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Surgical resection and vascularized bone reconstruction in advanced stage medication-related osteonecrosis of the jaw

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Abstract. A retrospective review of all patients with stage 3 medication-related osteonecrosis of the jaw (MRONJ), treated by surgical resection and immediate vascularized bone reconstruction at a tertiary care medical center, was performed. Eleven patients were included, seven female and four male; their mean age was 65.8 years (range 56–73 years). Mean follow-up was 25 months. Ten patients had received intravenous bisphosphonates. The most common pathology was breast cancer (4/11). Pain ($n = 8$) and pathological fracture ($n = 7$) were the most common presenting symptoms. Microvascular free flaps consisted of seven fibula osteocutaneous flaps and four scapula osteocutaneous free flaps. All patients reported resolution of symptoms, with complete bone union identified radiographically (100%). Complications occurred in three patients (27%). One patient required removal of hardware at 8 months postoperative. Dental implant rehabilitation was completed in two patients. Ten patients are tolerating an oral diet. Ten patients are alive without evidence of MRONJ at any of the surgical sites. One patient died 28 months after surgery from progression of metastatic disease. Advanced MRONJ can be successfully treated in patients using vascularized tissue transfer, including those patients with significant peripheral vascular disease. Dental rehabilitation is a viable option for advanced MRONJ patients treated by vascularized flap reconstruction.

Key words: MRONJ; osteonecrosis; vascularized tissue transfer; mandible.

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Medication-related osteonecrosis of the jaw (MRONJ), previously known as bisphosphonate-related osteonecrosis of the jaw (BRONJ), is a recognized complication of anti-resorptive and anti-angiogenic bone-related therapies. The name change is justified to accommodate the growing number of osteonecrosis cases associated with other anti-resorptive (denosumab) and anti-angiogenic medications.[1] The first reports of MRONJ were published more than a decade ago; however the pathophysiology has not yet been fully elucidated.[2,3].

MRONJ is especially associated with oncology-dose parenteral anti-resorptive therapy with bisphosphonates and the receptor activator of nuclear kappa B ligand (RANKL) inhibitor medication denosumab.[4] Denosumab is an anti-resorptive agent that exists as a fully humanized antibody against RANKL and inhibits osteoclast function and associated bone resorption.[5,6] It is also effective in decreasing systemic events related to metastatic bone disease from solid tumors.[7,8] Bisphosphonates, especially the nitrogen-containing subset such as zoledronate and pamidronate, similarly decrease bone resorption. This leads to osteoclast cytoskeleton disruption, intracellular vesicular trafficking impairment, increased osteoclast apoptosis, and decreased osteoclast function.[9] Bisphosphonates physiochemically bind to exposed hydroxyapatite and incorporate into the bone matrix with a half-life of many years. However unlike bisphosphonate medications, the incorporation and long-term effects of denosumab on bone remodeling and its half-life in the bone matrix are not well defined.[9]

The incidence of MRONJ is greatest in the oncology patient population (1% to 15%), where high doses are used at frequent intervals.[4] The incidence of MRONJ in the osteoporosis patient population is significantly lower (0.001% to 0.01%) and is only marginally higher than the incidence in the general population.[4] A prospective study, published in 2015, found that 22 of 80 patients (28%) receiving intravenous (IV) bisphosphonates for malignant neoplasms developed BRONJ.[10]

MRONJ is defined clinically in patients on current or previous treatment with anti-resorptive or anti-angiogenic medication, where the presence of exposed necrotic bone is evident through a fistula persisting over 8 weeks within the maxillofacial region that has not been irradiated previously.[1] Established MRONJ can manifest within a wide spectrum of clinical presentations in the affected jaw (Table 1).

Table 1. Medication-related osteonecrosis of the jaw—staging system.[a]

MRONJ staging	Definition
Stage 0	No clinical evidence of necrotic bone, radiographic changes only, non-specific symptoms
Stage 1	Exposed[b] and necrotic bone, fistulae that probe into bone, no evidence of infection
Stage 2	Exposed[b] and necrotic bone, fistulae that probe into bone, infection, pain, erythema ± purulent drainage
Stage 3	Exposed[b] and necrotic bone with associated infection, pain including one or more of the following: bone necrosis/exposure beyond the alveolar bone, pathological jaw fracture, extraoral fistula, oro-antral/nasal communication, osteolysis extending to the inferior border of the mandible or sinus floor

MRONJ, medication-related osteonecrosis of the jaw.

[a] Adapted from the Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg 2014: 72: 1938–1956.

Within the MRONJ continuum, stage 3 is the most advanced, where the exposed, necrotic bone and fistula occurs with evidence of infection, and with at least one of the following criteria: (1) exposed necrotic bone extending beyond the alveolar bone; (2) pathological fracture; (3) extraoral fistula; (4) oro-antral or oronasal communication; and (5) osteolysis extending to the inferior border of the mandible or sinus floor.[1] Stage 3 MRONJ is debilitating and significant morbidity is experienced, particularly with repeated bouts of infection and when pathological fracture is present. The problems experienced include chronic unpleasant symptoms (e.g., pain, swelling, halitosis, purulent discharge, sinonasal symptoms), neurosensory deficit, loosening of teeth, masticatory dysfunction, and overall decreased quality of life.

Despite a lack of high-quality evidence in regard to treatment, there is a general perception favoring conservative treatment over surgical therapy.[11] Limited surgery in the form of localized debridement or sequestrectomy is advocated with the aim of simply softening sharp bony edges to promote soft tissue healing over the exposed bone rather than eliminating the entire area of necrotic bone.[11,12] Aggressive radical surgery is offered only to symptomatic patients with extensive osteonecrosis, including those who have failed conservative treatment, with the aim of long-term palliation of infection and pain.[1,13–15] Some authors have reported that surgical approaches result in superior treatment outcomes than conservative therapy regimens, with success rates of 80–90% and 10–62%, respectively.[16] Nevertheless, an aggressive surgical treatment approach with wide bone resection and immediate reconstruction with microvascular free tissue transfer is considered controversial.

The aim of this study was to evaluate the outcomes of surgical resection and vascularized reconstruction in a cohort of advanced MRONJ patients at a single institution. The primary outcome measures included the presence of primary bone union and the recurrence of MRONJ. The secondary outcome measure was pain control and functional outcomes as they related to patient quality of life.

Materials and methods

Institutional review board approval was obtained for the study. A retrospective review of the departmental reconstruction database was undertaken. All patients with stage 3 MRONJ treated by surgical resection and vascularized bone reconstruction, performed in the Department of Oral and Maxillofacial Surgery, University of Maryland from September 2010 to December 2015, were identified.

A chart review of the subjects selected was completed to obtain demographic data, presenting clinical features, anti-resorptive medication history, risk habits, predisposing factors, site of MRONJ, surgical details including the type of resection and flap selection, perioperative complications, length of hospital stay, follow-up details including the length of follow-up, speech/swallowing outcomes, and recurrence of MRONJ. Functional status was determined using the Eastern Cooperative Oncology Group performance status (ECOG-PS) functional scale, which was noted preoperatively and at the 6-week follow-up. All patients received a computed tomography (CT) scan at least 8 weeks postoperatively to evaluate the outcomes of reconstruction. The three-dimensional (3D) digital images were retrieved from the hospital records using the eUnity diagnostic imaging system (Client Outlook Inc., Waterloo, ON, Canada) and