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Challenges in the Radiological Diagnosis of Osteoradionecrosis of the Jaw in Head and Neck Cancer Patients

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Abstract: One of the most common and severe side effects of radiotherapy or concurrent chemo-radiotherapy for head and neck cancers is osteoradionecrosis of the jaws, which affects 2–22% patients. Correct diagnosis is crucial for the effective and timely management of osteoradionecrosis of the jaws. However, various stages of osteoradionecrosis of the jaws resemble osteomyelitis, medication-related osteonecrosis of the jaw, or tumor recurrences, challenging the diagnostic certainty. The clinical and radiological resemblance of osteoradionecrosis of the jaws to these non-radiotherapy-related conditions are the main contributors to this challenging situation. Nevertheless, it may be possible to avoid diagnostic roadblocks by using image analysis methods such as orthopantomography, computed tomography (CT), magnetic resonance imaging, bone scintigraphy, positron emission tomography, and single-photon emission CT (SPECT). There is no widely accepted consensus on the precise diagnosis of osteoradionecrosis of the jaws, although its general characteristics have been reported in the literature. The current chapter covers osteoradionecrosis of the jaws and its clinical and radiological features and provides information on relevant strategies to be used for an accurate diagnosis, with a specific emphasis on radiological and nuclear medicine techniques.

Keywords: diagnostic challenges; head and neck cancer patients; osteoradionecrosis of the jaw; radiological diagnosis; radiotherapy

INTRODUCTION

With approximately 900,000 cases per year, head and neck cancer (HNC) is the seventh most common cancer worldwide, and its prevalence is increasing (1, 2). In the United States and Europe, cancers of the larynx, hypopharynx, nasopharynx, oropharynx, oral cavity, nasal cavity, paranasal sinuses, and salivary glands account for 4% of all cancer cases (3, 4). According to Asian reports, HNCs are responsible for about 5% of all cancer deaths in the peninsula (5). With advances in radiation delivery and planning systems, radiotherapy (RT) has become an effective but less toxic (than before) treatment option for treating HNC, with approximately 75% of patients receiving curative, adjuvant, or palliative RT (6). Unfortunately, this effective treatment can lead to osteoradionecrosis of the jaw (ORNJ), a serious complication of RT (7). Although newer, more innovative RT techniques such as three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), and intensity-modulated proton therapy (IMPT) have reduced the risk of ORNJ due to improved tissue-sparing properties, ORNJ still occurs in a substantial number of HNC patients depending on the radiation doses received by the nearby or involved mandibular bone (8).

Regaud was the first to clinically record ORNJ in 1922 (9). He called it one of the most detrimental issues in the practice of radiation oncology. In 1926, Eiving coined the term “radiation osteitis” to describe this condition (10). Meyer referred to ORNJ in the 1970s as a triad of radiation, trauma, and infection, but he left out the septic destruction of avascular tissue (11). Guttenberg (12) contrasted this, emphasizing the part played by microorganisms in the pathogenesis of ORNJ and referring to the condition as septic ORNJ. Later, it was acknowledged

that the "three-H" principle, which Marx introduced in the years that followed, was crucial to the pathophysiology of ORNJ (13). With this in mind, the modern definition of ORNJ states that it is caused by radiation-induced cellular and metabolic changes in hypoxic, hypovascular, and hypocellular tissue, as well as tissue loss and non-healing wounds. "RT-induced osteonecrosis" was a term coined by Epstein to describe ulceration or necrosis of mucous membranes exposed to the necrotic bone for more than three months (14). The fibroatrophic processes involved in the pathogenesis of ORNJ were subsequently described by Delian and Lefaix (15), while Lyons and Ghazali (16), and Bras et al. (17) proposed a theory linking fibrosis to vascular changes. The widely accepted ORNJ definition, which is currently used, despite the lack of a clear consensus, describes it as a late radiation complication that affects the jawbone and is characterized by a necrotic process that lasts for 3–6 months or longer in the radiation-damaged area. While facial or mandibular pain, purulent drainage, and mucosal and/or cutaneous fistula may be present, the absence of tumor recurrence/progression or metastasis is required to diagnose ORNJ (13, 18, 19). Numerous studies (14, 20–24) have shown that ORNJ is present in HNCs at frequencies ranging from 2% to 22%. Compared to the other facial bones, the mandible has a significantly higher prevalence of ORNJ (23–27). The mandible's vascular supply is only one-sixth that of the maxilla's centripetal blood supply, which provides a rational justification for this discovery (25–27). Another, conceivably less vital, issue is that the jaw is more frequently encased in the radiation portal and receives higher RT doses than the maxilla (28). Unfortunately, due to the critical positioning of the mandible, patients may experience severe functional impairments as a result of a gradual and typically permanent RT problem. ORNJ influences patients' vital functions such as swallowing, speech, and mastication by causing discomfort, deformity, limited mouth opening, mucosal fistula development, and pathological fractures (29–32). Patients with HNC who have ORNJ may experience anemia, inflammatory infections, leukocytosis, hyperproteinemia, and hypercoagulation, making the delivery of oncologic therapy more challenging (32). Furthermore, the additional emergence of trismus and numbness following ORNJ therapy may further worsen the quality of life (QoL) of such patients if they survive long enough (33). Additionally, dietary restrictions, eating in public, speech comprehension, halitosis, and lack of communication skills can all lead to a significantly lower QoL (34–36).

