Review Article

DIFFERENCES BETWEEN OSTEORADIONECROSIS AND MEDICATION-RELATED OSTEONECROSIS OF THE JAW

.

ABSTRACT

Two severe and challenging-to-treat side effects of head and neck cancer (HNC) oncological treatments are osteoradionecrosis of the jaws (ORNJ) and medication-related osteonecrosis of the jaws (MRONJ). In both cases, the bone loses vitality and develops in an area that cannot heal, which is exposed through the skin or mucosa; in more severe cases, fistulas and jaw fractures may coexist. They are similar in that they complicate medical and surgical treatments (such as radiation therapy or medications) and cause osteonecrosis of the jawbone. Despite many clinical similarities, they differ in etiology, histopathology, radiological features, and staging systems, leading to different treatment approaches. Despite having relatively low incidences, both have a detrimental effect on HNC patients' quality of life by causing various potentially unwholesome symptoms like pain, tooth loss, swelling, erythema, ulceration, dysphagia, trismus, or paresthesia. Because distinguishing ORNJ and MRONJ, two devastating complications of different origins with a similar presentation pattern and gross appearance, can be difficult, the purpose of this review is to discuss the major differences in their definitions, staging systems, clinical findings, underlying pathophysiologic mechanisms, histopathology, and treatment options.

Keywords: Osteoradionecrosis, medication-related osteonecrosis, head and cancer, radiotherapy

1. INTRODUCTION

Medication-related osteonecrosis (MRONJ) and osteoradionecrosis of the jaws (ORNJ) have similar physical features, although they are two distinct ailments. While radiation (RT) is the primary cause of ORNJ, antiresorptive or antiangiogenic medication treatment is the primary cause of MRONJ (1). Depending on the selected treatment modality, ORNJ and MRONJ can complicate the management of primary or metastatic tumors and osteoporosis (1, 2). Both harmful complications are uncommon (3, 4), but the introduction of new medications has led to an increasing trend in the number of patients with MRONJ (5). The advances in RT procedures (for example, intensity-modulated radiation therapy [IMRT]) have reduced the number of ORNJ patients, but they have not eliminated this complication yet. MRONJ and ORNJ occur in 1-15% and 1-37% of cancer patients (3, 6), respectively.

Despite having a similar clinical presentation (exposure of necrotic bone and infection of the surrounding soft tissue), ORNJ and MRONJ differ significantly from one another in terms of patient-related factors, imaging findings, etiology, and pathogenesis (7-9). The reported incidences of ORNJ and MRONJ may also differ due to variations in diagnostic standards and underlying genetic factors. However, differences in dental hygiene, patient compliance, RT mode, frequency of dental examinations, and the standard of dental and surgical care could explain these variations in the incidence rates (10).MRONJ and ORNJ might exhibit similar clinical symptoms, such as protracted asymptomatic periods. However, it happens frequently that these lesions develop symptoms with inflammation of the surrounding tissues, where signs and symptoms may appear before the development of bony exposure. Additionally, ORNJ and MRONJ patients may experience pain, tooth mobility, mucosal swelling, erythema, ulceration, dysphagia, malocclusion, trismus, paresthesia, or even anesthesia of the associated branch of the trigeminal nerve (5). Because the neurovascular bundle may become compressed by localized inflammation, some patients may also experience altered sensations in the affected area in both toxic conditions (3, 11, 12). Oral and maxillofacial surgeons, medical oncologists, and radiation

oncologists must comprehend the various factors underlying ORNJ and MRONJ to choose the best course of treatment for each disease and establish preventive measures. This chapter aims to discuss the key distinctions between ORNJ and MRONJ, two devastating complications of different origins with a similar presentation pattern and gross appearance, as it may be difficult to distinguish between them. These distinctions include their definitions, staging systems, clinical findings, underlying pathophysiologic mechanisms, histopathology, and available treatments.

2. DIFFERENCES BETWEEN THE CLINICAL CHARACTERISTICS, DEFINITIONS, AND STAGING OF MRONJ AND ORNJ

As was already mentioned, MRONJ and ORNJ are two distinct illnesses with strikingly similar outward symptoms that are extremely difficult to treat. Their underlying causes are different; ORNJ is brought on by RT, whereas MRONJ is primarily caused by antiresorptive or antiangiogenic drug therapy (1). The diagnosis of MRONJ is typically made using the definition offered by the American Association of Oral and Maxillofacial Surgeons (AAOMS) (11). If all of the following conditions are satisfied, MRONJ should be presumpted: (a) current or previous treatment with antiresorptive or antiangiogenic agents; (b) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks; and (c) no history of RT to the jaws or clearly manifest metastatic disease to the jaws. These three criteria must be met in order to avoid misdiagnosis with other conditions such as ORNJ, osteitis, osteosarcoma, osteomyelitis, malignancies such as chronic sclerosing osteomyelitis, or fibro-osseous disease. An accurate differential diagnosis can occasionally be challenging (1). A diagnosis cannot be made solely based on radiographic signs because they may overestimate the prevalence of the disease (stage 0 disease) (11). Therefore, it is necessary to investigate the presence of additional clinical features at the time of examination, such as the presence of tooth, jaw, or sinus pain, altered neurosensory function (hypoesthesia primarily in the lower lip and jaw), unexplained tooth movement, localized swelling, infections (including cellulitis and pus leakage), or halitosis (13) will help to diagnose MORNJ at stage 0.

