RESEARCH PAPER

Histopathological Margins in MRONJ: Defining the Boundary of Bony Vitality and Recurrence: A Systematic review

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ABSTRACT

Medication-Related Osteonecrosis of the Jaw (MRONJ) is defined as an adverse drug-related reaction characterized by progressive destruction and necrosis of the mandibular or the maxillary bone of individuals exposed to treatment of drugs for which an increased risk of disease has been established in the absence of prior radiation treatment.[1] The most common etiology is the inhibition of osteoblastic activity and chronic inflammation in addition to any periodontal disease[2] . It is more common in jaw bones compared to long bones as the former have rapid turnover, terminal vascularization, and presence of microflora in the oral cavity.[3] . Various drugs can cause MRONJ, of which bisphosphonates are more common followed by Denosumab and various tyrosine kinase inhibitors.[4] The gold standard for the treatment includes surgical resection followed by antibiotic prophylaxis [5]. Surgical management of advanced MRONJ has transitioned from conservative debridement toward radical segmental or marginal resection. While achieving complete resolution hinges on resecting back to "viable, healthy bone," the intraoperative definition of a safe bony resection margin remains highly subjective and clinically challenging. Such inflammatory and necrotic osseous pathologies present an expansive, ill-defined transitional zone. This review of literature synthesizes current evidence on the histopathologic presentation of margins in severe MRONJ, and explores the pathogenic impact of persistent osteocyte death and microbial colonization on reconstructive failure post-resection defect in MRONJ vascularized bone flaps.

Keywords: MRONJ, Histological margin, Bone vitality, Surgical margins, Recurrence

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INTRODUCTION

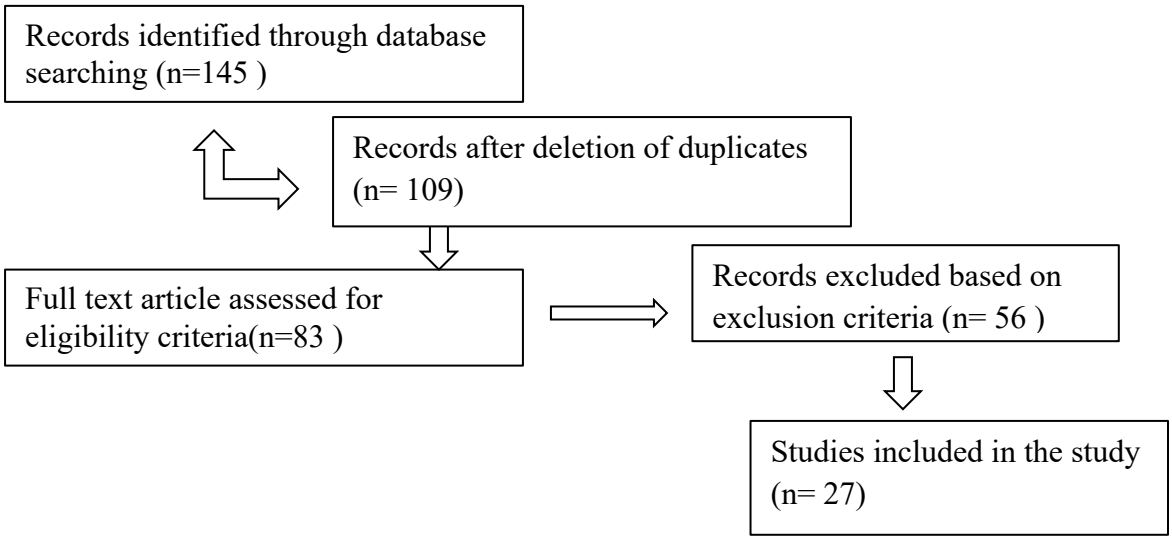
MRONJ is caused by osteoclast inhibition via bisphosphonate binding to hydroxyapatite or denosumab mediated RANKL inhibition suppressing normal bone remodeling, accelerating osteocyte apoptosis and predisposing the bone to secondary infection. The bone matrix in MRONJ remains macroscopically intact and hyper mineralized with preserved blood supply yet it may harbour dead lacunae, even the bone that bleeds may be still dead and non-viable microscopically. MRONJ arises from disrupted bone remodeling and impaired angiogenesis induced by antiresorptive (e.g., bisphosphonates, denosumab) or antiangiogenic therapies[6] . Historically, MRONJ was managed conservatively using local debridement and long-term antibiotics. However, literature strongly advocates for definitive surgical resection in advanced stages, which yields significantly higher cure and down-staging rates. Despite this surgical shift, defining the