For all reasons already stated, the optimum treatment of HNC patients depends, without any doubt, on a prompt and accurate ORNJ diagnosis. In this setting, one of the most notable diagnostic challenges is the definitive exclusion of local tumor recurrence, particularly in a suspected case of ORNJ (37). Additionally, in the very early and advanced stages of the disease, radiological evidence of ORNJ may be indiscernible. Clinicians may encounter a perplexing picture of the situation due to the challenges in accurately identifying the ORNJ and its extent, which is the primary determinant of the necessary therapy. To customize conventional therapy methods and create cutting-edge management strategies, it is essential to address the current complexity of ORNJ diagnosis (19). The main goal of this chapter is to provide an evidence-based discussion on the diagnostic issues associated with ORNJ, which may facilitate the choice and prompt implementation of appropriate preventative and therapeutic interventions in radiation oncology and dental clinics.

RISK FACTORS FOR THE DEVELOPMENT OF ORNJ

Several patients- and treatment-related risk factors have been postulated for ORNJ development. Understanding the ORNJ risk factors may help to lower the risk of ORNJ through the early implementation of preventative measures and to improve the prognosis of ORNJ through the prompt initiation of necessary therapies. According to the available research, the most relevant risk factors for the formation of ORNJ were pre- and post-RT tooth extractions, RT doses, and the RT technique (7, 8, 38). Chrcanovic and colleagues' investigation found additional risk factors for developing ORNJ, including pre-RT bone surgery, size, location, stage of the tumor, the proximity of the tumor to the bone, poor oral hygiene, alcohol use, smoking, the lack of hyperbaric oxygen therapy (HBO), and improper handling of radiation shields (39). Additionally, an increased risk of ORNJ has been linked to the use of bisphosphonates and antiangiogenic medications along with chemotherapy (40, 41).

Radiation dosage and technique-related risk factors

The general view is that the chance of ORNJ development increases as the maximum dosage of RT to the mandible increases (27, 42–44), particularly at doses higher than 60–75 Gy (43, 45, 46). It has been amply demonstrated that the risk of ORNJ can be reduced by minimizing dangerous hot spots and high-dose-receiving mandibular volumes (46, 47). A lower incidence of ORNJ may result from more drastic dose reductions in healthy tissues, such as the mandible, made possible by contemporary IMRT technology (48). According to Tsai et al., ORNJ was more prevalent in patients treated with 3D-CRT than with IMRT (6.3% vs. 13%, $P = 0.07$) (49). Moon et al.'s hypothesis that using IMRT would reduce toxicity in the mandible was confirmed when they discovered that ORNJ was much less common in IMRT patients than in those receiving 3D-CRT (19% vs. 4.0%, $P = 0.01$) (50). Proton therapy is an advanced form of RT in which the prescribed dose is transferred along a Bragg peak. A more advanced form of proton therapy, known as IMPT, targets the tumor while minimizing damage to nearby healthy tissues using various shaping techniques and beam modulation (8). In oropharyngeal cancer patients, lower mandibular doses delivered by IMPT as opposed to conventional IMRT decreased the ORNJ risk from 7.7% to 2.0% ($P < 0.05$), according to Zhang et al. (51).

Dental risk factors

Because RT causes osteoblast and cementoblast loss as well as microvascular damage, furnishing HNC patients with oral care before RT or concurrent chemoradiotherapy (CCRT) might be considered as the first step in lowering the rates of complications in the oral cavity and adjacent tissues (7, 28). Bacterial plaque toxins, dental caries, and periodontal disorders, which might compromise tooth structure and necessitate extractions in the irradiated region, are the primary risk factors for ORNJ (52–56). Additionally, RT may lead to alterations in oral flora and decreased salivary gland activity, which may cause cavitated dental damage, necessitating extractions, a well-established risk factor for ORNJ (57, 58).

It is undeniable that tooth extraction causes higher ORNJ in HNC patients (8), with radiation doses to the mandibular teeth exceeding 60 Gy posing the greatest risk (59). There may be an increased need for extractions during the riskier post-RT period if preventive tooth extractions are not carried out before the RT (60). Despite a well-established association between ORNJ risk and post-RT tooth extractions in the literature, some researchers discovered that pre-RT traumatic tooth extractions also carried a noticeably increased risk of ORNJ (25, 61). Hence, it is preferred to execute 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 (59, 62, 63).

