Bone Margin Analysis for Osteonecrosis and Osteomyelitis of the Jaws

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**KEYWORDS**
- Osteonecrosis
- MRONJ
- Osteomyelitis
- ORN
- Bone margins
- Bisphosphonates
- RANKL
- HBO

**KEY POINTS**
- In advanced osteomyelitis medical and surgical interventions become necessary. Imaging is helpful in preoperative planning.
- In MRONJ, negative margins correlate well with resolution of symptoms. Intraoperative adjuncts, such as fluorescence-guided resection, may become helpful in the future.
- In ORN patients may have persistent disease despite radical resection.
- Margin status on histopathology may not correlate with the clinical outcome.
- High-level evidence data regarding bone margin analysis in osteomyelitis and osteonecrosis of the jaw are lacking. Further studies are needed in this area to help guide treatment and create consensus.

**INTRODUCTION**

Osteoradionecrosis (ORN), osteomyelitis (OM), and medication-related osteonecrosis of the jaw (MRONJ) are three entities that have a similar appearance clinically, yet are different in their pathophysiology. All three conditions may present with exposed bone within the oral cavity that fails to heal within an 8-week period. The bone can progress to an advanced stage, presenting with suppuration, gross mandibular necrosis, and/or pathologic fractures. Because of their differing pathophysiology, their treatments are also different. The surgical approach to determining margins and subsequent approach to pathologic bone margin analysis are controversial topics, because of the lack of high-level evidence. This article reviews the available evidence regarding bone margin management and interpretation for each of these entities.

**OSTEOMYELITIS**

OM is defined as inflammation of the bone and bone marrow caused by an infectious process.\textsuperscript{1,2} Some of the etiologies that may result in OM include odontogenic infection, periodontal disease, trauma, inadequate treatment of mandibular fractures, failed mandibular implants or hardware, and hematogenous seeding from bacteremia.\textsuperscript{1,3}
Patients who have received radiation therapy or medications affecting bone metabolism (discussed later) may have an increased risk for OM.\(^4\) There is a higher predilection for involvement of the mandible likely caused by decreased vascularity when compared with the maxilla. With prevalent use of antibiotics, the incidence of OM has significantly decreased.\(^1,4\) The incidence in the jaws is reported to be around 3 to 4 cases per 100,000 annually.\(^3,8\)

Clinical signs and symptoms associated with OM may include deep boring pain, intraoral or extraoral purulent drainage, introral and cutaneous fistula, pathologic fracture, trismus, and neurosensory disturbance.\(^7\)

There is a lack of consensus on a classification system for OM, which may in part be caused by variability in presentation of OM.\(^8\) Several classification systems exist but generally OM is classified as acute or chronic depending on whether the symptoms last over a 1-month period of time.\(^1\) Chronic OM is usually divided into supplicative and nonsuppurative OM.\(^1,9\)

Imaging may be helpful in establishing a diagnosis of OM, determining the extent of disease and subsequent surgical planning.\(^10\) Computed tomography (CT) scan may show a moth-eaten appearance, bony erosion, sequestration, gross bony destruction, or any combination of these features. MRI may detect earlier stages of OM showing hypointensity of the marrow on T1-weighted images, and hyperintensity on T2 postcontrast images, signifying medullary inflammation. These changes appear on MRI before the occurrence of cortical osseous changes, making the MRI more sensitive and specific in the acute phase.\(^11-13\) The most common nuclear medicine imaging techniques involves bone scintigraphy using a radiopharmaceutical tracer diphosphonates coupled to the radionuclide technetium-99m (\(^{99m}\)Tc). The tracer selectively accumulates on bone mineral matrix in areas of high metabolic/osteoblastic activity. This test is sensitive but not specific and can be positive in cases of trauma, tumors, and aseptic conditions. Autologous tagged white blood cell (leukocytes) scintigraphy can help to localize the source as leukocytes accumulate by migration toward the bone infection. Another drawback to nuclear testing includes the time required (hours) and the poor image quality because of the spatial resolution of the gamma camera with the inability to detect bone sequestra less than 8 mm. Combined with other imaging modalities, such as single-photon emission CT or PET-CT, imaging can further improve the diagnostic yield and localize the infection.\(^14,15\)