optimal bony resection margin remains an ongoing challenge. Inadequate removal of compromised bone leads to chronic osteomyelitis or progressive necrosis causing reconstructive failure. However, over-resection increases the size of defect, and increases the challenge in the reconstructive procedures leading to patients' morbidity. This review describes the microscopic characteristics of the surgical borders and evaluates emerging methods to identify them to prevent recurrence and also to prevent the resection of healthy bone. Anchoring load-bearing osteosynthesis plates into partially necrotic or poorly vascularized margin bone leads to progressive osteolysis surrounding screws, hardware instability, chronic bacterial colonization, soft-tissue breakdown, and extraoral fistula formation. Achieving clear histopathologic margins is therefore mandatory to ensure osteointegration between the native jaw remnant and the vascularized bone graft.

Main Text

MATERIALS AND METHODS

This retrospective study includes various studies from search engines such as PubMed, Scopus, Google Scholar, ScienceDirect, and ResearchGate. The literature included was for the period of ten years from 2016-2026. Patients undergoing surgical treatment for MRONJ were included in the study. The surgical treatment in the literature involves removal of the necrotic bone and the specimens were evaluated histologically for viable bone, granulation tissue, bacterial colonies and inflammatory infiltrates. The aim of the study is to examine the various histopathological aspects of MRONJ. Literature with search strings such as MRONJ, histopathology, recurrence, were searched for a period of 10 years from 2016-2026. Inclusion criteria involve literature in English, patients clinically and radiographically diagnosed with MRONJ and under the antiresorptive and antiangiogenic therapy and patients who have undergone surgical intervention such as sequestrectomy, marginal or segmental resection to remove the necrotic bone. Exclusion criteria involve studies of patients who underwent any radiation therapy, patients having any malignancy related to jaw or osteomyelitis that is not related to MRONJ.



PRISMA GUIDELINES FLOW CHART

In MRONJ , the goal of the treatment is to achieve clear margins ie induce of bleed , and viable appearing bone but this does not guarantee microscopic clear margins[7]. There are various discrepancies between macroscopic clinical margins as well as microscopic margins as macroscopic clearance is based on the bleed and bone viability but microscopic channels harbour subliminal biofilms ,and chronic inflammatory cell infiltrates.

The Pathologic "Transitional Zone" between the necrotic and the healthy bone The primary obstacle in MRONJ surgery is that the boundary between completely dead bone and healthy bone is not demarcated but it is rather a wide "transitional zone" exhibiting varying degrees of microstructural degradation.[7]

Histopathology of the Necrotic Core vs. Margins: In the core of the lesion the histopathologic evaluation consistently shows complete loss of osteocytes characterized by empty lacunae within the mineralized matrix [8]. The bone marrow spaces lose their normal

fatty or hematopoietic structure, replaced instead by avascular, fibrotic tissue, acute inflammatory cells, and dense bacterial biofilms. The examination from necrotic to the clinical margin, comes the transitional phase.

The following characteristics transition between the necrotic to the viable bone.

The Osteocyte Survival Spectrum: the lacunae show unpredictable between being empty and containing viable osteocytes.[9]

Microvascular Degradation: Small vessels frequently display obliterative endarteritis or microthrombi[10] . more commonly seen in advanced ORN

Osteoclast Dysregulation: In MRONJ margins, there is evidence of detachment of osteoclasts from the bone surface, structurally altered, indicating failure in localized bone remodeling .[11]Deep Tissue Infection**:** Additionally, the margins show presence of micro-organisms, most commonly Actinomyces species. Histopathologic analyses of resected jaw specimens show Actinomyces sulfur granules embedded deep within necrotic bone spaces and reaching well into the transitional zone[12] This deep infiltration causes recurrence if the lesion is left behind.

