resection with free flap

[1]Facial Plastics and Reconstructive Surgery, Otolaryngology/Head and Neck Surgery, University of Florida–Gainesville, Florida, USA
[2]University of Texas Southwestern Medical Center, Dallas, Texas, USA
[3]Baylor Neuroscience Skullbase Center, Dallas–Fort Worth, Texas, USA
[4]Otolaryngology-Facial Plastic Surgery Associates, Fort Worth, Texas, USA

Corresponding Author:
Yadranko Ducic, MD, FRCS, Otolaryngology-Facial Plastic Surgery Associates, 923 Pennsylvania Avenue Suite 100, Fort Worth, TX 76104, USA
Email: yducic@sbcglobal.net

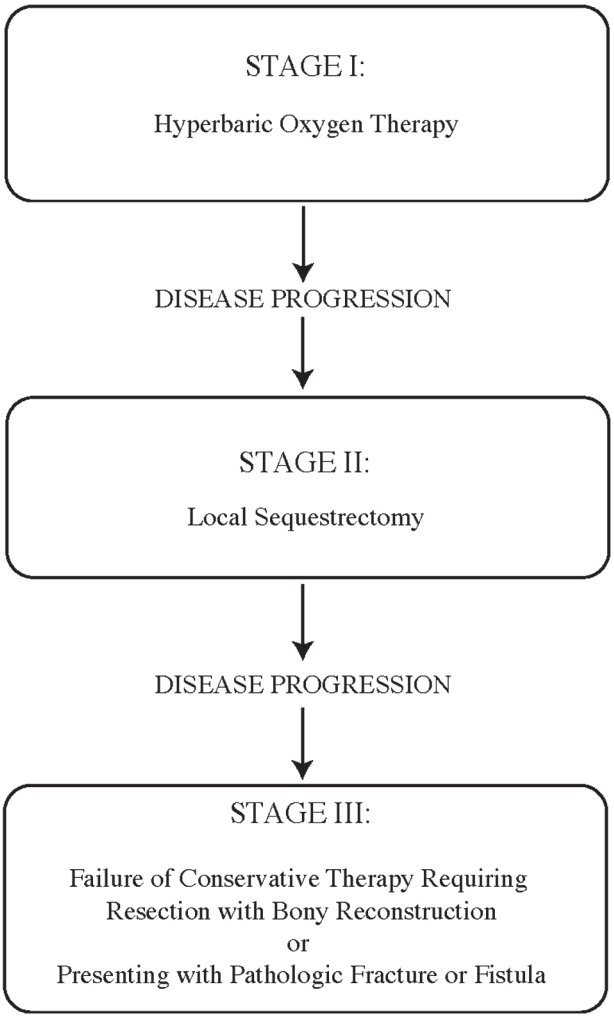

Figure 1. Marx staging for osteoradionecrosis.

reconstruction has become the mainstay of treatment for stage III disease.[9,10] While undoubtedly being a major leap forward, studies have shown a higher complication rate when using composite flaps in ORN versus their use in the treatment of other disease states.[2,5,11] Soft-tissue fibrosis as well as postradiation damage to vasculature within the radiation field are 2 reasons given for the increase in both flap complication and flap loss. The endovascular damage and progressive fibrosis worsen as the gap between the conclusion of radiation therapy and the nidus for the development of ORN widens. Atherosclerosis leads to the poor wound healing that initiates the onset of disease, making microvascular anastamosis more precarious when donor vessels are sewn to damaged recipient vessels.[9,12] Cannady et al[9] make specific reference to late stage III disease, with pathologic fracture of the mandible having higher complication rates when compared with early stage III disease.[12] According to these studies, pathologic fracture presents with advanced surrounding soft-tissue fibrosis that may be a primary cause for the increased complication rate.

This study was performed to examine the specific cohort of late stage III ORN patients who present with pathologic fracture. We also describe a varied treatment protocol that may decrease the rate of complications and flap loss in this unique patient population.

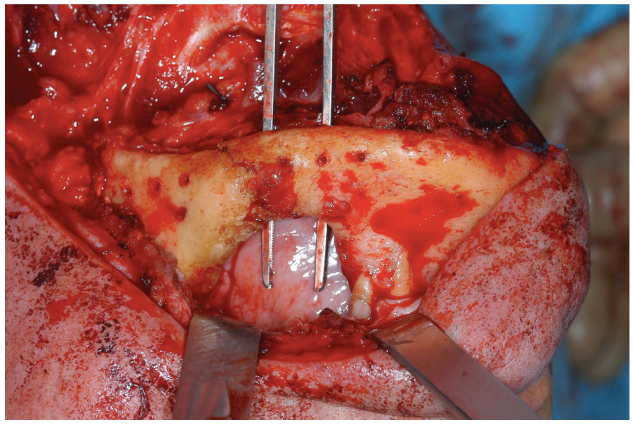

Figure 2. In vivo osteoradionecrosis with pathologic fracture.