There is currently no consistent protocol or accepted guideline in the literature for the treatment of OM.\(^8\) Most therapeutic recommendations are based of the findings of single reports or textbooks. Cases limited in extent, and/or cases of acute OM, may be managed with antibiotics with or without surgery. In chronic OM, surgical intervention is required in combination with antibiotics. The extent and type of surgical treatment depends on presentation and may include conservative debridement and/or sequestrectomy. Decortication and saucerization of the involved area of the mandible has also been reported to be successful in certain cases of OM.\(^16\) Segmental resection is reserved for advanced cases of OM that fail medical therapy and demonstrate gross necrosis of the mandible, suppuration, draining cutaneous fistula, intractable pain, and/or pathologic fracture (Fig. 1).\(^1,4\)

When segmental resection is deemed necessary for treatment, general consensus recommendation suggests a 1-cm bone margin beyond the identifiable boundary of the radiographic process when feasible. Additional bone should be resected if bleeding bone (a clinical surrogate for viability) is not observed.\(^4,17\) Although evidence-based research regarding the placement of the most appropriate margin for resection of mandibular OM is lacking, there seems to be good correlation between cross-sectional radiographic studies and pathologic bony margins.\(^10\) This correlation between preoperative imaging and accurate final pathologic bone margin status allows for ease in preoperative ablative and reconstructive planning. Microvascular free flap reconstruction is also helpful because it allows the surgeon the ability to attain generous resection margins with healthy viable bone (see Fig. 1).

Antibiotics are required in addition to surgery in the management of OM.\(^1\) Kim and Jang\(^15\) showed 95% control rates for OM when using surgery and 8 weeks of antibiotic therapy, compared with control rates of 60% in the surgery alone arm. Again, there is a lack of consensus with regards to the type and route of antibiotics to be used and the length of therapy.\(^8\) These cases are best treated in a multidisciplinary fashion with infectious disease specialists, with individualized treatment being based on tissue cultures and clinical response.\(^2,4\) The most commonly cultured microbes include normal oral flora, staphylococcus, and bacteroides.\(^16,18\) Because it is important to select an appropriate antibiotic, one must remember that deep tissue cultures or marrow cultures from the specimen should be attained before the main specimen being immersed in formalin and sent to pathology.
Microscopically, biopsy and resection specimens of OM are composed of necrotic bone with empty osteocyte lacunae, peripheral resorption, and acute or chronic inflammatory infiltrates (Fig. 2A). The bone sequestrum may demonstrate microorganisms on the surface (Fig. 2B) or within the marrow spaces, often morphologically suggestive of an Actinomyces species. As the infection progresses into the chronic stages, reactive viable bone formation with irregular basophilic reversal lines (Fig. 3) may be observed. The resection margins may exhibit normal or sclerotic viable bone, nonviable bone, or a mixture of new and necrotic bone.

The ability to accurately report the margin status in gnathic OM depends on the treatment and the resultant surgical pathology specimen, and good communication between the surgeon and the pathologist. For cases treated with debridement or curettage, the specimen is received by the laboratory as multiple fragments of unoriented bone, precluding accurate margin evaluation. In cases treated with marginal or segmental resection, intact specimens or those with separately submitted margins (eg, anterior, posterior) allow for histopathologic margin evaluation. When examining the bone margins, it may be helpful to subsequent

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**Fig. 1.** Mandibular osteomyelitis. (A) Long-standing osteomyelitis of the anterior mandible including the planned osteotomies. (B) Planned reconstruction with fibula free flap. (C) Submental chronic draining fistula and planned fistulectomy. (D) After mandibular resection and placement of reconstruction bar. (E) Fibula free flap before inset and anastomosis. (F) Three months postoperative. Intraoral view showing mucosalization of skin paddle.
treating physicians for the pathologist to report evidence of overtly necrotic bone and/or acute inflammation or abscess at the bone margin, versus finding scant chronic inflammation and/or viable bone devoid of inflammation.

In many institutions, categoric classification of bone margin status (positive or negative) or even descriptive findings (previous paragraph) are not routinely reported by pathologists in cases of resected gnathic OM, which limits the study of this disease, and correlation of pathologic and surgical variables contributing to recurrence. This may be caused by a multitude of reasons including specimen fragmentation, an institutional or pathologist bias where margin interpretation is not viewed as necessary in a benign and/or infectious process, lack of communication between surgeon and pathologist, or the submission of unoriented specimens may signal that margin analysis is not required. Therefore it is imperative for surgeons to indicate that bony margin analysis is required and to orient specimens even if orientation of the specimen seems obvious to the surgeon.