GRADING SYSTEMS FOR ORNJ

One of the challenges in ORNJ practice is the lack of a standardized staging approach, despite several researchers having proposed various ORNJ staging methods (13, 18, 29, 64–69). In 1983, Coffin divided ORNJ in HNC patients undergoing RT into minor and major types (64). The minor form refers to microscopic sequestrum that is clinically obvious but cannot be provable on a radiograph. The major ORNJ form is established when a necrotic pathologic fracture is seen on both radiographs and in clinical examination. As shown in Table 1, Marx suggested a three-stage protocol for ORNJ based on how patients responded to HBO therapy and surgery. Stages 2 and 3 ORNJ patients require sequestrectomy and HBO therapy, whereas stage 1 patients respond to HBO therapy. Stage 3 ORNJ is a catastrophic disease condition with the accompanying extra-oral fistula, pathological fracture, and expansion to neighboring anatomical regions (13). In 1986, Morton and Simpson divided ORNJ into three groups depending on the need for surgery, the degree of sequestration, and the duration of the recovery time (65). Epstein et al. developed the ORNJ three-phase approach in 1987 to evaluate disease severity, clinical symptoms, and the presence of pathological fractures (66). Clayman classified ORNJ into two forms in 1997: type 1, which may be treated conservatively; and type 2, or "radiation osteomyelitis," which cannot be treated conservatively (67). Schwartz and Kagan redefined the degree of bone involvement in the years after (68). Finally, Notani et al. (29) presented an ORNJ staging connected with the alveolar bone and canal: Stage I, ORNJ restricted to the dentoalveolar bone; Stage II, ORNJ limited to the dentoalveolar bone or the 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 (Table 1).

DIAGNOSTIC METHODS

Most ORNJ diagnoses are made by the demonstration of mucous membrane ulcers and the accompanying clinically apparent necrotic bone exposure. However, radiographic analyses highlight essential traits that support specialists in overcoming diagnostic challenges. Radiological findings alone may not be sufficient to diagnose ORNJ if tissue changes are not visible in the fitting location. In such

TABLE 1 Grading systems for osteoradionecrosis

Author(s)	Criteria of grading	Grades
Coffin 1983 (64)	Clinical and radiological evidences	Minor: Small sequestrum is clinically present, but no radiologically findings. Major: Necrosis and pathological fracture are clinically present, and also radiologically findings are clear.
Marx 1983 (12)	Requirement of treatment	I: HBO therapy is required. II: HBO therapy and sequestrectomy are required. III: Due to cutaneous fistula, pathological fracture, and severe resorption, surgical resection is required as well as HBO therapy.
Morton and Simpson 1986 (65)	Clinical evidence and requirement of treatment	Minor: Ulcerated site and spontaneous healing is present. Moderate: Minor sequestration with exposed bone is present, and conservative treatment is required. Major: Extensive sequestration with exposed bone is present, and advanced surgical treatment is required.
Epstein et al. 1987 (66)	*Grade of lesion and clinical evidence	I: Healing. II: Chronic lesion with no progression. III: Active lesion with progression.
Glanzmann and Grätz 1995 (69)	Time frame of exposure to bone, requirement and outcome of treatment	1: No inflammation but at least 3 months of exposure to bone. 2: Exposure to bone with inflammation and sequestration is present but no findings of grade 3-5. 3: The lesion requires mandibular resection and a positive outcome is observed. 4: The lesion requires mandibular resection, but satisfactory outcomes are not observed. 5: Death as outcome of ORNJ.
Clayman 1997 (67)	Clinical evidence	I: Intact mucosa but bone lysis is present. II: Aggressive lesion is present with soft tissue destruction and secondary contamination.
Støre and Boysen 2000 (18)	Clinical and radiological evidences	0: Damaged mucosal integrity 1: intact mucosa but necrotic bone is radiologically present. 2: Intraoral necrotic bone and radiological evidence are present. 3: Expose to bone, inflammation, cutaneous fistula and radiological evidence are present.
Schwartz and Kagan 2002 (68)	**Clinical and radiological evidences	I: Limited exposed cortical bone with minimal ulceration of soft tissue requires conservative treatment. II: Localized exposed cortical bone and medullary bone are necrotic. III: The full thickness of a bone segment is included and also pathological fractures may be seen.
Notani et al. 2003 (29)	Per to relation with the alveolar bone and mandibular alveolar canal	I: Lesion limited to alveolar bone surface. II: Lesion limited to the alveolar bone, above the mandibular alveolar canal, including the mandibular cortex and medullary bone. III: Lesion enlarging to the mandibular alveolar canal or with pathological fracture/cutaneous fistula.

* Grades as absent or present pathological fracture are divided into two within themselves.
** Grades 2 and 3 are divided into two as minimal soft tissue ulceration and soft tissue necrosis with cutaneous fistula.
Abbreviations: HBO: hyperbaric oxygen; ORNJ: osteoradionecrosis of the jaw.

situations, clinical and radiological evidence should be assessed simultaneously to overcome the challenges of an accurate diagnosis (8, 39). The RT procedure, the patient's dental history and examinations, panoramic radiographs, computed tomography (CT) scan, other advanced imaging modalities, biopsy of the lesion, and the disease stage should all be considered to make a firm diagnosis of ORNJ. Additionally, it is crucial to rule out any primary or secondary cancers (70–72).