To date, numerous staging proposals have been published (14). The most widely used and current MRONJ staging system is the AAOMS staging framework (Figure 1). This staging system states; Stage 0; No clinical evidence of necrotic bone but non-specific clinical findings and radiographic changes or symptoms, Stage 1; Asymptomatic exposed bone; Exposed and necrotic bone or fistulae that probe to the bone. No symptoms and no evidence of infections, Stage 2; Symptomatic exposed bone; Exposed and necrotic bone or fistulae that probe to bone Infection evidenced by pain and erythema in the region of exposed bone, and Stage 3; Complications; exposed and necrotic bone or fistulae that probes to bone infection, evidenced by pain and erythema in the region of exposed bone with the presence of one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) pathologic fracture and extra-oral fistula oral-antral or oral-nasal communication osteolysis extending to the inferior border of the mandible or sinus floor. Additionally, this classification applies to high-risk patients who received oral or intravenous anti-resorptive medications but did not appear to have necrotic bone. The anatomic border of the involvement of the necrotic lesion must also be taken into account, even though the current staging system lacks size criteria. The exposed bone is not necessary for the diagnosis of MRONJ. A histological examination reveals areas of non-viable necrotic bone, along with fibrotic mucosa and periosteum, hypocellularity, and hypovascularity, as well as necrosis and fibrosis of the marrow spaces (1).

A previously-irradiated site with exposed bone that fails to heal after at least three months but shows no signs of a persistent, recurrent, metastatic, or second tumor invading the jaw is declared to have ORNJ (15,16). For ORNJ, there are various staging systems. Marx et al. (17) classified ORNJ in 1983 based on its clinical characteristics and response to hyperbaric oxygen therapy (HBOT). ORNJ was divided into three stages based on this classification: Stage I: exposed alveolar bone without pathologic fracture, which response to HBOT; Stage II: disease not responding to HBOT and requiring sequestrectomy and cauterization; and Stage III: full-thickness bone damage or pathologic fracture, which usually requires complete resection and reconstruction with free tissue.

Epstein et al. have classified ORNJ in a different way (18). The authors categorized ORNJ based on how the illness progressed: Stage I: resolved and healed (Ia: no pathological fracture; Ib: pathological fracture); Stage II: chronic but non-progressive (IIa: no pathological fracture; IIb: pathological fracture); and Stage III: active and progressive (IIIa: no pathological fracture; IIIb: pathological fracture). The classification developed by Notani et al. based on the clinical findings of ORNJ is the most prevalent and recent ORNJ grading system (19). This staging system defines ORNJ as Stage I: confined to the alveolar bone; Stage II: limited to the alveolar bone and/or mandible above the level of the inferior alveolar canal; and Stage III: involving the mandible below the level of the inferior alveolar canal and/or a skin fistula and/or a pathological fracture (Figure 1).

Various clinical symptoms of the disease may manifest, such as advanced skin ulceration or the exposure of necrotic bone through the mucosa. Clinical manifestations like pain, dysesthesia, dysgeusia, localized food impaction, trismus, or halitosis are frequently observed. Swelling, suppuration, cellulitis, infections, and even sepsis are additional symptoms that may be present. Rough and irregularly shaped necrotic bone frequently irritates nearby tissues. Pathological fracture symptoms, intra- or extra-oral fistulae, and issues with mastication, chewing, swallowing, and speech are also common (15, 16, 20). The presence of necrotic bone tissue in the later stages of MRNOJ is its most

distinguishing feature, despite the fact that the clinical characteristics of the two diseases are almost identical at every stage (particularly the early stages), including pain, swelling, and gingival erythema. Hence, radiological imaging may be beneficial in distinguishing between these two diseases in their advanced forms.

3.DIFFERENCES BETWEEN THE RADIOLOGIC FEATURES OF MRONJ AND ORNJ

Bone is a specialized connective tissue that offers a microenvironment and structural support for a variety of physiological functions, including calcium homeostasis and the production of red and white blood cells. Osteoblasts (bone-forming cells), osteoclasts (bone-resorbing cells), and osteocytes make up the cellular components of bone. Bone's dynamic nature can be perceived via its constant structural adaptation to mechanical forces, local disease, and systemic hormonal influences. To maintain continuous and healthy bone turnover, osteoblastic and osteoclastic activity must be well-balanced. This equilibrium may be oftentimes disturbed by external factors like therapeutic ionizing radiation and pharmaceutical treatments like antiresorptive drugs (29).

Typically, dental periapical and panoramic radiography is used as the first line of diagnostic imaging for patients with suspect ORNJ. Subtle areas of altered trabecular architecture and rarefaction are the first signs of changes in ORNJ. Since dental infection frequently serves as a catalyst for the onset of ORNJ, it is important to carefully inspect the teeth for caries, periodontal disease, and periapical inflammations (21). A common observation in the irradiated mandible is the expansion of the periodontal ligament space along the mandibular tooth roots and the absence of adjacent bone destruction (22). Significant lytic bone destruction, which gives a patchy radiolucent appearance with radiopaque necrotic bone islands or sequestrums instead of radiolucent lytic changes, becomes radiographically evident as the disease progresses. The extent of the bone loss could be so extensive that it compromises the mandible's integrity and leads to a pathological fracture. It is prudent to note that the radiologic manifestation of ORNJ is nonspecific and needs to be discriminated from other causes of bone necrosis, like osteomyelitis, and metastatic or recurrent cancers (21). When there is a high level of clinical suspicion and ambiguous panoramic radiography findings, CT is the preferred imaging modality. On CT imaging, sequestrations, central necrosis, and cortical destruction are more readily visible in ORNJ cases (23). Before they manifest clinically, MRI can detect early ORNJ-induced changes in the bone marrow. These changes appear as a decrease in the bone marrow signal's intensity on a T1-weighted image and an increase in the signal's intensity on a T2-weighted image. On MRI images, one can also see cortical erosions and changes in the nearby soft tissues (24,25).