Although persistence of disease may be related to residual necrotic bone, there are no specific articles in the literature regarding the importance of microscopically viable bone margins in OM of the mandible and maxilla. In the diabetic foot, studies have shown that patients with positive resection margins via histopathology or bone culture had poor outcomes, often requiring further surgery.21–23 The applicability of these findings to cases of jaw OM may be limited because of differences in anatomy, vascularity, type of bacteria (when present), patient comorbidities, or other factors unique to the maxilla and mandible. Further studies are needed to determine the clinical significance of microscopically negative bone margin status in gnathic OM.

**MEDICATION-RELATED OSTEONECROSIS**

Antiresorptive medications including bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors have been used in the treatment of distant bony metastasis, as in the cases of breast and prostate cancer,
and in the prevention of osteoporosis.24,25 Both drug classes are available in oral and parenteral formulations depending on the indication. Bisphosphonates have been used for more than 40 years, whereas RANKL inhibitors have only been approved by the Food and Drug Administration since 2010.25,26 Although these drugs fulfill their intended purpose of effectively reducing skeletal-related events in these patients, an important side effect in the maxillofacial region is development of MRONJ. MRONJ is defined as exposure of bone for a period greater than 8 weeks in a patient on or with a history of antiresorptive medication use, and no prior history of radiation therapy.27 An overview of all the antiresorptive and antiangiogenic agents that result in MRONJ is beyond the scope of this text and the reader is encouraged to refer to the position paper provided by the American Association of Oral and Maxillofacial Surgery.24

Although the mechanism of action of these medications has not been fully elucidated, the negative impact on osteoclast function and thus bone turnover is widely accepted.28–30 Bisphosphonates covalently bind to bone accounting for its very slow elimination from the body, often persisting in bone for several years after the cessation of the drug. Conversely, RANKL inhibitors have a very slow elimination from the body, often persisting in bone for several years after the cessation of the drug. Because tetracycline is absorbed only by viable bone, bone removal is carried out until all the dark necrotic bone is removed, leaving behind a homogenous green fluorescent viable bone. This showed 85% success rate in a prospective descriptive pilot study. Autofluorescence, using the lamp without the preoperative tetracycline, has also been reported to be helpful in guiding surgical decision making.42

Another factor that should be taken into consideration is the quality of the overlying gingival tissue and the negative effect bisphosphonates have on oral mucosal healing.24 For that reason it may be strategic to place osteotomies in areas with robust vascularized soft tissue covering, such as the pterygomasseteric sling, and to avoid osteotomies within 1 cm of a tooth.39 If a fibula free flap is used to reconstruct a continuity defect, either a skin paddle or an adequate length of muscle should also be harvested to reline the oral cavity with adequate soft tissue coverage in a tension-free fashion to minimize bone exposure postreconstruction. Despite the diffuse uptake of antiresorptive medications in the body, resection and fibula free flap reconstruction seems successful in eradicating MRONJ in more than 90% of cases, provided negative margins are obtained.43 The fibula is rarely the site of metastatic bone disease or multiple myeloma, when compared with the ileum or scapula, and therefore could be considered a first-line flap for reconstruction in MRONJ cases.43 PET imaging or bone scan should be obtained to assess donor site viability and rule out the transfer of a metastatic deposit to the newly reconstructed jaws. Furthermore, because of the diffuse uptake antiresorptive medications, subtotal mandibulectomy is sometimes needed to clear the involved bone as demonstrated in a series of seven patients by Nocini and colleagues38,43 One must carefully examine the mandible clinically and radiographically, to ensure that the disease is localized before embarking on a unilateral resection, because the possibility of multifocal disease secondary to the systemic effect of the drug may explain why subtotal mandibulectomy is prevalent in some series (Figs. 4 and 5).43

Although there is no evidence to recommend a temporary cessation of bisphosphonate medication (drug holiday) before undergoing surgical
resection of MRONJ-related diseased tissue, many prescribing physicians endorse this for their patients.36,39,43 Bisphosphonates are incorporated into the matrix of the skeleton for years, but on balance, RANKL inhibitors are almost completely eliminated from the body after a period of 6 months. Based on the latter, one may hypothesize that a drug holiday maybe helpful in these situations.31 Further studies need to validate this hypothesis.