Clinical evaluation

Pain is one of the ORNJ's clinically crippling symptoms, which can make diagnosis challenging (19, 39, 73) because it may be present in some cases but not in others (74). Additionally, due to the loss of sensory nerve fibers in late-stage ORNJ, the pain might not even exist. The clinical examination should consider dysesthesia and anesthesia due to the numerous neurological illnesses connected to ORNJ. Halitosis and dysgeusia are often reported in ORNJ patients. Because the uneven surface and sharpened-edge bone in the gingival area imply ORNJ, a comprehensive intraoral examination may help in the diagnosis. Soft tissue damage nearby can also be visible in such circumstances. In addition to intraoral or extraoral fistulas, the clinical picture may include local or systemic infections, trismus, and pathological fractures in the diagnosis of advanced ORNJ cases (75–77) (Figure 1).

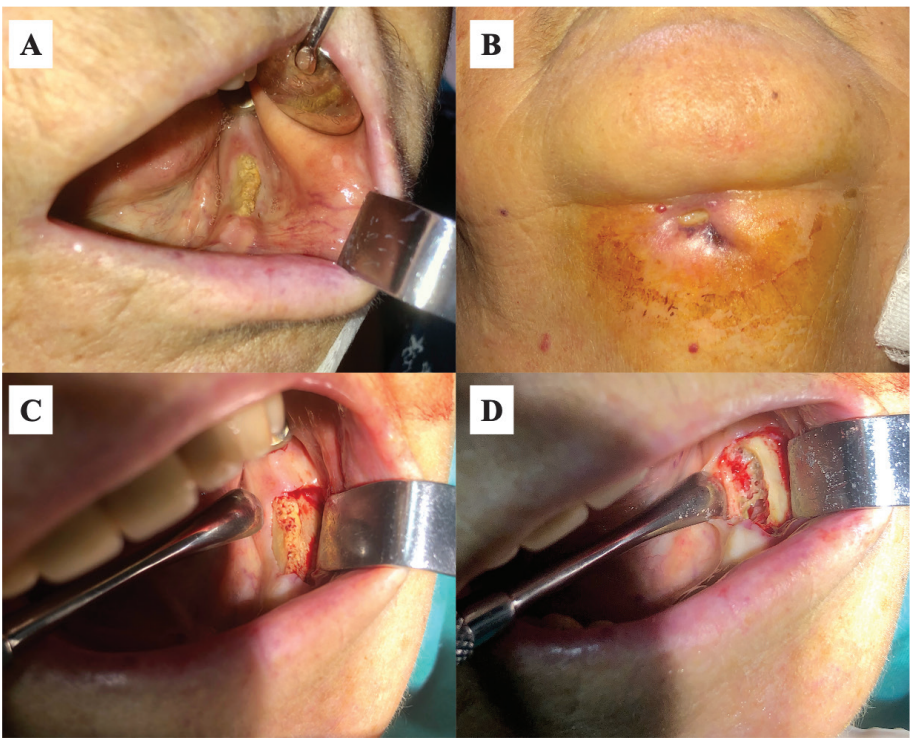

Figure 1. Images of osteoradionecrosis in the clinical left mandibular angulus of the same patient. A: necrotic area in the intraoral view; **B:** cutaneous fistula in the mental region in extraoral view; **C:** dehiscence of alveolar bone before reflecting mucoperiosteal flap during surgery; D: alveolar bone image is observed after reflecting mucoperiosteal flap.

ORNJ and MRONJ (medication-related osteonecrosis of the jaw) have clinical similarities that render the exact diagnosis difficulty (72). Both conditions have limited prevalence (2–22% for ORNJ and 0.001–7% for MRONJ), are generally restricted to the mandible, and share similar clinical characteristics such as pain, exposed bone, and intra-oral or oro-cutaneous fistula (14, 20–22, 78, 79). Also, no pathognomonic histologic feature that would distinguish MRONJ from ORNJ has been pinpointed (73). Nevertheless, the following considerations may help resolve this ambiguity in diagnosis (73, 78, 79):

- Patients with MRONJ are typically older than those with ORNJ.
- MRONJ ensues more frequently than ORNJ in the maxilla.
- Pathological fractures occur more commonly in ORNJ than in MRONJ patients.
- For a precise diagnosis of ORNJ, any primary or recurrent tumors should be ruled out histologically.

Due to the association of MRONJ with antiresorptive or antiangiogenic drug therapy, and ORNJ with RT or CCRT, a thorough medical history is the most helpful tool in the differential diagnosis process.

Radiological evaluation

Orthopantomography (OPT), cone-beam computed tomography (CBCT), and computed tomography (CT) are the frequently used imaging modalities for the diagnosis and evaluation of ORNJ (8). The recommended additional imaging techniques include bone scintigraphy, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) (19, 39) (Table 2).

The possibility that the disease may not present in the early stages presents the first difficult issue in the radiological diagnosis of ORNJ (19). Additionally, the full extent of the disease's severity may not be revealed by radiological findings (9, 80). The affected ORNJ region may initially appear normal or progress into pathological fractures, isolated or widespread osteolytic sites, or sequestration (19). However, a rise in radiodensity and mixed radiopaque or radiolucent lesion regions, which indicates bone degradation, can be recognized in the early stages. Sharply bound bone resorption is an early change witnessed in the outer cortical plate of the mandible. Jaw fractures may become visible when the bone's physiological and morphological structure is seriously hampered. The posterior mandible, which typically has less vascularization than the maxilla, is where early ORNJ changes are more noticeable. Spots of atypical bone resorption and sclerosis with hazy non-cortical borders may be present (74). Another challenge is that ORNJ-related bone loss and sclerosis might be mistaken for periodontal disease. The sequestrum's identification and the patient's prior medical history are the key factors in the final radiological diagnosis of ORNJ. The mandible is the most common location for the sequestrum, which is as an isolated cortical bone fragment. A CBCT or CT scan is advocated to reveal the sequestrum because the imaging characteristics of ORNJ are comparable to those of osteomyelitis. A decisive diagnosis cannot be made solely based on a pathological fracture. Using additional imaging modalities in these situations would be beneficial (74).