There are various limitations of Traditional Margin Assessment. The literature describes two main criteria to establish margins during surgery: bleeding capacity and bone color, i.e., the change from yellowish grey to the fresh bone. Antiresorptive agents (ARAs) cause changes in the bone matrix without necessarily destroying its macroscopic blood supply. So even though there is fresh bleed post resection, it may still consist of extensive necrotic osteocytes and microcracks that act as a source of infection in future. The most standard imaging is computed tomography (CT) scans which focus on bone density and osteolysis; advanced cases of MRONJ can exist without any visible osteolysis on a CT scan making the preoperative plan deficient.

To overcome these limitations of subjective assessment, several advanced diagnostic and surgical technologies have been introduced to more accurately identify healthy bone margins. Pathological indicators essential for defining clear histopathologic margins:

Osteocyte Lacunar Occupancy Rate: Quantitative threshold of filled versus empty osteocyte lacunae per high-power field (HPF) defining true tissue viability. Osteoblast Seam Continuity: Presence of osteoblastic activity along trabecular borders as a possible indicator of viable bone.[14]

Vascular Luminal Integrity: Assessment of microvascular density and endothelial markers as possible indicators of healing potential[15] .

Depth of Microbial Infiltration: Assessment of Actinomyces sulfur granules within bone specimens as a possible histopathologic indicator[16] . Various new modalities have been developed for identifying clear margins intraoperatively and reducing unnecessary resection.[17] .

Autofluorescence-Guided Resection: Healthy bone contains collagen and mineral structures that naturally emit a bright green fluorescence when exposed to specific wavelengths of light (around 400–460 nm). Conversely, necrotic bone loses this property, appearing dark or "hypo fluorescent" under specialized scopes. The biofluorescence detects demineralization by irradiating at a wavelength of 405 nm [18]. Bacterial species exhibit autofluorescence which makes biofluorescence a non-invasive tool. Matured biofilm increases the intensity of red fluorescence.

A wavelength of 480 nm can amplify this red fluorescence. Recent prospective studies evaluating bone autofluorescence have found a highly significant correlation with laboratory histopathology: 86% of hyperfluorescent (glowing) samples demonstrated normal, living bone tissue, whereas hypo fluorescent samples consistently showed necrosis.[19]Autofluorescence allows surgeons to actively trim the bone edges until a continuous, healthy glow is achieved. Both autofluorescence and drug-induced fluorescence (particularly with tetracycline and minocycline) have shown encouraging results in distinguishing healthy bone from necrotic areas. This distinction is crucial, as it allows for more conservative yet effective surgeries, preserving as much viable bone as possible while ensuring complete removal of compromised tissue. As a result, these approaches are associated with better healing and improved postoperative outcomes.

Although autofluorescence helps in irradiating the necrotic bone, it has critical clinical limitation, such as intense intraoperative bleeding can absorb light in the 400–460 nm spectrum, causing vital, hyperfluorescent bone to appear dark leading to false negative results . Superficial bacterial colonization by specific oral pathogens (such as Porphyromonas gingivalis) can emit exogenous porphyrin fluorescence, masking bone necrosis or generating red fluorescence giving false-positive results. Drug-induced fluorescence protocols using preoperative tetracycline or minocycline labeling require specific dosing regimens, administration windows, and clearance periods that must be detailed to provide actionable value to clinicians.

