

DIAGNOSTIC CHALLENGES IN OSTEORADIONECROSIS OF THE JAW

Abstract

Osteoradionecrosis of the jaws (ORNJ) is a severe radiotherapy (RT) complication that occurs in 2% to 22% of individuals with head and neck cancers (HNC) who are treated with RT or concurrent chemo-RT. The accurate diagnosis of ORNJ is crucial for appropriate and prompt management. ORNJ at various stages may mimic osteomyelitis, medication-related osteonecrosis of the jaw (MRONJ), and tumor recurrence due to the effects of RT on irradiated tissues and the clinical and radiological features of ORNJ. Image analysis techniques such as panoramic imaging (PI), computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, positron emission tomography (PET), and single photon emission CT (SPECT) might help to avoid diagnostic obstacles. Despite the fact that the general characteristics of ORNJ have been reported in the literature, there is no clear consensus on its definitive diagnosis. Therefore, the current review aims to address ORNJ and its clinical and radiological aspects, as well as provide evidence to inform on the approaches to be used in removing the complexity in diagnosis, with a specific focus on radiological and nuclear medicine techniques.

Keywords: Radiotherapy, toxicity, osteoradionecrosis, jaw, diagnostic challenges.

Introduction

Head and neck cancers (HNCs) are rising globally, accounting for approximately 900,000 cases per year and ranking seventh among the most prevailing cancers (1,2). Laryngeal and hypopharyngeal, nasal cavity and paranasal sinuses, nasopharyngeal, oral and oropharyngeal, and salivary gland cancers constitute 4% of all cancers in the United States and Europe (3, 4). Reports from Asia have shown that HNCs are responsible for roughly 5% of all cancer fatalities on this continent (5). In parallel to the advancements in radiation delivery and planning systems, radiotherapy (RT) has established itself as an efficient but less toxic (than past) therapeutic option in the treatment of HNCs, with almost 75% of these patients receiving curative, adjuvant, or palliative RT (6). Nonetheless, this successful therapeutic procedure may result in osteoradionecrosis of the jaw (ORNJ), a detrimental complication of RT (7).

Although many researchers have defined ORNJ, it was originally documented clinically by Regaud in 1922 and stipulated as one of the most serious problems in radiation oncology practice (8). Eiving only introduced the term "radiation osteitis" to describe this condition in 1926. (9). In the 1970s, Meyer characterized ORNJ as a triad of radiation, trauma, and infection, but made no reference to septic destruction of avascular tissue (10). On the other hand, Guttenberg emphasized the significance of microorganisms in the pathogenesis of ORNJ and referred to the condition as septic ORNJ (11). Marx introduced the "three H" principle in the years that followed, and it was acknowledged as being crucial to the pathophysiology of ORNJ (12). Accordingly, the definition of ORNJ stated that it developed as a result of cellular and metabolic changes in radiation-induced hypoxic-hypovascular-hypocellular tissues, together with associated tissue loss and non-healing wounds. Epstein used the term of "RT-induced osteonecrosis" for ulceration or necrosis of mucous membranes exposed to necrotic bone for more than three months (13). Although there is no explicit consensus, the current widely acknowledged ORNJ definition describes it as a late

RT complication characterized by a necrotic process occurring in the jawbone, persisting for 3-6 months or longer in the irradiated site without tumor recurrence, non-healing, pain, denuded bone, purulent drainage, and mucosal and/or cutaneous fistula (12, 14, 15).

According to many studies, the frequency of ORNJ in HNCs ranges from 2% to 22%. (13, 16-20), which is significantly more prevalent in the mandible than in the other bones in this location (19-23). The fundamental explanation for this discovery is that the mandible has one-sixth the vascular supply of the maxilla (21-23). The additional, although less important, factor might be that the jaw is more frequently encompassed in the radiation portal and receives larger RT doses than the maxilla (24). Because of its critical location, such a gradual and frequently permanent RT problem has serious ramifications for the affected patients' functioning. The ORNJ has been found to influence patients' vital functions like swallowing, speech, and mastication via triggering discomfort, deformity, limited mouth opening, mucosal fistula development, and pathological fractures (25-28). ORNJ may cause anemia, inflammatory infections, leukocytosis, hyperproteinemia, and hypercoagulation, rendering oncologic treatment more difficult in HNC patients (28). Furthermore, ORNJ has a severe impact on the quality of life (QoL) of long-term HNC survivors (29), and the emergence of trismus and numbness following ORNJ therapy worsens QoL measures even more. Also, dietary restrictions, eating in public, speech intelligibility, halitosis, and an inability to communicate can all result in much lower QoL. (30-32).