Lytic and sclerotic changes are radiographic changes in MRONJ. Some of the first indicators of lytic changes are regions with altered trabecular architecture and density. These changes may progress to frank, patchy radiolucent bone destruction with cortical erosion and eventually to discernible bone destruction. The lytic changes may disrupt the anatomic boundaries of the maxillary sinus and nasal cavity, neurovascular canals, and mandibular cortical boundaries, resulting in pathological fractures. It is critical to identify any surgical bone defects or non-healing extraction sockets. Lytic and sclerotic changes can frequently be observed even in the absence of frank bone exposure, highlighting the importance of taking clinical and radiographic information into account for proper disease staging (26,27). Except for ORNJ, sclerosing changes manifest as localized to diffusely widespread osteosclerosis in MRONJ and osteonecrosis of the jaw for other reasons. These alterations could be significant and affect the entire jaw's height. Sclerotic changes are frequently accompanied by periosteal bone formation, which can be excessive and cause anatomic expansion of the jaws. As the necrotic changes worsen and coalesce, islands of the necrotic bone sequestrate form (21).

Although the radiographic appearance of ORNJ and MRONJ can overlap, one of the key differences between the two is that on CT imaging, periosteal movement is seen in bone tissue in ORNJ cases but not in MRONJ cases (28). A rare appearance with loss of cortical outlines and trabecular density is typically the result of prominent osteoclastic activation and diminished osteoblastic function during ORNJ (21). Additionally, it has been noted that patients receiving RT experience impaired bone nutrition because of decreased periosteal vascularity in the bone, even though periosteal effects are not always seen in ORNJ patients. MRONJ, in contrast to ORNJ, exhibits a high degree of periosteal vascularity (28). Furthermore, a residual or recurrent tumor must be ruled out using a histological examination in order to diagnose ORNJ (1). Because of this, it should be remembered that using standard radiographs alone may not be sufficient to diagnose MRONJ and ORNJ radiographically, and it may be necessary to enlist the aid of cutting-edge imaging techniques.

4. DIFFERENCES BETWEEN HISTOPATHOLOGICAL FEATURES OF MRONJ AND ORNJ

Under microscopic examination of the MRONJ (29), empty Haversian and Volkmann canals, empty osteocytic lacunae, the absence of osteoblastic rimming, and visibility of empty osteocytic lacunae all point to a necrotic bone. The necrotic bone is typically wrapped by bacterial colonies and exhibits irregular peripheral resorption with prominent reverse lines (30,31). The bone marrow cavity is bereft of inflammatory cells and blood vessels. The entire bone marrow cavity is acellular and devoid of extracellular collagen or cellular byproducts (29).In the intertrabecular spaces and on the periphery of the bony trabeculae (32), osteoclasts with numerous intracytoplasmic vacuoles are visible. Cellular debris in varying quantities is occasionally observed (30). In most MORNJ cases, a healthy periosteum and responsive bone are also present (29).

In the microscopic evaluation of ORNJ, the necrotic bone is seen as in MRONJ (29). When examined under a microscope, necrotic bone exhibits neither osteoblastic nor osteoclastic activity (33). Inflammatory cells, healthy bone marrow components, and fat cells are conspicuously absent from the marrow. Instead, the bone marrow's composition is mainly acellular collagen, with only a few cell nuclei visible (29). The bone marrow spaces are replaced with fibrosis, and inflammatory cell infiltration is limited (34). At the bone's periphery, there are frequently empty Howship's lacunae to be seen. Old blood vessels' ghosts can also be seen. It has been proposed that this microscopic finding indicates that osteoclasts have undergone apoptotic cell death (35). In addition, the periosteum is typically acellular and avascular in most cases of ORNJ (29).

The presence of bone necrosis is frequent in MRONJ and ORNJ, and it plays a crucial role in the disease process (30). However, according to existing recommendations, a biopsy is not mandatory for the MRONJ or ORNJ diagnosis (11, 17, 36). Marx et al. reported the presence of inflammation in 100% of osteomyelitis cases and 0% in MRONJ and ORNJ cases when comparing 23 cases of osteomyelitis, 37 MRONJ, and 45 ORNJ with similar clinical features (29). It was clear that in osteomyelitis, bacteria were only present in the marrow spaces, whereas, in MRONJ and ORNJ, bacteria were only present on the surface. This study also found osteoclasts in 96% of cases of osteomyelitis compared to none in MRONJ and ORNJ. However, a study claimed that while osteoclasts were uncommon, they were present in 12.5% of all MRONJ specimens (29), whereas no osteoclasts were noted in ORNJ (30). According to Shuster and colleagues' study (30), the only parameter that did correlate with the diagnosis of MRONJ but not ORNJ was the presence of Actinomyces colonies. Thus, according to some researchers, this microorganism is involved in the pathogenesis of MRONJ (37,38). Additionally, ORNJ exhibits a nonviable periosteum and no indication of reactive bone, whereas MRONJ may, in many instances, exhibit a viable periosteum and even reactive bone.

5.DIFFERENCES BETWEEN THE PATHOPHYSIOLOGIC MECHANISM OF ORNJ AND MRONJ DEVELOPMENT

Osteonecrosis is a general term for the devitalization of bone and ensuing lytic changes. At some locations, like the femoral head, osteonecrosis frequently results in avascular (aseptic) necrosis as a result of altered vascular supply. Although altered perfusion may play a role in their pathogeneses, it is critical to recognize that ORN and MRONJ differ from other types of avascular necrosis.