The histopathology of MRONJ shows overlap with OM and ORN. Similar to OM and ORN, portions of the affected bone in MRONJ are devoid of osteocytes and osteoblasts and lack normal bone marrow cells.18,44 MRONJ specimens tend to lack the inflammatory infiltrates seen in OM or the marrow fibrosis seen in ORN (Fig. 6A), unless superinfected or pathologic fracture has occurred.20 The periphery of the bone in areas of active MRONJ is often irregular with evidence of resorption and detached or absent osteoclasts.27,43,45 Exposed bone and sequestrum exhibit bacterial colonization of the surface, most often morphologically consistent with an Actinomyces species, whereas the overlying mucosa may demonstrate pseudoepitheliomatous hyperplasia and inflammation (Fig. 6B).46 In regions of viable bone, hyperemia and inflammatory infiltrates may be noted in the marrow spaces (Fig. 7A) and new bone formation or periosteal reaction may be observed.35 The bone may also exhibit a pagetoid pattern with prominent basophilic reversal lines and enlarged or irregular osteoclasts in viable areas (Fig. 7B).19 Overall, MRONJ specimens tend to exhibit a mixed pattern of necrosis with areas of lamellar bone containing viable osteocytes adjacent to areas with empty lacunae.44

In a multicenter retrospective review, Carlson and colleagues47 identified microscopic evidence of malignancy in 5.3% of biopsies and resection specimens of patients clinically diagnosed with MRONJ. Therefore, bony specimens require thorough sampling to exclude deposits of malignancy contributing to the underlying bone destruction, which may be radiographically undetectable in the background of osteonecrosis.38–40 Where surgical margin status can be determined, the pathologist could consider reporting several data points when observed at the bony surgical margins including the presence or absence of organisms, nature of the inflammatory response (acute or chronic), and if malignancy is detected within the specimen, then an assessment of adequacy in

**Fig. 4.** MRONJ with multifocal exposure. (A) Patient with history of denosumab (Prolia) use for osteoporosis. Notice multifocal nature of disease with left posterior mandible exposure and small exposure in the anterior mandible. (B) There is small exposure and minimal suppuration in the right posterior mandible.

**Fig. 5.** MRONJ with multifocal bone exposure. (A) Patient with previous history of bisphosphonate use for breast cancer. Notice multifocality of involvement with exposed bone in the anterior mandible and pinpoint exposure along the right myelohyoid ridge. (B) Showing exposure along left myelohyoid ridge.
relation to the specimen margin. The histopathologic findings in resection specimens seem to correlate well with CT and MRI findings, allowing for removal of affected bone with uninvolved margins, despite the diffuse nature of the disease, in most cases.44 Specimens obtained by some forms of surgical intervention for MRONJ, such as debridement and sequestrectomy, are not amenable to accurate margin reporting because these specimens are received fragmented, unoriented, and portions of the specimen may be diverted for culture and/or other testing. In cases where a surgical resection has been performed with the expectation that a pathologic evaluation of margin status will be provided, there is no consensus on which parameters are prognostically relevant for reporting. In comparison with OM and ORN, which may develop in bones other than the jaws, MRONJ tends to favor the gnathic bones, which limits extrapolation of research data from other anatomic sites. This lack of data, and possible multifocality of disease, makes it even more challenging to correlate margin status and clinical course. Studies specifically examining the relationship of margins and clinical outcome have found that patients with “normal bone” present at the resection margins demonstrated good long-term disease control and those with margins exhibiting “osteomyelitis” developed recurrent MRONJ within 3 to 6 months of follow-up.38,43

**OSTEORADIONECROSIS**

ORN is clinically defined by exposed bone for more than 2 months in a previously radiated area without prior history of antiresorptive medication use.48–51 ORN is a side effect of radiation therapy and is more likely to occur when the dose of radiation to the mandible exceeds 60 Gy.52 The

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**Fig. 6.** Medication-related osteonecrosis. (A) Necrotic bone with empty lacunae (arrowheads), peripheral resorption, and marrow spaces containing bacterial colonies (arrows), but lacking inflammation or fibrosis (H&E, original magnification ×100). (B) Area of bone exposed to oral cavity showing epithelial hyperplasia (arrows) adjacent to necrotic bone with *Actinomyces* bacterial colonization (arrowheads) (H&E, original magnification ×100).