For all the aforementioned reasons, an early and accurate ORNJ diagnosis is critically important for the best patient care in HNC. The conclusive exclusion of local tumor recurrence, particularly in a suspected case of ORNJ, is one of the primary diagnostic mysteries, in addition to the problems in the proper diagnosis of ORNJ (33). Furthermore, radiological evidence of ORNJ may be inconspicuous in both the very advanced and early phases of disease. As a result of the difficulty in correctly identifying the ORNJ itself and its

extent, clinicians may face a perplexing image of the situation, which will act as the principal determinant of the therapy required by the disease state. Therefore, addressing the existing complexities in ORNJ diagnosis is crucial for customizing traditional therapy techniques and developing cutting-edge management strategies (15). The present review is intended to focus primarily on the diagnostic challenges of ORNJ, which may serve usefully in the choice and timely onset of fitting preventive and therapeutic maneuvers in the radiation oncology and dentistry clinics.

Risk Factors for ORNJ Development

Recognition of the ORNJ risk factors may lower the risk of ORNJ through the timely application of preventive measures and improve its prognosis via the prompt initiation of necessary interventions in HNC patients receiving RT or CCRT. The most salient risk factors for the development of ORNJ were notably linked to RT dosage and method as well as pre-RT and post-RT tooth extractions in the existing literature (7, 34, 35). The investigation by Chrcanovic and colleagues identified additional risk factors for the occurrence of ORNJ, including pre-RT bone surgery, the size, location, and stage of the tumor, its proximity to the bone, poor oral hygiene, alcohol use, smoking, the absence of hyperbaric oxygen therapy (HBO), and improper handling of radiation shields (36). Additionally, it has been reported that using bisphosphonates in conjunction with chemotherapy and antiangiogenic agents may further increase this risk (37, 38).

Factors related to radiation dose and technique

The consensus is that as the maximal dose of RT to the mandible increases, so does the likelihood of ORNJ formation (23, 39-41). ORNJ development has been associated with maximal RT doses higher than 60-75 Gy in several studies (40, 42, 43). Therefore, it was advised to minimize the mandibular volumes that get high doses and to reduce potentially

dangerous hot spots in the jaw in order to prevent the emergence of ORNJ (43, 44). Modern IMRT technology enables more acceptable dosage reductions, better preservation of healthy tissues, and a reduced occurrence of ORNJ (45). Tsai et al. discovered that three-dimensional conformal radiation (3D-CRT) patients had a higher incidence of ORNJ than IMRT patients (6.3% vs. 13%, $P = 0.07$). (46). Moon et al. postulated that employing IMRT would reduce toxicity in the mandible and verified this hypothesis by finding a significantly reduced incidence of ORNJ in IMRT patients compared to 3D-CRT (19% vs. 4.0%, $P = 0.01$) (47). Proton therapy is an advanced form of RT, in which the prescribed dose is transferred along a Bragg peak. Intensity-modulated proton treatment (IMPT) is a more sophisticated form of proton therapy in which the tumor is targeted using various shaping techniques and beam modulation while the harm to surrounding normal tissues is minimized (34). Zhang et al. (48) revealed that the lower mandibular doses delivered by IMPT compared to normal IMRT reduced the ORNJ risk in oropharyngeal cancer patients from 7.7% to 2.0% ($P < 0.05$).

Factors related to dental risk

Providing oral care before RT or CCRT for HNC patients could be considered the initial step in minimizing complications in the oral cavity and related structures (7, 24). This viewpoint is reinforced by the fact that RT induces osteoblast and cementoblast loss with microvascular damage. Additionally, bacterial toxins in tooth plaque contribute to this condition, including caries and periodontal diseases (49, 50). The two major risk factors for ORNJ are dental decay and periodontal disease, both of which can harm teeth and require extractions in the irradiated area (51-53). Furthermore, RT may cause dental caries, prompting tooth extractions, as well as changes in oral flora and impaired salivary gland activities (54, 55).