Metabolic and Functional Imaging (SPECT-CT): Single-Photon Emission Computed tomography combined with CT (SPECT-CT) integrates structural scanning with metabolic tracking by using radiopharmaceuticals like Technetium-99m. While a standard CT scan shows changes after substantial bone mineral loss has occurred, SPECT detects early shifts in blood flow and cellular metabolism[20] . This helps identify the boundary where bone retains healing capacity, allowing for highly accurate, computer-assisted planning. Although it helps in identifying the bone margins, the increased tracer uptake can also indicate bone having high turnover rate, which can be caused by normal bone healing or other inflammatory pathologies. In modern maxillofacial reconstructive surgery, SPECT-CT radiotracer uptake maps are converted into Quantitative Standardized Uptake Values[21]. These metabolic datasets are co-registered with high-resolution anatomical CT scans and imported into Virtual Surgical Planning software. Surgeons utilize these fused data sets to design patient-specific 3D-printed CAD/CAM cutting guides.

Er:YAG Laser-Assisted Osteotomy: When clearing diseased bone, the surgical tools themselves can influence margin healing. Traditional mechanical burs generates friction and heat, which can cause micro-fractures and localized thermal necrosis along the cut edge. Use of Erbium-doped Yttrium Aluminum Garnet (Er:YAG) laser avoids these complications. The Er:YAG laser cuts bone through a vaporization process (photoacoustic ablation) that leaves behind a clean, micro-structured surface without a charred layer[22] Additionally, it has bactericidal properties that help eliminate deep-seated bacterial colonies at the surgical border[23] The Er:YAG laser operates at a wavelength that matches the major absorption peak of water molecules in biological tissues. Energy absorption causes explosive micro-vaporization of intra-bony water, resulting in photoacoustic ablation of the mineralized matrix without micro-cracking or deep thermal conduction. This leaves a clean micro-structured bony margin with a lesser thermal injury zone compared to conventional mechanical rotary burs which routinely generate thermal necrosis zones exceeding if under-irrigated.[22]

DISCUSSION

The prevention of recurrence in MRONJ depends fundamentally on accurate identification and complete removal of necrotic, infected, and biologically compromised bone while preserving the maximum possible volume of viable tissue. Although the clinical appearance of the resection surface—particularly bleeding, color, and consistency—remains useful intraoperatively, these findings do not always provide a reliable distinction between viable and nonviable bone. Consequently, reliance on visual and tactile assessment alone may result in either inadequate debridement, with residual necrotic tissue and subsequent recurrence, or excessive resection, producing a larger defect and complicating functional and reconstructive rehabilitation. The histological assessment of resection margins therefore provides an important means of validating whether the surgical boundary corresponds to biologically viable bone. A viable margin should be assessed using several complementary histopathological parameters rather than a single finding. The presence of filled osteocyte lacunae indicates cellular survival, whereas numerous empty lacunae support the diagnosis of necrotic bone. Osteoblast seam continuity along trabecular surfaces may further indicate preserved bone-forming activity, while the presence of osteoclasts or remodelling activity should be interpreted in relation to the surrounding inflammatory and necrotic changes. These features are particularly important in the transitional zone, where apparently intact bone may still demonstrate reduced cellularity, impaired remodeling, and microvascular compromise. Assessment of the vascular compartment may provide additional information because microvascular density and endothelial-marker expression have been associated with the healing potential of surgically treated MRONJ lesions[15]. Thus, a margin that appears macroscopically healthy but contains extensive empty lacunae, absent osteoblastic activity, or marked vascular disruption may not represent a dependable foundation for healing. The microbiological and inflammatory characteristics of the margin are equally relevant to recurrence. Actinomyces colonies and sulfur granules may be present within necrotic bone or along its surface, and targeted histological staining has demonstrated that Actinomyces infection can be overlooked when specimens are evaluated using routine methods alone[16]. The persistence of bacterial colonies within or adjacent to the resection margin may maintain chronic inflammation, impair soft-tissue closure, and increase the likelihood of recurrent exposure. Accordingly, histological sampling should include the necrotic core, the transitional zone, and the apparently viable peripheral bone. This approach may help determine whether the margin contains residual microbial infiltration rather than relying solely on the gross appearance of the operative field. Advanced intraoperative methods may assist the surgeon in locating the histological transition between necrotic and viable bone. Autofluorescence-guided resection is based on the observation that viable bone generally exhibits hyper-fluorescence, whereas necrotic bone demonstrates reduced or absent fluorescence. In a recent histological correlation study, most hyperfluorescent samples showed vital bone, while hypo-fluorescent samples were predominantly necrotic[19]. These findings support the use of autofluorescence as an adjunct for margin selection, particularly when conventional visual criteria are ambiguous. However, fluorescence should