**Fig. 7.** Medication-related osteonecrosis. (A) Margin of resection specimen showing areas of viable bone with inflamed, vascular marrow spaces and numerous osteoclasts (arrowheads) (H&E, original magnification ×100). (B) Higher magnification of A showing enlarged osteoclasts and osteocytes within lacunae (H&E, original magnification ×400).
Incidence of ORN has decreased over the years from an estimated 15% in the 1970s to 0% to 5% in the 2000s. Some of this might be attributed to advances in radiation therapy and the improved dose distribution of intensity-modulated radiation therapy.53–56

Clinical presentation may vary based on stage, ranging from an asymptomatic area of exposed bone increasing in severity to include gross bone necrosis involving the full thickness and height of the mandible with pathologic fracture (Fig. 8). Other associated clinical signs and symptoms may include dysesthesia, pain, malodor, swelling, ulcerations, suppurative, and trismus.48,57 Radiographically ORN can show findings that are indistinguishable from the two entities described previously. These include areas of osteolysis and resorption extending to the inferior mandibular border, bone sequestration, increased bone opacification, and mottling.1

ORN is classified as stage 1 through 3 based on severity and extent of involvement. The two most commonly used staging systems are the ones described by Marx51 and Notani and colleagues58 (Table 1). The exact pathophysiology of ORN remains controversial.48 Marx’s 3-H theory proposes direct damage by ionizing radiation leading to hypoxia, hypocellularity, and hypovascularity.51 This theory led to the adoption of hyperbaric oxygen (HBO) in the treatment algorithm of ORN. The protocol usually involves 20 to 30 dives at 2.4 atmospheric pressure before a surgical intervention or dental extraction and an additional 10 dives afterward.59,60 Although a few early studies examining the role of HBO in the treatment of ORN showed promise, more recent data have been less supportive, and there remains a paucity of evidence in support of HBO in the treatment of ORN.61,62 A recent multicenter randomized double-blinded clinical trial examining the use of HBO in the treatment of ORN was discontinued before the conclusion of the study because of worse outcomes in the HBO group compared with the placebo group.60 Although criticized for design flaws, this study has led to the questioning of the 3-H theory and the role HBO therapy in ORN.48,57,63 Others authors reported higher perioperative complications when performing segmental resection with microvascular reconstruction in patients previously treated with HBO when compared with HBO-naive patients.64

A competing theory for the pathogenesis of ORN by Delanian and colleagues65 suggests radiation-induced fibrosis as the mechanism of injury. Cells in the bone are damaged as a result of acute inflammation, free radicals, and the chronic activation and dysregulation of fibroblasts leading to matrix densification and tissue necrosis.64 Based on this, pentoxifylline and tocopherol in synergy have been shown to be effective in the treatment of ORN through their antioxidant and antifibrotic effects.65 A second phase II trial confirmed these results showing the combination of pentoxifylline, tocopherol, and clodronate to be effective in the treatment of refractory ORN, inducing mucosal and bone healing with significant symptom improvement.66 A histopathologic study by Marx and Tursun20 in 2012 showed marrow fibrosis in ORN specimens, which could be interpreted to be in line with this theory.

Early stage disease and asymptomatic patients can be managed conservatively with oral care, antibiotics if necessary, and the use of pentoxifylline and tocopherol.65 Some advocate for the use of these medications prophylactically before and after dental extractions, in a fashion similar to the way HBO was traditionally used.57 Debridement, curettage, and sequestrectomy may be used...
when there is clinical evidence of a sequestrum, or if the patient is symptomatic. These specimens are submitted to pathology for microscopic evaluation, although portions may be considered for culture in the correct clinical context. There is no expectation of a formal pathologic margin status evaluation.

Advanced ORN as identified by marked necrosis, pathologic fracture, or orocutaneous fistulas is best treated with segmental resection and microvascular reconstruction. Microvascular free tissue transfer not only allows for reconstruction of the bony defect, but also provides for healthy soft tissue to help with tension-free closure of heavily irradiated, fibrotic inelastic skin that would be otherwise difficult to close primarily. Resection is usually planned with a 1-cm margin beyond the radiographic changes or until bleeding and healthy-appearing bone is reached.

As with the case of MRONJ and OM, there is minimal evidence to guide the surgical placement of bone margins. One recent report found that approximately 25% of patients with mandibular ORN developed recurrent disease despite extensive mandibular resection. A subsequent follow-up study by the same authors attempted to correlate histologic findings of surgical bone margins with progression of ORN. In this study, Zaghi and colleagues evaluated 34 patients treated with radical resection of the mandible and found no correlation between residual necrotic bone margins and persistent disease. Of the 26 cases with histologically negative margins for necrosis, eight developed progression of ORN. The authors reported that of the eight patients who were identified to have positive bone necrosis at the margins on initial histologic evaluation, none showed evidence of persistent disease at follow-up visits. Additional studies are needed to identify clinical parameters that impact placement of surgical margins, in addition to identification of histologic variables within the specimen and at the margin that better correlate with clinical outcome.