Tooth extraction in HNC patients is a risk factor for ORNJ (34), with mandibular teeth enduring radiation doses of more than 60 Gy being the most significant risk (56). An increased need for extractions during the riskier post-RT periods may result from failing to

perform prophylactic tooth extractions before the RT (57). Even though a strong link between ORNJ risk and post-RT tooth extractions has been well documented in the literature, other researchers found that pre-RT traumatic tooth extractions also carried a significantly elevated risk of ORNJ (21, 58). Therefore, it is advised to perform any extraction as soon as is practical before RT, using atraumatic or minimally traumatic procedures, and to use prophylactic peri- and post-interventional antibiotics to reduce the risk of ORNJ associated with tooth extractions (56, 59, 60).

Classification of ORNJ

The lack of a standardized staging approach is one of the difficulties in making an accurate diagnosis, although several researchers have proposed various ORNJ staging methods (12, 25, 61–65). In HNCs undergoing RT, Coffin classified the ORNJ into minor and major forms in 1983. (61). The minor form is composed of microscopic sequestrum that could not be radiographically shown but were clinically evident. The major ORNJ form was established when a pathologic fracture was identified clinically and radiologically due to necrosis. Marx proposed a three-stage protocol for ORNJ based on how patients responded to treatment with HBO and surgery in the same year. Stage 1 of the procedure responds to HBO therapy, while Stages 2 and 3 call for sequestrectomy and HBO therapy. With an extraoral fistula, a pathological fracture, and extension to nearby anatomical areas, stage 3 is deficient and catastrophic (12). Morton and Simpson classified ORNJ into minor, moderate, and major categories in 1986 based on the requirement for surgery, the degree of sequestration, and the length of the recovery period (62). In 1987, Epstein created the ORNJ three-phase system for assessing disease severity, clinical symptoms, and the presence of pathological fractures (63). Ten years later, Clayman divided ORNJ into two types: Type 1, which can be treated conservatively, and Type 2, or "radiation osteomyelitis," which cannot be treated conservatively (64). In the years afterwards, Schwartz and Kagan have reinterpreted the

degree of bone involvement (65). And finally, Notani et al. have described a staging ORNJ associated with the alveolar bone and canal (25): Stage I: ORNJ confined to dentoalveolar bone, Stage II: ORNJ limited to dentoalveolar bone or mandible above the inferior dental canal, or both, and Stage III: ORNJ involving the mandible below the inferior alveolar canal, or pathological fracture, or skin fistula.

Diagnostic methods

Although the diagnosis of ORNJ is mostly based on mucous membrane ulcers with clinically visible exposure of necrotic bone, radiographic investigations disclose critical features in overcoming diagnostic obstacles. It should be emphasized that radiological findings alone may not be sufficient to diagnose ORNJ in circumstances when tissue changes are not evident in the relevant location. To overcome the difficulties in diagnosis, both clinic and radiologic evidence should be evaluated simultaneously (34, 36). As a result, in order to establish a definitive diagnosis of ORNJ, the RT process and the patient's dental history and exams, panoramic radiographs and computed tomography (CT) scans, as well as other sophisticated imaging modalities, a biopsy of the lesion, and the disease stage should all be considered. Furthermore, the occurrence of primary or secondary malignancies should be ruled out (66-68).

Clinical evaluation

Pain, one of the clinically debilitating signs of ORNJ, may pose a diagnostic problem (15, 36, 69), since it may be present in some instances but not in others (70). Furthermore, due to sensory nerve fiber loss, pain may be absent in late-stage ORNJ. As a result of various neurological disorders associated to ORNJ, dysesthesia and anesthesia should be explored during clinical evaluation. Patients frequently complain of halitosis and dysgeusia. A thorough intraoral examination may aid with the diagnosis, since the uneven surface and sharpened-edge bone in the gingiva suggest ORNJ. In such circumstances, surrounding soft

tissue destruction can also be seen. In the diagnosis of advanced ORNJ, local or systemic infections and trismus may accompany the clinical picture in which pathological fracture, intraoral or extraoral fistulas are evident (71-73).