By affecting the tiny blood vessels in the bone and causing inflammation (endarteritis), RTcan lead to ORNJ (39). Endarteritis encourages the growth of small thrombi that block the vascular lumen and thwart local injury repair and warfare against infections. However, early experimental models of the pathophysiology of ORNJ revealed bacterial contamination in the affected tissues and documented microscopic tissue changes, including thickening of arterial and arteriolar walls, loss of osteocytes and osteoblasts, and filling of bony cavities with inflammatory cells (40).

Several hypothetical mechanisms of the ORNJ have been proposed up to now, with Meyer's theory being the first reported one. This theory postulates that ORNJ is caused by radiation exposure, trauma, and infection, where a tissue injury creates a pathway for oral microbiota to invade the underlying irradiated bone. Meyer's theory persisted for a decade and served as the cornerstone for the widely accepted use of antibiotics in conjunction with surgery to treat ORNJ (41). Marx introduced the 3H theory, also known as the hypoxic-hypocellular-hypovascular theory, in 1983. Marx defined the pathophysiology of ORNJ as the breakdown of tissue (cell death and breakdown of collagen that exceeds the capacity of cellular replication and synthesis) caused by persistent hypoxia, which can result in a chronic non-healing wound (a wound in which metabolic demands exceed supply) (17). Finally, Delanian et al. (42) described the fibro-atrophic theory in 2004. This theory proposes that activation and dysregulation of fibroblastic activity cause atrophic tissue within a previously irradiated area, resulting in ORNJ (42, 43).

Although the pathophysiology of ORNJ is, to some extent, well understood, the pathophysiology and metabolic mechanisms of MRONJ have not yet fully evolved in the last 20 years, despite the fact that the first cases were reported in 2003 and 2004, respectively (5). Many hypotheses have been put forth, but given that MRONJ is a multifactorial disease entity, it is unlikely that any one of them can fully explain the precise pathophysiology of the disease. One of the most prevalent hypotheses to explain the peculiar localization of MRONJ in the jaws is that it is brought on by immune dysfunction, soft tissue toxicity, infection, excessive suppression of bone resorption, inflammation, and inflammatory responses (44). None of these theories, however, appears to be able to account for every MRONJ case.

Bisphosphonates and anti-receptor-activated nuclear factor kappa B ligand (anti-RANKL) monoclonal antibodies, like denosumab, have reportedly been implicated in most MRONJ cases diagnosed in recent years (45–47). The fact that neither of these medications allows osteoclasts to reabsorb bone unites them. According to Perini et al. (48), the pathophysiology of MRONJ may be explained by three different theories: (1) inhibition of osteoclastic bone remodeling and resorption; (2) inflammation or infection; and (3) inhibition of angiogenesis. Despite the fact that several mechanisms are mentioned, inhibition of bone remodeling appears to be the key player in the pathogenesis of MRONJ (49).

Antiresorptive drugs reduce the number of osteoclasts on the surface of the bone. Osteoclastic bone resorption is crucial for proper bone healing after injuries caused by invasive procedures like tooth extraction. Therefore, inhibiting osteoclasts may impede and prolong the healing of osseous wounds (50). Although MRONJ was initially defined as "avascular necrosis of the jaw" (51), it is now known that medications such as systemic bisphosphonates promote

MRONJ by causing inflammation and bacterial infections in bone tissue (48). Angiogenesis suppression is the primary factor in the pathophysiology of MRONJ since osteonecrosis is typically regarded as an interruption in vascular supply or avascular necrosis. This theory is supported by in vitro research by Smith et al., which showed a sustained decrease in angiogenesis in response to the bisphosphonate zoledronic acid (52).

The basis of ORNJ is vascular disruption, thrombosis, and hypoxia, as well as hypoxia-induced inflammation and the response created by inflammatory cells, resulting in a fibrotic process. This process may also exacerbate local damage by increasing the synthesis and release of inflammatory chemokines and cytokines such as hypoxia-induced factor-1 alpha (HIF-1), transforming growth factor-beta (TGF-ß), interleukin-6 (IL-6), and insulin-like growth factor 2 (IGF-2) (53-56). However, it is very likely that MRONJ develops as a direct result of disruption of bone turnover, suppression of osteoclast activation, infection, and inflammation in the later stages. The inhibition of angiogenesis and the addition of bone malnutrition to this scenario are thought to be additional factors that contribute to bone necrosis (48).

6.DIFFERENCES BETWEEN THE TREATMENT PRINCIPLES OF MRONJ AND ORNJ

Despite their similarities, MRONJ and ORNJ cannot be treated in the same way. A flawless diagnosis is the only way to choose the optimal course of treatment for MRONJ and ORNJ. A realistic, interdisciplinary strategy that prioritizes the patient's quality of life and management of their skeletal illness is necessary for patients with a confirmed diagnosis of MRONJ (57). The mainstay of care is conservative treatment, which can offer long-term relief even though it may not completely eradicate the lesion (1, 3). Controlling pain, infections, and osteonecrosis progression are the main goals of treatment (58). If feasible, antiresorptive therapy must be discontinued in the event of MRONJ formation until soft tissue closure.

The treatment approaches for each MRONJ stage are summarized in Figure 2. At any stage, it is always necessary to enhance oral hygiene, educate patients, and manage current periodontal and dental illnesses. Surgical removal of necrotic bone sequestrum should be considered, regardless of the disease stage, if it is achievable without exposing healthy bone (57). Although surgical therapy for MRONJ is not suggested owing to a lack of evidence, evidence is now accumulating to support the use of surgery at any disease stage, with increasing experience in recent years (59-61). When non-operative therapy fails in MRONJ stage 3, surgical resection should be explored. To thoroughly remove necrotic bone, sequestrectomy or resection must be utilized, sharp bony edges must be softened, and the incision wound must be meticulously closed (57). Larger volumes of bone excision tend to yield better results than restricted debridement (62-64). Perioperative antibiotic therapy is always required in conjunction with surgical procedures. Despite the lack of proof, antiresorptive medication should be discontinued before any operation and until complete healing, just as in preventative care.