not be regarded as a substitute for histological confirmation. Bleeding, bacterial fluorescence, inflammation, and variations in mineralization may alter the optical appearance of the surgical field and produce false-positive or false-negative interpretations. Evidence supporting fluorescence-guided surgery remains encouraging but is not yet sufficient to establish that it independently reduces recurrence compared with conventional surgery[18]. Metabolic imaging may provide complementary preoperative information about the extent of biologically altered bone. SPECT/CT combines functional tracer uptake with anatomical localization and may help identify regions of altered bone turnover that are not fully apparent on conventional imaging[20]. Nevertheless, increased uptake is not synonymous with viable bone, because inflammation, repair, and other high-turnover conditions may produce similar findings. Therefore, SPECT/CT should be interpreted alongside CT or MRI findings, clinical examination, and histological evaluation rather than used as an isolated determinant of the resection margin. Its principal value may lie in improving the initial surgical plan and directing biopsy or sampling toward radiologically heterogeneous regions. The method used to remove the diseased bone may also influence the biological quality of the final margin. Er:YAG laser-assisted osteotomy uses water-mediated ablation and has been described as producing precise bone removal with limited carbonization and thermal injury[22]. Its noncontact action and potential to reduce mechanical trauma may be advantageous when the objective is to create a clean margin while avoiding additional injury to the remaining viable bone. In addition, the Er:YAG laser has demonstrated the ability to remove contaminated material from surfaces with minimal thermal damage[23]. These properties are relevant to recurrence prevention because residual necrotic tissue, bacterial contamination, and iatrogenic injury at the resection edge may each compromise healing. However, the use of laser ablation should be considered an adjunct to—not a replacement for—adequate removal of histologically and clinically diseased bone. The integration of imaging, intraoperative fluorescence, precision osteotomy, and histological examination represents a more reliable margin-assessment strategy than any individual modality. Digital planning and patient-specific guides may improve the reproducibility of the planned resection[22] while robotic guidance may enhance the accuracy of complex osteotomies. These technologies can help translate the intended margin into the operative field, but technical precision alone cannot confirm tissue vitality. The definitive assessment remains biological: the resection should remove bone with necrosis, empty osteocyte lacunae, absent or markedly reduced remodeling activity, vascular compromise, and persistent microbial infiltration, while retaining bone with cellular viability and healing potential. Accordingly, the most defensible approach to recurrence prevention is a multimodal and margin-directed protocol. Preoperative CT, MRI, or functional imaging can define the suspected extent of disease; intraoperative autofluorescence and careful inspection can guide the surgeon through the transitional zone; and histological examination can confirm whether the final margin contains viable bone or residual pathological tissue. This strategy supports the central surgical objective in MRONJ: complete debridement of the diseased lesion without unnecessary sacrifice of healthy bone. Because recurrence is influenced not only by the amount of bone removed but also by infection, vascularity, inflammation, and soft-tissue closure, future studies should evaluate histological margin characteristics together with long-term recurrence outcomes. Establishing standardised definitions of a "viable" and "safe" margin may ultimately improve comparability between studies and provide a more dependable basis for surgical decision-making.

CONCLUSION

Evaluating surgical margins in severe MRONJ and ORN requires careful assessment and surgical planning to preserve the vital bone and also complete debridement of the infected lesion. Surgeons should carefully examine the transitional zone characterized by presence of minimal osteocytes, micro vascular damage and bacterial biofilms. There are various assessment tools apart from clinically visualizing bone color and bleeding such as SPECT-CT imaging, intraoperative autofluorescence, and clean laser osteotomies[7] that allow oral and maxillofacial surgeons to achieve cleaner margins, lower recurrence rates, and establish a dependable foundation for complex jaw reconstruction.

Ethics Approval and Consent to participate :Not applicable

Conflict of interest: NIL

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