The clinical similarities between ORNJ and MRONJ pose a significant diagnostic challenge (69). Both ailments have a low incidence (2-22% for ORNJ vs. 0.001-7% for MRONJ), are usually confined to the mandible, and share many clinical features, such as presence of pain, exposed bone, and intraoral or orocutaneous fistula (13, 16-18, 74, 75). Furthermore, no pathognomonic histologic characteristic has been established to distinguish MRONJ from ORNJ (69). Nonetheless, the following considerations may help resolving this ambiguity in diagnosis (69, 74, 75):

- Patients with MRONJ are usually older than those with ORNJ.
- MRONJ occurs more frequently in the maxilla than ORNJ.
- ORNJ has a higher rate of pathological fractures than MRONJ.
- The existence of primary or recurrent tumor should be ruled out histologically

for the accurate diagnosis of ORNJ.

A careful and detailed medical history is the most useful tool in differential diagnosis, owing to the fact that MRONJ is associated with antiresorptive or antiangiogenic medication therapy and ORNJ with RT or CCRT.

Radiological evaluation

For the diagnosis and assessment of ORN, the imaging modalities of choice are commonly panoramic imaging (PI), cone-beam computed tomography (CBCT), and computed tomography (CT) (34). Magnetic resonance imaging (MRI), bone scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET) are among recommended imaging methods (15, 36).

The first important problem in diagnosing ORNJ radiologically is that the disease may not manifest in the early stages (15). Furthermore, radiological findings may not indicate the full severity of the disease (8, 76). The ORNJ region may appear normal at first, or it may develop into isolated or extensive osteolytic sites, sequestration, and pathological fractures (15). The precise alteration that may be seen in the early phase, however, is an increase in radiodensity and the mixed radiopaque/radiolucent lesion areas, indicating bone destruction. An early change seen in the outer cortical plate of the mandible is a sharply bounded bone resorption. Jaw fractures can be seen, when the bone's normal structure is substantially compromised. Particularly in the posterior mandible, which has typically less vascularization than the maxilla, early changes of ORNJ can be recognized. There may be spots of atypical bone resorption and sclerosis with vague non-cortical margins (70).

Radiolucent post-extraction sockets can be followed for more than a year in the images examined (8,15). Another difficulty is that bone loss and sclerosis found in ORNJ may be mistaken as periodontal disease. The final radiological examination of ORNJ is dependent on the identification of the sequestrum, in addition to the patient's past medical history. The sequestrum is defined as isolated cortical bone pieces and is most typically found in the mandible. Because the imaging findings of ORNJ are similar to those of osteomyelitis, a CBCT or CT scan is advised to locate the sequestrum. Pathological fracture alone does not provide an unequivocal diagnosis. In such circumstances, it will be useful to employ additional imaging modalities (70).

Panoramic Imaging (PI)

PI, which is often employed in regular dental checkups, is widely acknowledged as the first step in imaging procedures used to diagnose ORNJ (15, 34). Intraoral and extraoral radiographs are used to support PI, providing for two-dimensional examination of both jaws (15, 77). The presence of a sequestrum, radiolucency without discernible sclerotic boundaries

encircling a region of necrotic bone, or a radiodense area in low-density tissue are all signs of ORNJ in the PI (13, 33). The sequestrum, which represents the necrotic bone fragment, is radiopaque. However, it may be distinguished in PI by pronounced alterations in the mineral composition of bone created in later stages of ORNJ (13). Enlargements of the periodontal ligament space along the apex of the teeth exposed to mandibular doses more than 45 Gy are seen in particular. This may, on the other hand, be related with numerous periodontal disorders and does not confirm the presence of an ORNJ (70, 77). Furthermore, whereas PI can reveal pathological fractures, identifying the sequestrum is required to establish the diagnosis of ORNJ (70).

Because of their radiological similarities, osteomyelitis and MRONJ are included in the differential diagnosis of ORNJ. Gaêta-Araujo et al. examined the radiological characteristics of osteomyelitis, ORNJ, and MRONJ, all of which are osteonecrotic lesions, and concluded that while PI had a predictive value of 74%, it may be insufficient in separating the diseases. Only permitting two-dimensional assessments, intrinsic magnification and distortion of the images in PI, and a lack of formalized follow-up all contribute to flaws in evaluating the characteristics and phases of the ORNJ (78).