TABLE 2 Advantages, disadvantages, and prospective radiological findings of imaging techniques used in the diagnosis of osteoradionecrosis

Imaging technique	Advantages of imaging	Disadvantages of imaging	Feature	Prospective imaging findings
OPT (14, 74)	• Routine use • Low radiation dose • Reveal possible bone deformities • Identifying the sequestrum	• Only permitting 2D exams • Magnification and distortion • Missing in showing features and grades of ORNJ	Abnormalities of bone	• Radiolucency without discernible sclerotic boundaries or a radiodense area in low-density tissue (sequestrum) • Pathological fracture
CBCT (8, 79, 86)	• Revealing 3D images of jaws • Lower radiation dose and cost than CT • More details on bone deformity from OPT • Identifying the sequestrum • Facilitating the differential diagnosis of ORNJ from other necrotic lesions	• Not provide ample soft tissue contrast • Costs more than 2D imaging	Abnormalities of bone	• Lytic changes • Cortical bone resorption • Sclerotic areas • Pathological fracture • Sequestrum
CT (19, 39, 85, 88)	• Revealing 3D images of jaws • More details on bone deformity from OPT • Distinguishing ORNJ from tumor recurrence or second primary cancer • Facilitating the differential diagnosis of ORNJ from other necrotic lesions	• High radiation dose • Long scan time	Abnormalities of bone	• Cortical defects • Osteolysis • Changes in trabecular structure • Lingual and buccal bone deterioration • Pathological fractures • Sequestrum • Bone sclerosis • Loss of bone trabeculae in cancellous bone with bicortical involvement
MRI (85, 92–94)	• Non-invasive technique • Nonionizing radiation • Distinguishing between soft and hard tissues • Better tissue contrast and higher spatial resolution than other modalities • Detecting ORNJ earlier than CT	• High costs • Long scan time • The artifacts due to dental implants, restorations and orthodontic appliances • Ferromagnetic objects can be damaged by entering a strong magnetic field	Changes of bone marrow Muscular abnormality	• Aberrant, homogenous, low marrow signal intensity on T1-weighted images • Increased signal intensity on T2-weighted images • Masticatory muscles thickening
Bone scintigraphy, SPECT (93, 97–99)	• Detecting location and severity of ORNJ • Indicate healing of the lesion	• Bone scintigraphy has limited spatial resolution and soft tissue over-projection, but SPECT removes these disadvantages	The competence of bone metabolic	• Changes in phosphate metabolisms • Enhanced homogenous bone metabolism
PET (100, 101)	• Revealing inflammatory soft tissue or tumor recurrence	• Difficulty distinguishing between soft tissue and bone involvement in the presence of osteomyelitis	Bone marrow and glucose metabolism activity	• Hypermetabolic bone marrow • Increased glucose metabolism • Inflammatory soft tissue or tumor recurrence

Abbreviations: 2D: two dimensional; 3D: three dimensional; CBCT: cone beam computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; OPT: orthopantomography; ORNJ: osteoradionecrosis of the jaw; PET: positron emission tomography; SPECT: single-photon emission CT

Orthopantomography (OPT)

OPT used in routine dental examinations is the initial imaging procedure used to diagnose ORNJ (8, 19). One common technique employed to support OPT imaging is to perform two-dimensional (2D) examinations of both jaws through intraoral and extraoral radiographs (19, 81). Indicators of ORNJ in the OPT include the presence of a sequestrum, radiolucency around a zone of necrotic bone without obvious sclerotic borders, or a radiodense area in low-density tissue (14, 37). On OPT imaging, the sequestrum typically represents a radiopaque necrotic bone fragment. Yet, it may be discriminated on OPT imaging by the presence of significant changes in the mineral content of bone (>30–50%) that occurs in later stages of ORNJ (14, 82–84). OPT may efficiently reveal bone loss and osteolytic regions that match clinical involvement. However, OPT may be unable to distinguish necrotic bone from the normal bone and subperiosteal new bone formation (85). Particularly noticeable are enlargements of the periodontal ligament space along the apex of the teeth exposed to mandibular doses exceeding 45 Gy. This may be linked to several periodontal diseases and does not always indicate the existence of an ORNJ (73, 81). Additionally, while OPT can detect pathological fractures, ORNJ diagnosis requires the identification of the sequestrum (74).