In stage 3 patients with significant necrosis and pathological fractures, segmental excision with immediate reconstruction might be contemplated as a last option. After dental or jaw surgery, soft tissues must be closed using appropriate local flaps. Reconstruction with vascularized free flaps appears to outperform alternative approaches, such as reconstruction plates (65, 66). Along with these treatments, HBOT may help MRONJ patients heal necrotized bone tissue and close soft tissue wounds.

There are currently a number of medical or surgical treatment options that have been suggested in the literature and are being used, but there is still no universally recognized treatment for ORNJ (67). Conservative management includes changes to diet, oral hygiene, analgesics, mouthwashes (with saline solution, sodium bicarbonate, or chlorhexidine), and the use of systemic antibiotics (amoxicillin with clavulanic acid or clindamycin) in cases of acute infection episodes. The disease can be treated at any stage, even early on. Due to its inability to treat osteonecrotic wounds when used alone, hyperbaric oxygen therapy (HBO) is only used as adjuvant therapy, particularly before and after surgery (68, 69). Ultrasound therapy (UST) has the potential to increase blood flow, promote angiogenesis, and treat ischemic ulcers (70). Shock wave therapy, also used to treat the femoral head, was advised for ORNJ by Wu et al. (71) and Harris (72). Based on the fibro atrophic theory (42), a well-known ORNJ mechanism theory, antifibrotic drugs, such as tocopherol and their combinations, are currently frequently used in the treatment of ORNJ (60). Surgical management can be as straightforward as gentle curettage, debridement, and sequestrectomy or more or less extensive surgical resection (with reconstruction, if necessary). It is critical to be aware that ORNJ may relapse in the residual bone following necrotic bone removal and reconstruction, resulting in reconstruction failure. Thus, extensive bone resections should be preferred to avoid such regrettable conditions, if feasible (Figure 3).

7.CONCLUSION

The two challenging complications, MRONJ and ORNJ, are still distinct pathophysiological entities, though they share many similarities (Table 1). They differ in terms of some clinical, radiological, and clinical characteristics, but mostly in their treatment protocols. The diagnosis must be accurate to treat these complications as soon as possible in both situations. To accomplish this, all clinical and radiographic characteristics of diseases must be fully understood by medical oncologists, radiation oncologists, oral and maxillofacial surgeons and radiologists, otolaryngologists, and plastic and

reconstructive surgeons. Improved patient knowledge, oral hygiene, and dental treatment, planned and executed by a highly competent multidisciplinary team, will also help MRONJ and ORNJ management

CONSENT (WHEREEVER APPLICABLE)

Not applicable

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

Not applicable

REFERENCES

1. Kün-Darbois JD, Fauvel F. Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management. Morphologie. 2021;105(349):170-87. doi: 10.1016/j.morpho.2020.11.008.
2. Akashi M, Wanifuchi S, Iwata E, Takeda D, Kusumoto J, Furudoi S, et.al. Differences between osteoradionecrosis and medication-related osteonecrosis of the jaw. Oral Maxillofac Surg. 2018;22(1):59-63. doi: 10.1007/s10006-017-0667-5.
3. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, et.al.On behalf of the International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015; 30(1):3–23.
4. Chen JA, Wang CC, Wong YK, Wang CP, Jiang RS, Lin JC, et. al. Osteoradionecrosis of mandible bone in patients with oral cancer—associated factors and treatment outcomes. Head Neck. 2016; 38(5):762–68.
5. Grisar K, Schol M, Schoenaers J, Dormaar T, Coropciuc R, Vander Poorten V, et.al Osteoradionecrosis and medication related osteonecrosis of the jaw: similarities and differences. Int J Oral Maxillofac Surg. 2016; 45(12):1592–99.
6. Sciubba JJ, Goldenberg D. Oral complications of radiotherapy. Lancet Oncol. 2006;7:175–183.
7. Obinata K, Shirai S, Ito H, Nakamura M, Carrozzo M, Macleod I, et.al. Image findings of bisphosphonate related osteonecrosis of jaws comparing with osteoradionecrosis. DentomaxillofacRadiol. 2017;46(5):20160281.
8. Bagan JV, Jiménez Y, Hernández S, Murillo J, Díaz JM, Poveda R, et. al. Osteonecrosis of the jaws by intravenous bisphosphonates and osteoradionecrosis: a comparative study. Med Oral Patol Oral Cir Bucal. 2009;14(12):e616–e619
9. Hansen T, Kunkel M, Weber A, James Kirkpatrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates—histomorphologic analysis in comparison with infected osteoradionecrosis. J Oral Pathol Med. 2006; 35(3):155–60.
10. Hoff AO, Toth B, Hu M, Hortobagyi GN, Gagel RF. Epidemiology and risk factors for osteonecrosis of the jaw in cancer patients. Ann N Y Acad Sci. 2011;1218:47–4.
11. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral MaxillofacSurg2014;72:1938–56.
12. Reuther T, Schuster T, Mende U, Ku¨bler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumor patients—a report of a thirty-year retrospective review. Int J Oral Maxillofac Surg. 2003;32:289–95
13. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiodt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 2018;69:177—87
14. Eguia A, Bagan-Debon L, Cardona F. Review and update on drugs related to the development of osteonecrosis of the jaw. Med Oral Patol Oral Cir Bucal 2020;25:e71—83.
15. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. Int Dent J 2018;68:22—30.
16. Chrcanovic BR, Reher P, Sousa AA, Harris M. Osteoradionecrosis of the jaws — a current overview — part 1: physiopathology and risk and predisposing factors. Oral MaxillofacSurg2010;14:3—16.
17. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral MaxillofacSurg1983;41:283–8.
18. Epstein JB, Wong FLW, Stevenson-Moore P. Osteoradionecrosis: clinical experience and a proposal for classification. J Oral Maxillofac Surg. 1987;45:104–10
19. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, et. al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. Head Neck. 2003;25:181–86