Cone beam computed tomography (CBCT)

Dental CBCT is a type of x-ray machine that is utilized when standard dental or face x-rays are insufficient. Using this technique, physicians can get three-dimensional (3-D) images of teeth, soft tissues, nerve pathways, and bone all in one scan. In comparison to conventional CT, CBCT delivers volumetric imaging of the bone structures of the craniofacial area at lower doses and costs. Although CBCT imaging may not ensure ample soft tissue contrast, it does provide precise information regarding the morphological aspects and extent of lesions. It can be used to determine the amount of osteomyelitis in the differential diagnosis of cysts, tumors, and ORNJ (70). The use of CBCT in the investigation of ORNJ allows for the assessment of

lytic changes, cortical bone resorption, and surrounding structures (34). Sclerotic areas, pathological fractures, and sequestrum are all shown by CBCT, which is critical for an accurate diagnosis. CBCT can distinguish osteomyelitis from ORNJ and MRONJ, and the predictive value between these three lesions has been shown to be 90%. When characterizing necrotic regions, CBCT provides better detail than PI. Furthermore, CBCT examination may aid in differential diagnosis by detecting greater periosteal bone growth in MRONJ than in ORNJ, and cortical bone resorption rather than osteomyelitis in ORNJ (78). The use of CBCT assists in identifying necrosis from other suspected cases of osteolysis (75). In essence, given all of these important properties, CBCT provides reliable results in the detection of bone disorders (78).

Computed tomography (CT)

Cortical discontinuity, osteolysis, changes in trabecular structure, thickening of soft tissues, pathological fractures, and bone sequestrum are among the CT findings of ORNJ (15, 36). One of the distinguishing characteristics of the disease on a CT scan in the latter stages of ORNJ is loss of bone trabeculae in bone cancellous with bicortical involvement. On CT scans, the lesion appears as gas bubbles that might represent an infectious process that is pathognomonic for osteomyelitis (33, 79). To rule out the likelihood of a tumor recurrence or second primary cancer, any development in the soft tissue nearby should be an indication of primary or second cancers (33). When bone sclerosis and permeating trabeculation are seen on a CT scan, ORNJ can be distinguished from these conditions (80). Cortical defects that are localized far from the underlying tumor enhance ORNJ diagnosis (81).

ORNJ-related cortical discontinuities may be seen on the buccal or lingual side of the jaw, as well as on both sides. The presence of discontinuities in both lingual and corresponding buccal cortex is widely recognized as an indication of a jaw fracture (82). Due to the three-dimensional character of CT compared to PI, bone alterations in the anterior-

posterior direction and involvement of the buccal or lingual cortex are more obvious. Additionally, PI is unable to distinguish between lingual and buccal bone deterioration, which can easily be detected by CT (81, 83). A fusiform swelling clarifies soft tissue thickening around the pathological fracture. In the absence of a pathological fracture, the lesion is restricted to bone degradation (82). Mandibular bone destruction in the absence of soft tissue involvement simplifies ORNJ diagnosis (84). Because advanced ORNJ frequently includes soft tissue swelling, the differential diagnosis with tumor recurrence is complicated. However, it may be helpful to know that a malignant squamous cell carcinoma commonly causes damage in the alveolar process or through the lingual cortex to aid in the diagnosis (82). ORNJ also differs from tumor recurrence in that, whereas recurrences occurs usually during the first two years of treatment, there is a longer period of time between original tumor therapy and ORNJ formation, with a median ORNJ development gap following RT or CCRT of nearly three years (85).

Magnetic resonance imaging (MRI)

MRI is a non-invasive technique to identify interior structures, distinguish between soft and hard tissues, and examine various bodily functions. The basic idea underlying MRI is to produce high-quality cross-sectional images of the body by using non-ionizing radio frequency electromagnetic radiation in the presence of regulated magnetic fields. MRI has better tissue contrast and higher spatial resolution than other imaging techniques (86). With aberrant, homogenous, low marrow signal intensity on T1-weighted images and increased signal intensity on T2-weighted images, MRI reveals altered bone marrow in the ORNJ site (85, 86). Because the masticatory muscles nearby the lesion have thickened, MRI has the benefit of detecting ORNJ earlier than CT. But, it is challenging to make a diagnosis, since the muscle thickening might signify a tumor recurrence as well. Consequently, the utilization of CT imaging may aid in overcoming this difficulty (82). Cortical damage, an aberrant bone

marrow signal, and a modest to moderately uneven contrast enhancement are all visible on gadolinium-enhanced MRI scans of the ORNJ (87, 88). MRI with dynamic contrast is additionally useful because it can demonstrate quantitative differences in vascular leakage at ORNJ locations (89).