Methods

Charts were reviewed for patients who underwent resection of Marx grade III ORN with pathologic fracture of the mandible (**Figure 2**). When possible, patients were subsequently given 20 HBO dives followed by free tissue reconstruction and then given another 10 HBO dives. A portion of the cohort received a different protocol, receiving no HBO therapy and undergoing either immediate or staged reconstruction. This deviation from the normal protocol was due to either insurance issues or patient wishes. All surgery was performed by the senior author (Y.D.) between June 1998 and August 2010 in a tertiary referral-based private practice. Institutional review board approval from John Peter Hospital was obtained. The free flap database, preoperative dental records, operative and surgical pathology reports, and follow-up visit notes were reviewed. Data gathered from chart review were composed of demographics, dental records, pathologic diagnosis, resection margins, use of reconstruction plate, exposure to radiation or chemotherapy, flap type, and any associated complications.

Results

Thirty-seven cases were identified as meeting criteria of having presented with late stage III ORN with pathologic fracture. There were 29 men and 8 women with an average age of 68.5 years. The presenting site of pathologic fracture was 28 (76%) at the angle of the mandible, 8 (22%) at the body, and 1 (3%) at the ascending ramus. Twenty-five patients (68%) originally had surgical resection of their primary tumor followed by postoperative external beam radiation therapy (EBRT), while 12 (32%) had primary radiation therapy with postoperative salvage. Patients received 60 to 95 gy of radiation with an average dose of 72 gy. The time lapse between EBRT and the development of pathologic fracture ranged from 13 months to 21 years, with an average of 3.2 years. Twenty-five (68%) patients were seen by an oral surgery clinician prior to being treated with EBRT, with 6 (16%)

undergoing complete dental extraction. Of the 37 patients in the cohort, 16 (43%) developed ORN after dental extraction, with 6 of these receiving HBO therapy both before and after tooth extraction. Sixteen patients (43%) had no known ORN detected prior to presenting with pathologic fracture. A further 4 patients were treated with only HBO therapy and antibiotics prior to fracture development. The final 17 patients progressed though each stage of the Marx system after previously undergoing local debridement performed mostly by an oral surgeon or dentist. The exact details of the type and number of procedures performed were not available to the authors.

All patients had reconstruction with locking reconstruction plates performed with an average of 4 bicortical screws placed on either side of the resection. Surgical reconstruction was performed transorally in 32 cases, while an open approach was required in 5 patients. The amount of diseased bone resected averaged 6.2 cm. A further 1 to 1.5 cm of healthy bleeding bone was also resected from the bony margin to decrease the likelihood of leaving behind microscopic disease. Those patients with significant soft-tissue deficits after resection had mucosal advancements to close the deficits after initial resection and had definitive reconstruction with a skin paddle during free tissue reconstruction. Most patients did not require tracheostomy as part of resection or reconstruction.

Twenty-six patients (70%) underwent our staged protocol, which consists of segmental mandibulectomy of visually diseased bone plus 1-cm margins on each edge. Next, reconstruction plate placement and primary soft-tissue reconstruction was performed with permanent pathologic section control of resection margin to confirm removal of diseased bone. Three patients, who had healthy bone edges on gross examination, had necrotic bone seen on pathologic examination. These patients were taken back to the OR for repeat bone resection and pathologic confirmation. Patients then received 20 HBO dives followed by free tissue reconstruction and, finally, a further 10 HBO treatments. The time between resection and composite reconstruction was on average 5 weeks, allowing adequate time for the initial HBO treatment. Those patients treated with HBO therapy prior to definitive surgical treatment did not receive a second course of therapy. Flap reconstruction consisted of 22 patients receiving fibula free flap reconstruction, 2 patients undergoing osteocutaneous radial forearm flaps, and 2 receiving scapula flaps. In this portion of the cohort, there was no flap loss or bony nonunions. Outside of the 3 patients with positive margins, who required re-resection, there were no complications associated with the patients undergoing 2 separate procedures.