20. Somay E, Yilmaz B, Topkan E, Kucuk A, Pehlivan B, Selek U. Assessment of the Impact of Osteoradionecrosis on Quality-of-Life Measures in Patients with Head and Neck Cancer. In: Sergi CM, editor. Advancements in Cancer Research. Brisbane (AU): Exon Publications; Online first 28 Oct 2022. p. 41–56
21. Mallya SM, Tetradis S. Imaging of Radiation- and Medication-Related Osteonecrosis. RadiolClin North Am. 2018;56(1):77-89. doi: 10.1016/j.rcl.2017.08.006.
22. Chan KC, Perschbacher SE, Lam EW, Hope AJ, McNiven A, Atenafu EG, Lee L, et.al. Mandibular changes on panoramic imaging after head and neck radiotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(6):666–72
23. Store G, Larheim TA. Mandibular osteoradionecrosis: a comparison of computed tomography with panoramic radiography. DentomaxillofacRadiol. 1999;28(5):295–300.
24. Chong J, Hinckley LK, Ginsberg LE. Masticator space abnormalities associated with mandibular osteoradionecrosis: MR and CT findings in five patients. AJNR American journal of neuroradiology. 2000;21(1):175–78
25. Hermans R. Imaging of mandibular osteoradionecrosis. Neuroimaging Clin N Am. 2003;13(3):597–604
26. Bedogni A, Fusco V, Agrillo A, Campisi G. Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ) Oral Dis. 2012;18(6):621–23
27. O'Ryan FS, Khoury S, Liao W, Han MM, Hui RL, Baer D, et.al. Intravenous bisphosphonate-related osteonecrosis of the jaw: bone scintigraphy as an early indicator. J Oral Maxillofac Surg. 2009;67(7):1363–72.
28. Akashi M, Wanifuchi S, Iwata E, Takeda D, Kusumoto J, Furudoi S, et.al. Differences between osteoradionecrosis and medication-related osteonecrosis of the jaw. Oral Maxillofac Surg. 2018;22(1):59-63.
29. Marx RE, Tursun R. Suppurative osteomyelitis, bisphosphonate induced osteonecrosis, osteoradionecrosis: a blinded histopathologic comparison and its implications for the mechanism of each disease. Int J Oral MaxillofacSurg2012;41:283–9
30. Shuster A, Reiser V, Trejo L, Ianculovici C, Kleinman S, Kaplan I. Comparison of the histopathological characteristics of osteomyelitis, medication-related osteonecrosis of the jaw, and osteoradionecrosis. Int J Oral Maxillofac Surg. 2019;48(1):17-22.
31. Ogura I, Minami Y, Ono J, Kanri Y, Okada Y, Igarashi K, et.al. CBCT imaging and histopathological characteristics of osteoradionecrosis and medication-related osteonecrosis of the jaw. Imaging Sci Dent. 2021;51(1):73-80.
32. McLeod NM, Brennan PA, Ruggiero SL. Bisphosphonate osteonecrosis of the jaw: a historical and contemporary review. Surgeon. 2012;10(1):36–42.
33. Fondi C, Franchi A. Definition of bone necrosis by the pathologist. Clin Cases Miner Bone Metab. 2007;4(1):21-6.
34. Damek-Poprawa M, Both S, Wright AC, Maity A, Akintoye SO. Onset of mandible and tibia osteoradionecrosis: a comparative pilot study in the rat. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(2):201-11.
35. Youm YS, Lee SY, Lee SH. Apoptosis in the osteonecrosis of the femoral head. ClinOrthop Surg. 2010;2(4):250-5.
36. O'Dell K, Sinha U. Osteoradionecrosis. Oral MaxillofacSurgClin North Am 2011;23:455– 64
37. Anavi-Lev K, Anavi Y, Chaushu G, Alon DM, Gal G, Kaplan I. Bisphosphonate related osteonecrosis of the jaws: clinico-pathological investigation and histomorphometric analysis. Oral Surg Oral Med Oral Pathol Oral Radiol2013;115:660–6.
38. Schipmann S, Metzler P, Rössle M, Zemann W, von Jackowski J, Obwegeser JA, et.al. Osteopathology associated with bone resorption inhibitors—which role does Actinomyces play? A presentation of 51 cases with systematic review of the literature. J Oral Pathol Med 2013;42:587–93
39. Watson WL, Scarborough JE. Osteoradionecrosis in intraoral cancer. Am J Roengenol. 1938; 40:524–34
40. Gowgiel JM. Experimental radio-osteonecrosis of the jaws. J Dent Res.1960. 39:176–97
41. Titterington WP. Osteomyelitis and osteoradionecrosis of the jaws. J Oral Med.1971; 26:7–16
42. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. RadiotherOncol2004;73:119–31.
43. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral MaxillofacSurg2008;46:653–60.
44. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. J Oral MaxillofacSurg2009;67(5 Suppl.):61–70.
45. Aguirre JI, Castillo EJ, Kimmel DB. Preclinical models of medication-related osteonecrosis of the jaw (MRONJ). Bone. 2021;153:116184. doi: 10.1016/j.bone.2021.116184.
46. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2020;1;25(3):e326-e336.
47. Patel, V., Mansi, J., Ghosh, S. et al. MRONJ risk of adjuvant bisphosphonates in early stage breast cancer. Br Dent J.2018; 224, 74–9.
48. Perini, A. T., de Oliveira, G. R., and Seguin, F. Medication-related osteonecrosis of the jaw (MRONJ) treated with piezosurgery–case report and review of literature. RSBO.2018; 15(2), 123-09.
49. Kimme DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. J Dent Res 2007;86: 1022–33.