Bone scintigraphy, Single photon emission computed tomography (SPECT), and Positron emission tomography (PET)

Bone scintigraphy is utilized to pinpoint the location and severity of the illness since it has a sensitivity of up to 100% in the diagnosis of ORNJ (86). Early-stage ORNJ can be detected via bone scintigraphy employing ^{99m}Tc-marked diphosphonates (^{99m}Tc-MDP), and depending on altered phosphate metabolisms, it may signify osteoblastic activity and healthy blood flow (90). However, this imaging technique has limited spatial resolution and soft tissue over-projection, whereas SPECT removes these drawbacks (86). Three-phase bone scintigraphy, according to Lapa et al., demonstrated an enhanced homogenous bone metabolism caused by inflammatory processes in instances with ORNJ, and late phase SPECT was adequate for ORNJ diagnosis (91). Inflammatory soft tissue or tumor recurrence are shown by PET/CT. PET/CT shows both hypermetabolic bone marrow and increased glucose metabolism. However, localized changes in clearance rate, vascular perfusion, permeability, and chemical bonding have an impact on both PET/CT and SPECT pictures (92). Additionally, when osteomyelitis is present, it may be difficult to discern between soft tissue and bone involvement. For a conclusive diagnosis of tumor recurrence, an incisional biopsy is advised for indiscernible cases (93). However, to prevent the development of a fistula track, the biopsy method must be as minimally invasive as possible.

Discussion

ORNJ is a dreaded consequence of RT or CCRT affecting the mandibular bone, but there is no broadly acknowledged consensus in the literature on a definition of the disorder.

Furthermore, the lack of a consistent classification makes comparing clinical findings and outcomes across research problematic. The diagnosis of ORNJ is also difficult since there is no broad agreement on its specific diagnostic criteria. Therefore, due to the lack of a specific staging system and clinical risk factors that correspond to ORNJ diagnostic criteria, as well as the inability to create a general radiographic diagnosis guideline using the data at hand, the literature presented here displays that diagnosing ORNJ presents glaring difficulties. These challenges were demonstrated by the findings of a review of 12 published articles that attempted to define ORNJ. In this study, Wong et al. found that the only characteristic that all of the papers had in common was clinical exposure to the non-vital bone (94).

Although the clinically observed exposure of necrotic bone in the previously irradiated area and ulceration of the mucous membrane form the basis of the recognized fundamental description of ORNJ in the literature, examples of ORNJ with radiologically necrotic but intact mucosa have been documented (12, 14, 40, 63, 95). Owosho et al. included ORNJ patients with only radiological evidence of necrosis in their staging method, suggesting that this illness might be neglected if just the crucial clinical diagnosis is used, and that radiological findings have a significant influence on both diagnosis and staging (63). Miyamoto et al. examined the diagnostic component of ORNJ by combining clinical symptoms with imaging modalities CT, MRI, PET/CT, bone scintigraphy, and SPECT in a cohort of 57 locations in 54 patients with a history of RT and suspected ORN. In this investigation, diagnostic imaging examinations showed long-term RT-related bone marrow degeneration on MRI and sclerotic alterations in 82% of the bone marrow on CT. The efficacy of these techniques in diagnosis was proven in the same study, with PET/CT revealing involvement surrounding the symptomatic bone and SPECT identifying the ORNJ lesion uptake (93).