All others in the cohort underwent different protocols either because of insurance issues or patient preference. Seven patients had no HBO therapy and immediate reconstruction of the defect after resection. Six fibula free flaps were performed with loss of a single soft-tissue paddle and 3 nonunions. Hardware was removed in 3 patients because of plate exposure. A single osteocutaneous radial forearm free flap was performed without complication. The final portion of the cohort received no HBO therapy but received a staged reconstruction. All patients in this group received fibula free flaps, with 3 of 4 having no complications. The fourth had loss of skin paddle as well as developed a nonunion. In the entire cohort, we had no postoperative pathologic fractures. All 4 cases of nonunion were diagnosed by clinical examination and computed tomography scan and were treated successfully with decortication and reconstruction using free iliac bone graft and bone morphogenic protein. There were no cases of ORN recurrence in the entire cohort. The overall complication rate was 24% with no total flap loss. Although all patients had their nutrition maintained via G-tube as part of the treatment process, all but 2 patients (95%) returned to prefracture dietary intake. Follow-up after surgery ranged from 10 months to 12 years, with an average of 4½ years.

Discussion

The sheer volume of recent articles dedicated to the treatment of ORN and, specifically, the use of composite free tissue transfer in its reconstruction gives some idea of the complexity of treating this disease entity and its associated complications. Disease prevention is still the goal for those at risk with proper dental hygiene before, during, and after radiation therapy as well as prophylactic extraction of diseased teeth prior to the initiation of radiation therapy.[2] Those patients who require extraction after 4 months of completing radiation therapy should undergo HBO therapy following the Marx protocol, which consists of 20 dives prior to extraction followed by another 10 after completion. Once onset of ORN occurs, treatment with conservative therapy including HBO therapy, sequestrectomy, free bone replacement, antibiotics, the use of anti-inflammatories, and possibly the use of antioxidants is paramount.[6,12-14] Unfortunately, ORN treated conservatively still has a disease progression rate higher than 70%.[4] Thus, these Marx early stage III patients are best treated with segmental mandibulectomy with free tissue transfer.[5,6,12] As stated previously, treatment of late-stage ORN, such as those with associated pathologic fracture, has a higher rate of complications and flap loss when compared with treatment of early stage III disease. Understanding the similarities and differences may give insight into this disease process and help improve outcomes for this select population.

A study by Epstein et al,[15] which examined 1000 patients exposed to radiation therapy for treatment of head and neck cancer, found 2.6% developed ORN and 0.6% developed ORN with associated pathologic fracture. In a study by Coletti and Ord[16] focusing on pathologic fractures from all etiology, ORN was the underlying etiology in 21 of 44 patients (49%). A second study by Gerhards et al[17] also focused on various causes of pathologic fractures and found 30% (9 of 30) of their cohort had fractures due to ORN. These studies, beyond showing the surprisingly high incidence of ORN-associated pathologic fractures, also show that treatment requires the most complicated repair and results in a high number of postoperative complications, especially when treated with less aggressive therapy.

When comparing our patient population to that reported in the review article by Jacobson et al,[2] which looked at the full spectrum of patients presenting with ORN, a number of risk

factors are consistent for all ORN patients regardless of the presence of pathologic fracture. These include advanced initial tumor stage, exposure to a radiation dose greater than 60 gy, concomitant use of chemoradiation, and dental extraction as an initiating event. Most cases of ORN, to some degree regardless of stage, develop from tumor primary sites of the base of tongue and oropharynx. These sites exist in close proximity to the mandible, leading to greater radiation exposure to susceptible bone. A number of studies have suggested that the posterior portion of the mandibular body is the most common area affected by ORN because of its compact makeup and poor vascularity when compared with the anterior mandible.[1,2,18] While the fractures occurred in the posterior mandible, 75% of our cohort presented with pathologic fractures at the angle of the mandible. This is not surprising given the high number of mandibular fractures, including those of pathologic and traumatic origin occurring at the mandibular angle.[16] Unfortunately, fractures located in this area are also associated with the highest rates of complications.[19] Finally, a significant portion of pathologic fractures present without previous signs or symptoms of ORN, which is in stark contrast to its classic presentation of necrotic bone exposed through the mucosa.[2,14,20] In our study, 43% had no prior indication of ORN until the fracture occurred. This distinction is important in that it may actually delay diagnosis and treatment of patients with ORN fracture. These patients may also receive less than definitive therapy, having the fracture reduced and fixated without treatment of the surrounding pathologic bone.[16]

A number of authors have shown that flap failure is higher in ORN reconstruction versus other disease processes.[5,12,21,22] Disease progression, hardware exposure and extrusion, local wound defects, and pathologic fracture have all been described as complications in free flap treatment for ORN.[5,21] Some suggest this increased morbidity is due to radiation exposure, although this is far from a clear etiology. While Pohlenz et al[23] showed increased complication rates when flaps are placed into a radiated surgical bed, Suh et al[24] found no such relationship after examining 400 microvascular cases. Given the elevated complication rate of ORN treated with free tissue flaps, which ranges between 20% and 60% with markedly higher partial and total flap loss, versus the complication rate of free flaps for all types of head and neck pathology, which is usually reported as less than 3%, ORN would seem to be its own unique variable when it comes to free flap complications.