50. Kuroshima S, Sasaki M, Sawase T. Medication-related osteonecrosis of the jaw: A literature review. J Oral Biosci. 2019;61(2):99-104.
51. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral MaxillofacSurg2003;61: 1115e7
52. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, et. al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. New England Journal of Medicine. 2009;361(8), 745-55.
53. Reher P, Doan N, Bradnock B, Meghji S, Harris M. Effect of ultrasound on the production of IL-8, basic FGF and VEGF. Cytokine. 1999;11(6):416-23. doi: 10.1006/cyto.1998.0444.
54. Albisinni S, Pretot D, Al Hajj Obeid W, Aoun F, Quackels T, Peltier A, et.al. The impact of neutrophil-to-lymphocyte, platelet-to-lymphocyte and haemoglobin-to-platelet ratio on localised renal cell carcinoma oncologic outcomes. Prog Urol. 2019;29(8-9):423-31.
55. Beresford MJ, Burcombe R, Ah-See ML, Stott D, Makris A. Pre-treatment haemoglobin levels and the prediction of response to neoadjuvant chemotherapy in breast cancer. Clin Oncol (R Coll Radiol). 2006;18(6):453-8.
56. Mo CJ, Hu ZJ, Qin SZ, Chen HP, Huang L, Li S, et. al. Diagnostic value of platelet-lymphocyte ratio and hemoglobin-platelet ratio in patients with rectal cancer. J Clin Lab Anal. 2020;34(4):e23153.
57. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiodt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 2018;69:177—87
58. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. J IntSocPrev Community Dent. 2016;6(2):97-104. doi: 10.4103/2231-0762.178742.
59. Otto S, Marx RE, Tröltzsch M, Ristow O, Ziebart T, Al-Nawas B, et al. Comments on ‘‘diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus’’. J Bone Miner Res 2015;30:1113—5.
60. Schiodt M, Otto S, Fedele S, Bedogni A, Nicolatou-Galitis O, Guggenberger R, et al. Workshop of European task force on medication-related osteonecrosis of the jaw — current challenges. Oral Dis 2019;25:1815—21.
61. Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol2014;50:1049—57.
62. Carlson ER. Management of antiresorptive osteonecrosis of the jaws with primary surgical resection. J Oral MaxillofacSurg2014;72:655—7.
63. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral MaxillofacSurg2009;67:85—95.
64. Jasper V, Laurence V, Maximiliaan S, Ferri J, Nicot R, Constantinus P. Medication-related osteonecrosis of the jaw (MRONJ) stage III: conservative and conservative surgical approaches versus an aggressive surgical intervention: a systematic review. 2020 ;48(4):435-443. doi: 10.1016/j.jcms.2020.02.017.
65. Seth R, Futran ND, Alam DS, Knott PD. Outcomes of vascularised bone graft reconstruction of the mandible in bisphosphonate-related osteonecrosis of the jaws. Laryngoscope 2010;120:2165—71.
66. Paré A, Bossard A, Laure B, Weiss P, Gauthier O, Corre P. Reconstruction of segmental mandibular defects: current procedures and perspectives. Laryngoscope Invest Otolaryngol2019;4:587—96.
67. Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LF. The management of osteoradionecrosis of the jaws — a review. Surgeon 2015;13:101—9.
68. Mainous E, Boyne P, Hart G. Elimination of sequestrum and healing of osteoradionecrosis of the mandible after hyperbaric oxygen therapy: report of a case. J Oral Surg1973;31:336—9.
69. Mainous EG, Boyne PJ. Hyperbaric oxygen in total rehabilitation of patients with mandibular osteoradionecrosis. Int J Oral Surg1974;3:297—301
70. Doan N, Reher P, Meghji S, Harris M. In vitro effects of therapeutic ultrasound on cell proliferation, protein synthesis, and cytokine production by human fibroblasts, osteoblasts, and monocytes. J Oral MaxillofacSurg1999;57:409—19.
71. Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. Br J Oral MaxillofacSurg1992;30:313—8.
72. Wu G, Chen L, Zhu G, Wang Y. Low-intensity ultrasound accelerates mandibular implant bone integration in dogs with mandibular osteoradionecrosis. J Surg Res 2013;182:55—61
73. Heifetz-Li JJ, Abdelsamie S, Campbell CB, Roth S, Fielding AF, Mulligan JP. Systematic review of the use of pentoxifylline and tocopherol for the treatment of medication-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol2019;128:491e2—7e2.

Stages of MRONJ (AAOMS)	Exposed or necrotic bone	History and clinical findings	Notani et. al classification for ORNJ	Clinical features
Stage 0	No clinical evidence	Non-specific clinical and radiographic findings	Type I	ORNJ confined to dentoalveolar bone
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone	Asymptomatic with no evidence of infection	Type II	ORNJ limited to dentoalveolar bone or mandible above the inferior canal or both
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone	Associated with infection, Pain and erythema in the region of the exposed bone with or without purulent drainage	Type III	ORNJ involving the mandible below the inferior dental canal or pathological fracture or skin fistula
			Epstein et. al classification for ORNJ	**Clinical features**
Stage 3	Exposed and necrotic bone, or fistulae that probes to bone	Pain, infection, and one or more of the following: • Exposed necrotic bone extending beyond the alveolar bone region resulting in pathological fracture • Extraoral fistula, oro-antral or oro-nasal communication • Lytic changes extending to the lower border of the mandible or sinus floor	Type I	Resolved, healed; a. No pathologic fracture, b. Pathologic fracture
			Type II	Chronic persistent (nonprogressive); a. No pathologic fracture, b. Pathologic fracture
			Type III	Active progressive; a. No pathologic fracture, b. Pathologic fracture

FIGURE 1.COMPARISONS OF STAGES OF OSTEORADIONECROSIS OF THE JAW ACCORDING TO AAOMS AND MRONJ ACCORDING TO NOTANI ET AL. AND EPSTEIN ET.AL.