Osteomyelitis and MRONJ are included in the differential diagnosis of ORNJ because of their radiological resemblances. All three osteonecrotic lesions—osteomyelitis, ORNJ, and MRONJ—have radiological features in common with one another. Gaêta-Araujo et al. concluded that while OPT had a 74% predictive value, it might not be enough to distinguish between the diseases. The limitations of evaluating the characteristics and phases of the ORNJ solely with OPT imaging include its allowance of only 2D assessments, inherent magnification, distortion of the images, and lack of formalized follow-up (86).

Cone Beam Computed Tomography (CBCT)

A dental CBCT is a specialized X-ray device used when conventional dental or facial X-rays are judged unsatisfactory for a comprehensive evaluation. With the help of this technology, physicians can get 3D images of bones, soft tissues, nerve networks, and teeth in a single scan. CBCT provides volumetric imaging of the bone structures in the craniofacial region at lower doses and costs than conventional CT. Even though CBCT imaging might not guarantee enough soft tissue contrast, it does offer precise details on the morphological characteristics and extent of lesions. Practitioners can also use dental CBCT to assess the probable existence and degree of osteomyelitis in the differential diagnosis of cysts, tumors, and ORNJ (74). Additionally, it is possible to evaluate lytic changes, cortical bone resorption, and surrounding structures when ORNJ is investigated using CBCT (8) (Figure 2). CBCT is essential for a precise diagnosis since it can reveal sclerotic regions, pathological fractures, and sequestrum. Osteomyelitis may be distinguished from ORNJ and MRONJ using CBCT with an accuracy rate of 90%. CBCT offers more information when describing necrotic zones than OPT. By demonstrating higher amounts of periosteal bone development in MRONJ than in ORNJ and cortical bone resorption rather than osteomyelitis in ORNJ, CBCT examination may also help distinguish the two disorders (86). CBCT can distinguish

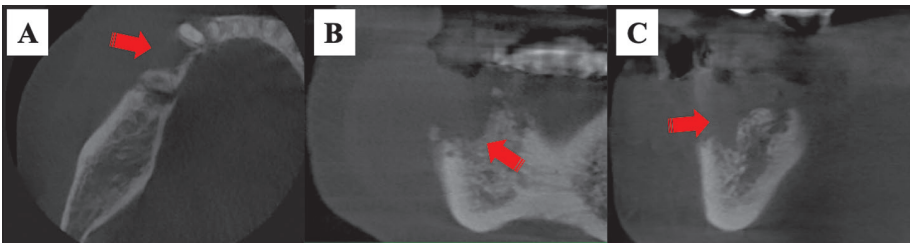

Figure 2. Cone beam computed tomography. Images showing extensive bone resorption and sequestration of osteoradionecrosis in the right mandibular premolar region (red arrows). **A:** axial; **B:** coronal; **C:** sagittal.

necrosis from other osteolysis cases that may be present (79). In summary, all these significant properties of CBCT make it a reliable method for the discriminative diagnosis of bone disorders (86).

Computed tomography (CT)

The typical CT findings of ORNJ include bone sequestrum, pathological fractures, osteolysis, changes in the trabecular structure, thickening of soft tissues, and cortical discontinuity (19, 39) (Figure 3). The loss of bone trabeculae in the cancellous bone with bicortical involvement on a CT scan in the later stages of ORNJ is one of the distinctive features of the disease. Gas bubble-like lesions can be seen on CT scans, which may be indicative of an infectious process that is pathognomonic for osteomyelitis (37, 87). Any abnormal growth in the surrounding soft tissue should be considered a second primary cancer or a tumor recurrence to rule out the possibility of either (37). ORNJ can be distinguished from these conditions when permeating trabeculation and bone sclerosis are visible on a CT scan (88). The diagnosis of ORNJ is improved by localized cortical defects that are located far from the primary tumor (89).

The buccal, lingual, or both sides of the jaw may have cortical discontinuities associated with ORNJ. The presence of discontinuities in both the lingual and corresponding buccal cortex is widely recognized as an indication of a jaw fracture (85). Because CT is 3D rather than 2D, bone changes in the anterior-posterior direction and involvement of the buccal or lingual cortex are more visible. Furthermore, OPT cannot discriminate between lingual and buccal bone degeneration, which is easily seen by CT (89, 90). The pathology is confined to the bone in the absence of a pathological fracture, but the presence of a nearby fusiform swelling reveals soft tissue thickening and involvement around the pathological fracture, if one exists (85). In the absence of soft tissue involvement, mandibular bone deterioration aids in ORNJ diagnosis (91). It may be difficult to distinguish advanced ORNJ from tumor recurrence because it frequently coexists soft tissue edema. To assist in the diagnosis, it might be beneficial to be aware that a malignant squamous cell carcinoma frequently results in damage to the alveolar process or the lingual cortex (85). Additionally, ORNJ varies from tumor recurrence in that the median ORNJ development gap following RT or CCRT is approximately three years, whereas tumor recurrences often occur during the first two years of treatment (92).