In addition to bone sclerosis caused by RT-induced damage, the ORNJ genesis process also includes hypovascularization, hypoxia, and fibrosis that are brought on by abnormal bone marrow changes. (7, 41, 80, 93). Additionally, one of the symptoms of ORNJ, trismus, may be brought on by inflammation and fibrosis in the nearby masticatory muscles (96). Thus, by displaying abnormalities in bone and soft tissue and supporting the clinical scenario, the combined use of CT and MRI in the diagnosis of ORNJ may serve as the most reliable radiological tool to overcome the diagnostic obstacle (93). RT can lessen or even halt periosteal reactions in patients with ORNJ (93, 97, 98), whereas periosteal reactions frequently last a long time in MRONJ patients (97, 98). As a result, CT evaluation of the periosteal responses in RT locales may help to clarify the ORNJ and MRONJ enigmas, which have similar clinical manifestations. Advanced ORNJ-related neurological symptoms may be a precursor to primary or secondary malignancies, as well as MRONJ. Biopsies guided by PET and SPECT imaging are recommended for a definitive diagnosis in such cases (93). In order to lower the risk of fistula tract formation, the biopsy procedure should be as minimally invasive as possible.

The emergence of a necrotic bone, such as ORNJ in osteomyelitis, is another source of consternation. However, in ORNJ, the periosteum is permanent and there is no reactive bone, whereas in osteomyelitis, both the periosteum and the reactive bone are viable. The therapeutic radiation energy received by the initial ORNJ site in the bone is expected to cause far more severe symptoms and tissue destruction than chronic osteomyelitis (99). Although CBCT examination of lesion details is advised, MRI will be the appropriate imaging modality to assess soft tissues in the case of ORNJ due to the lack of radiation exposure in MRI examinations (33, 100).

Conclusion

Finally, to reliably identify ORNJ in HNC patients, selecting the most suitable imaging modalities in accordance with their clinical characteristics may help to accurately demonstrate the lesion and its bony or soft tissue extensions. Robust, multi-institutional, and prospective data examining all facets of ORNJ are needed to resolve the complex diagnostic enigma. A comprehensive diagnosis of ORNJ and its severity appears to benefit from collaboration between clinical findings, CT/MRI, and biopsy, according to the evidence in the literature that is currently accessible.

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Figure Legends

Figure 1. Panoramic radiography of the left mandibular posterior region shows the sequestrum of osteoradionecrosis (red arrows).

Figure 2. In the axial cone beam computed tomography section of the left mandibular posterior region, the sequestrum of osteoradionecrosis is observed (red arrows).

Tables

Table 1. The most commonly used classifications of osteoradionecrosis

Researcher(s)	Year	Principle of classification	Characteristic of classification
Marx (12)	1983	Response to management with HBO therapy and surgery	I: Responds to HBO therapy II: Requires HBO therapy and sequestrectomy III: Requires HBO therapy and advances surgical resection, also presented with pathological fracture, cutaneous fistula, and radiologically

			profound resorbed site.
Epstein et al. (63)	1987	*Clinical presentation and level of disease	I: Recovering II: Non-progressive, chronic disease III: Progressive, active disease
Notani et al. (25)	2003	The association of the disease with the alveolar bone and canal	I: Circumscribed to superficial alveolar bone II: Circumscribed to alveolar bone and above the level of the mandibular canal, involving the mandibular cortex and medullary bone III: Involving the mandible below the inferior alveolar canal, or pathological fracture, or skin fistula

* Divided into secondary groups to indicate the absence or presence of pathological fracture.

Abbreviation: Hyperbaric oxygen; HBO.

Table 2. Radiological findings of osteoradionecrosis in different imaging techniques

Imaging technique	Point of reference	Radiological findings
PI	Bone alterations	Sclerotic boundaries Sequestrum Pathological fracture
CBCT	Bone alterations	Lytic changes Cortical bone resorption Sclerotic areas Pathological fracture Sequestrum

CT	Bone alterations	Cortical discontinuity Osteolysis Changes in trabecular structure Lingual and buccal bone deterioration Pathological fractures Sequestrum Bone sclerosis
MRI	Bone marrow alterations	Aberrant, homogenous, low marrow signal intensity on T1-weighted images Increased signal intensity on T2-weighted images
	Muscular differences	Masticatory muscles thickening
Bone scintigraphy, SPECT	The efficiency of bone metabolic	Altered phosphate metabolisms Enhanced homogenous bone metabolism
PET	Bone marrow and glucose metabolism activity	Hypermetabolic bone marrow Increased glucose metabolism Inflammatory soft tissue or tumor recurrence

Abbreviations: PI, Panoramic imaging; CBCT, cone beam computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission CT.

Figures

Figure 1



Figure 2