One of the most common problems is ORN recurrence at what was intraoperatively considered a healthy bone margin. Suh et al[5] found that 25% of their patients had persistent or recurrent ORN after microvascular reconstruction, while Alam et al[18] found a 9% recurrence rate. Surgical margins are normally determined by resecting pathologic-appearing bone until vascularized bone that bleeds readily is obtained. A number of authors lament the nonscientific nature of this approach. While not specifically stated in articles, most surgeons concerned about leaving behind microscopic disease resect a portion of grossly appearing healthy bone. In our patients, typically an additional 1 to 1.5 cm of healthy appearing bone is resected. While for the vast majority of patients this approach is sufficient, a minority were found to have microscopic disease on pathologic examination of healthy margins. This led to staging our ORN reconstructions, with those with positive margins undergoing repeat resection until clear margins are obtained. With this process, we have found our disease recurrence to have significantly dropped.

Table 1. Complications of Fibula Free Tissue Reconstruction

	Staged Protocol with HBO Therapy	Alternative Protocol
Patients reconstructed with fibula	22	10
Complications		
Positive margins requiring re-resection	3	0
Nonunion	0	4
Loss of skin paddle	0	2
Plate exposure	0	3

Staged reconstruction also allowed us to implement Marx's HBO protocol for our patients. After resection of all diseased bone, the patient undergoes 20 HBO dives. Free tissue reconstruction is performed, followed by a further 10 HBO dives. It is our opinion that implementing the Marx protocol along with pathologic examination of surgical margins has minimized the rate of ORN recurrence as well as nonunion in our patient cohort. Although a very small sample size, the large number of nonunions and other complications within our cohort of patients who did not undergo HBO therapy does suggest this possibility (**Table 1**). The patients following a more traditional protocol that bypassed HBO therapy had similar complication rates when compared with other authors' findings. While a number of articles have recently questioned the benefit of HBO therapy in ORN cases, especially when it comes to stage III disease, there is a portion of these patients who benefit from it.[2] Those patients with the highest risk of complications, such as those with pathologic fracture, seem to fall into that category. It may be that the HBO keeps the bone that is at high risk of developing ORN from progressing to fulminant disease.

The addition of HBO therapy and staged reconstruction is obviously not without its drawbacks. The additional expenses of HBO therapy along with the added time and expense for multiple operating room procedures are not negligible. This is especially notable when compared with single-stage surgery without adjuvant HBO treatment, which has become the protocol of choice for cost-effective stage III ORN surgery.[4] From a patient standpoint, our opinion is that it is better to have 2 shorter procedures than 1 long one. A number of these patients are older, many with cardiac concerns and poor overall nutrition. Transoral resection with plate reconstruction takes only about 1½ hours. The inpatient stay, after resection, is only a few days. The staged protocol allows the patient time to recover, improve overall nutrition, and start HBO therapy, all while waiting for pathologic clearance.

From a financial standpoint, what becomes the great equalizer between the 2 protocols is the additional cost of treating

complications related to late-stage ORN. While not specifically examined in this article, one can imagine the additional expense incurred with this population and its known high complication rate. We are of the opinion that the 3 patients in this study who had grossly negative margins but persistent disease on pathologic examination would have gone on to have recurrent disease if not identified. Between pathologically clearance and HBO therapy, those with subclinical disease are treated prior to re-recurrence. The added expenditures of our protocol incurred in treating these complicated patients on the front end versus the financial cost, as well as the patient's and surgeon's time and frustration in dealing with recurrent disease, is well worth it.

Conclusion

Pathologic fracture in conjunction with ORN has a relatively high incidence and treatment complication rate. These patients have similar risk factors for disease development as all ORN patients do, although they tend to vary in presentation and location of disease. Most reconstructions are performed using fibula free flap and large reconstruction plate. It is our feeling that a staged treatment that uses Marx's HBO protocol improves outcomes for this difficult-to-treat cohort. Most of our complications were seen in those who did not undergo our typical protocol. Our overall complication rate of 24% is also markedly lower when compared with studies that include a high number of pathologic fractures. The significant decrease in severe complications such as total flap loss and ORN recurrence makes this approach tremendously beneficial.

Author Contributions

Raja Sawhney, article concept and design, analysis of data, drafting and revising article, final approval; **Yadranko Ducic**, article concept and design, acquisition of data, analysis of data, revising article, final approval.

Disclosures

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