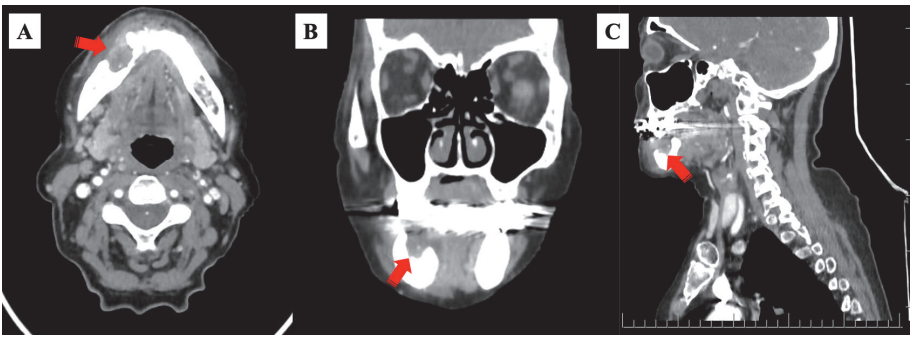

Figure 3. Computed tomography. Osteoradionecrosis in the anterior of the right mandible corpus is demonstrated as a lytic, slightly expansile, and defective region (red arrows). **A:** axial; **B:** coronal; **C:** sagittal.

Magnetic Resonance Imaging (MRI)

MRI is a non-invasive technique for identifying internal organs or tissues, analyzing various biological processes, and distinguishing between soft and hard tissues. Using regulated magnetic fields and non-ionizing radio frequency electromagnetic radiation, MRI operates under the basic tenet of producing high-quality cross-sectional images of the body. MRI has superior spatial resolution and better tissue clarity than conventional imaging modalities (93). MRI can demonstrate altered bone marrow in the ORNJ region with aberrant, homogeneous, low marrow signal intensity on T1-weighted images and elevated signal intensity on T2-weighted images (92, 93). The advantage of MRI over CT is that it can identify ORNJ earlier because the masticatory muscles close to the lesion have thickened. Making a diagnosis, however, may still be problematic because muscle thickening might also be a sign of a tumor recurrence. As a result, using CT imaging along with an MRI may help overcome this impediment in most, if not all, situations (85). Cortical damage, an aberrant bone marrow signal, and a mild to moderately uneven contrast enhancement are all shown on gadolinium-enhanced MRI of the ORNJ (94). MRI with dynamic contrast is also advantageous because it may demonstrate quantitative changes in vascular leakage at ORNJ locations (95). It should be noted, however, that the existence of dental implants, restorations, and orthodontic appliances in HNC patients may generate artifacts in the MRI images to be studied. Another issue with MRI is that ferromagnetic items may inadvertently damage the patient if they penetrate the high magnetic field (96).

Bone Scintigraphy, Single Photon Emission Computed Tomography (Spect), and Positron Emission Tomography (PET)

Because it has a sensitivity of up to 100% in the diagnosis of ORNJ, bone scintigraphy can efficiently determine the location and severity of the ailment (92). Early-stage ORNJ can be diagnosed by bone scintigraphy with 99mTc-marked diphosphonates (99mTc-MDP). A scintigraphic examination may also reveal osteoblastic activity in bone based on altered phosphate metabolism and blood

flow (97). Bone scintigraphy can also be useful in assessing how effectively HBO treatment is performing in ORNJ patients (98). However, compared to SPECT, this imaging technique has poor spatial resolution and over-projection of soft tissues (93). According to Lapa et al., three-phase bone scintigraphy showed increased homogenous bone metabolism brought on by inflammatory processes in cases of ORNJ, and late-phase SPECT was sufficient for ORNJ diagnosis (99). The excellent metabolic imaging tool known as PET/CT makes it simple to visualize inflammatory soft tissues, tumor recurrences, and/or secondary primaries. Both hypermetabolic bone marrow and increased glucose metabolism in affected tissues are visible on PET/CT. However, both PET/CT and SPECT images are adversely affected by localized variations in the tracer's clearance rate, vascular perfusion, permeability, and chemical bonding. Furthermore, it could be challenging to distinguish between the involvement of the soft tissues and the bones when osteomyelitis is present. In cases where it is difficult to make an exact distinction, incisional biopsy is recommended for a definitive diagnosis of tumor recurrence (100, 101). However, the biopsy procedure must be as minimally invasive as possible to avoid the formation of a fistula.

DISCUSSION

The literature reviewed here shows that diagnosing ORNJ is quite challenging due to the lack of a widely acknowledged staging system, clinical risk factors that correspond to ORNJ diagnostic criteria, and the inability to develop a general radiographic diagnosis guideline using the available data. Reviewing 12 articles that attempted to define ORNJ in the literature revealed how challenging it was to find solutions. Wong et al. discovered that the only factor that all the papers in this study had in common was clinical exposure to the non-vital bone (102).

The oncological treatment of HNC patients may be complicated by a delayed or incorrect diagnosis of ORNJ. Inflammation in the masticatory muscles leads to bone pain and trismus, restricting speech and nutrition, and leading to poor oral hygiene. In addition to the physiological issues that make it difficult to eat, the negative impact of ORNJ on social interactions and sexual life can have adverse psychological effects. The patient might consequently be forced into social isolation. Hence, enhancing the patient's quality of life may depend on making an early and accurate diagnosis of ORNJ (103).