Abbreviations: ORNJ; osteoradionecrosis of the jaw, AAOMS; American Associations of Oral and Maxillofacial Surgeons, MRONJ; medication-related osteonecrosis of the jaw.

MRONJ STAGES	TREATMENT STRATEGIES
Stage 0	Patient education Reduction of modifiable risk factors Pain control or oral antibiotics if needed Quarterly follow-up
Stage 1	Patient education Reduction of modifiable risk factors Pain control or oral antibiotics if needed Quarterly follow-up Antibacterial mouth rinse Consider surgical debridement
Stage 2	Patient education Reduction of modifiable risk factors Pain control Frequently follow-up Symptomatic treatment with oral antibiotics Surgical debridement to relieve soft tissue irritation and infection control
Stage 3	Patient education Reduction of modifiable risk factors Pain control if needed Frequently follow-up Antibacterial mouth rinse Symptomatic treatment with oral antibiotics Surgical debridement/resection for longer term palliation of infection and pain

FIGURE 2.THE TREATMENT STRATEGIES ACCORDING TO DIFFERENT STAGES OF MRONJ

Abbreviations: MRONJ; medication-related osteonecrosis of jaw.

ORNJ STAGES	TREATMENT STRATEGIES (General)	
Stage 1	(a) Superficial alveolar bone Patient education Reduction of modifiable risk factors Conservative management (oral hygiene, analgesics, mouthwashes, antibiotics) 'Pentoclo' protocol Quarterly follow-up	(b) Profound alveolar bone or stage I with treatment failure Patient education Reduction of modifiable risk factors Conservative management (oral hygiene, analgesics, mouthwashes, antibiotics) Surgical management (local anesthesia): Gentle curettage, debridement, and sequestrectomy 'Pentoclo' protocol Hyperbaric oxygen therapy
Stage 2	(a) Mandibular alveolar canal or stage I with treatment failure Patient education Reduction of modifiable risk factors Conservative management (oral hygiene, analgesics, mouthwashes, antibiotics) 'Pentoclo' protocol Quarterly follow-up More extensive surgical resection mandibulectomy without section (nor reconstruction) 'Pentoclo' protocol Hyperbaric oxygen therapy	(b) Mandibular inferior border or stage I with treatment failure Patient education Reduction of modifiable risk factors Conservative management (oral hygiene, analgesics, mouthwashes, antibiotics) 'Pentoclo' protocol Quarterly follow-up Extensive surgical resection: mandibulectomy with section (and reconstruction using free flap)
Stage 3	(a) Pathological fracture Patient education Reduction of modifiable risk factors Conservative management (oral hygiene, analgesics, mouthwashes, antibiotics) 'Pentoclo' protocol Quarterly follow-up Conservative management, surgical management, extensive more extensive surgical resection are failed Pre and postoperative possible associations or in case of surgical contraindications: Pathological fracture "Pentoclo" protocol Hyperbaric oxygen therapy Non-validated treatments: Ultrasound therapy, Low-intensity pulsed ultrasound therapy, Shock wave therapy	

FIGURE 3.THE TREATMENT STRATEGIES ACCORDING TO DIFFERENT STAGES OF ORNJ

Abbreviations: ORNJ; osteoradionecrosis of jaw

TABLE 1.THE DIFFERENCES BETWEEN OSTEORADIONECROSIS OF JAW AND MEDICATION-RELATED OSTEONECROSIS OF JAW

DIFFERENCES

VARIABLES	ORNJ	MRONJ
ETIOLOGIC	• Occurs due to radiotherapy	• Occurs due to bisphosphonates, anti-resorptive and anti-angiogenic
CLINICAL	• Presence of pathologic fracture in later stage	• Presence of necrotic bone in later stage
RADIOLOGICAL	• Patchy radiolucent appearance with radiopaque necrotic bone islands in the radiograph	• Presence of moth-eaten appearance in the jaw bone in the radiograph
HISTOPATHOLOGICAL	• Exhibits a nonviable periosteum and no indication of reactive bone • The bone marrow spaces are replaced with fibrosis, and inflammatory cell infiltration is limited • Necrotic bone exhibits neither osteoblastic nor osteoclastic activity • Absence of Actinomyces colonies	• Exhibit a viable periosteum and even reactive bone • In the intertrabecular spaces and on the periphery of the bony trabeculae, osteoclasts with numerous intracytoplasmic vacuoles are visible • The presence of Actinomyces colonies
THEORIES OF DISEASES **MECHANISMS**	• Radiation exposure, trauma, and infection • Hypoxic-hypocellular-hypovascular theory • Fibro-atrophic theory	• Inhibition of osteoclastic bone remodeling and resorption • Inflammation or infection • Inhibition of angiogenesis
TREATMENT PRINCIPLES	• Hyperbaric oxygen therapy • Ultrasound therapy • Antifibrotic drugs, such as tocopherol and their combinations • Frequently conservative treatment is preferred	• Surgical removal of necrotic bone sequestrum should be considered

ABBREVIATIONS: ORNJ; OSTEORADIONECROSIS OF JAW, MRONJ; MEDICATION-RELATED OSTEONECROSIS OF JAW,