Maurer and Meyer reported a case in which ORN resection was guided by the partial pressure of oxygen (PO2) within the bone measured using a fine-needle Eppendorf probe, measured via bur holes drilled into the mandible. In prior work, the investigators established a partial pressure value of greater than 71.7 mm Hg as a surrogate for healthy bone, whereas values less than 32.3 were consistent with ORN. Although novel, no additional studies examining this technique have been published since the initial case report in 2006. Similar to MRONJ, tetracycline bone fluorescence was found to be helpful as an adjunct in guiding intraoperative resection margins in

Table 1
Notani classification system for ORN

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<tr>
<th>Notani Class</th>
<th>Features</th>
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<tr>
<td>Class I</td>
<td>ORN confined to alveolar bone</td>
</tr>
<tr>
<td>Class II</td>
<td>ORN of alveolar bone and/or mandible above the level of the inferior alveolar canal</td>
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<tr>
<td>Class III</td>
<td>ORN involving the mandible below the level of the inferior alveolar canal, presence of cutaneous fistula, or pathologic fracture</td>
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Fig. 9. Osteoradionecrosis. (A) Surface of necrotic bone exposed to oral cavity with pseudoepitheliomatous hyperplasia (arrows), inflammation, and fibrosis of the mucosa (H&E, original magnification ×40). (B) Another area from same specimen as A showing peripheral resorption of the necrotic bone by aggregates of Actinomyces bacteria (H&E, original magnification ×100).
ORN according to a single case report. Other reports have shown the use of near infrared fluorescence for the evaluation of bony margins. Indocyanine green dye is injected intravenously and the perfusion to bony margins is assessed using a portable infrared imager. Further studies are needed to validate all of these adjuncts.

On histologic evaluation, specimens of ORN demonstrate death of osteocytes with empty lacunae and lack of osteoblastic rimming, similar to OM and MRONJ. The overlying mucosa may demonstrate pseudopitheliomatous hyperplasia in the areas where the bone is exposed to the oral cavity (Fig. 9A), and fibrosis of the connective tissue with decreased cellularity and vascularity. In ORN and MRONJ, the Actinomyces microorganisms are usually seen on the surface of the bone exposed to the oral cavity (Fig. 9B), rather than throughout the bone, as is the case with suppurative OM. The pattern of bone necrosis in ORN is appreciated in resection specimens or large biopsies. In ORN, the pattern is reported as uniform in appearance with large areas of necrosis and empty lacunae, whereas in MRONJ the necrosis is often patchy with alternating areas of viable and nonviable bone. These features may be obscured by prior instrumentation, superinfection, and/or pathologic fracture. ORN tends to demonstrate more significant fibrosis of the marrow (Fig. 10A) with an absence of normal marrow elements and lack of functioning blood vessels or inflammatory cells, when compared with suppurative OM or MRONJ. At the resection margins, the bone may appear viable with visible osteocytes within lacunae (Fig. 10B) and blood vessels within haversian canals, or necrotic with empty lacunae and canals.

Most patients with ORN have a prior history of malignancy; therefore, careful sampling of the specimen for recurrent, metastatic or posttreatment malignancy is imperative. In a retrospective review by Marwan and colleagues, 2.48% of patients had microscopic evidence of malignancy in the resection specimen of cases presumed to be ORN.

When a surgical resection has been performed with the expectation that a pathologic evaluation of margin status will be provided, traditional histologic parameters might include presence or absence of necrosis, inflammation, nature of the inflammatory response (acute or chronic), and the presence or absence of malignancy at the margin. The lack of concordance between absence of necrosis and progression of disease identified by Zaghi and colleagues suggests additional clinical and histologic prognostic parameters should be explored.

**SUMMARY**

Bone margin analysis in cases of OM, ORN, and MRONJ is a controversial topic. As discussed in this article, there is a paucity of evidence to guide therapy and interpretation of bone margins. Using imaging in planning surgery seems to be helpful, because often the radiographic changes are more extensive than what is seen clinically. Intraoperative adjuncts, such as tetracycline fluorescence, show some promise in margin assessment for surgical management of MRONJ, although this needs to be evaluated further. Other adjuncts including infrared fluorescence, autofluorescence, and the use of bone PO2 measurements have been reported in case reports only, and need to be investigated further. Obtaining clear margins seems to correlate with better outcomes in OM and MRONJ, but this was not demonstrated in ORN. Nonetheless, one should attempt to obtain clear margins whenever feasible. Pathologists are encouraged to evaluate and report on bony margins in these entities as they would for malignant disease. This
REFERENCES


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