The literature is divided about whether there is a direct link between tooth extraction timing (before vs. after RT) and ORNJ risk (8). In 82% of the ORNJ cases described in Owosho and colleagues' study (43), there were no dental interventions. However, Nabil et al. found that tooth extractions increased the risk of ORNJ by 23% between the 2- and 5-years following RT. It is important to remember that failing to remove the suspect teeth prior to RT will lead to many more tooth extractions and a higher risk of ORNJ (59). It is strongly advised to use IMRT rather than 2D-RT or 3D-CRT and to keep RT doses as low as possible to preclude or reduce ORNJ formation in HNC patients (8, 50). When treating oropharyngeal cancers, Zhang et al. emphasized that mandibular doses with IMPT were significantly lower than those with IMRT (51). The superior capability of dosage confinements in IMPT to safeguard neighboring healthy tissues lends

credence to this view. In situations where it is feasible, IMPT may thus be chosen as the preferable RT method for these individuals. Along with using contemporary RT techniques, xerostomia, tooth decay, and tooth extraction—all of which pose significant risks for developing ORNJ—may be avoided by using fluoride solutions and artificial saliva preparations (7, 28).

The reduction in mandibular canal width and cortex thickness in OPT can help detect bony alterations that may also be seen in lesion findings after RT, such as ORNJ, according to a study by Khojastepour et al. (104). OPT determined that the jawbone changes in 60% of the 126 eligible patients who underwent IMRT were significant. According to the same study, it is essential to monitor the growth of the periodontal space in the radiation-damaged area to prevent dental procedures that will increase the risk of ORNJ development. Detecting changes in OPT after RT and starting the appropriate treatment maneuvers may help prevent ORNJ in this regard (105). Furthermore, Seu et al. used OPT to monitor the progression of the disease following the administration of pentoxifylline and tocopherol for treating ORNJ, BRONJ, and chronic osteomyelitis. The efficacy of OPT in this study was based on the increase in radiographic densities of the lesion and surrounding bone structures following bone healing (106). OPT's ability to detect bone healing with an increase in radiopacity, routine and straightforward use in dental exams, and noninvasive nature without impairing the bone healing process may aid in the reliable follow-up of ORNJ and other necrotic lesions (106, 107). Although OPT gives reliable predictions for disease healing or progression, it may be inadequate for the diagnosis of necrotic pathologies. In a recent study, specific characteristics of lesion diversity were revealed by comparing the radiographic diagnostic features of OPT and CBCT in the differential diagnosis of osteomyelitis, ORNJ, and MRONJ. For instance, while lytic areas and pathological fractures may benefit from a differential diagnosis of ORNJ in CBCT, it may not be possible to do so in OPT (86). Planning a treatment strategy for ORNJ can also profit from the use of CBCT. By comparing CBCT and histopathological features, Ogura et al. investigated the differences between ORNJ and MRONJ. The authors found that MRONJ had significantly higher levels of periosteal reactions (100% vs. 0%, $P < 0.05$) and osteoclasts (85.7% vs. 0%, $P < 0.05$) than ORNJ (108). Because CBCT is capable of 3D image analysis and volumetric measurements, the authors' findings may aid in the detection of osteolytic areas, the separation of MRONJ and ORNJ, and the prediction of disease prognoses. Weijs et al. could identify the extent and size of ORNJ lesions in four patients and planned resection with a template created by CBCT, confirming the significant contributions of CBCT findings to treatment planning for ORNJ (109). According to the authors of this study, CBCT scanning could provide precise surgical planning.

Although the definition of ORNJ in the literature is based on the clinically apparent exposure of necrotic bone in the previously irradiated region and ulceration of the mucous membrane, cases of ORNJ with radiologically necrotic but intact mucosa have been recorded (13, 18, 43, 66, 110). Owosho et al. included ORNJ patients with only radiological signs of necrosis in their staging method, suggesting that if only the critical clinical diagnosis is used, this disease may be overlooked, and those radiological findings have a significant impact on both diagnosis and staging (110). By combining clinical symptoms with imaging techniques like 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, Miyamoto et al. investigated the diagnostic component of ORNJ. Diagnostic imaging studies revealed long-term RT-related bone marrow deterioration on MRI, and sclerotic changes in 82% of the bone marrow on CT. In the same study, PET/CT and SPECT were confirmed to be beneficial in the diagnosis of ORNJ, with PET/CT revealing the involvement of the tissue surrounding the affected bone and SPECT recognizing ORNJ's tracer uptake (101).

The ORNJ genesis process includes hypovascularization, hypoxia, and fibrosis that are brought on by abnormal bone marrow changes in addition to bone sclerosis brought on by RT-induced damage (7, 44, 88, 101). Additionally, fibrosis and inflammation in the nearby masticatory muscles may cause one of the signs of ORNJ, trismus (111). Thus, the combined use of CT and MRI in the diagnosis of ORNJ may serve as the most accurate radiological tool to circumvent the diagnostic challenge by identifying abnormalities in bone and soft tissue and supporting the clinical scenario (101). RT can reduce or even thwart periosteal reactions in patients with ORNJ (101, 108, 112), whereas, in patients with MRONJ, periosteal reactions frequently last a long time (108, 112).

Numerous researchers have stated that the radiological diagnostic distinction between ORNJ and MRONJ could be made by defining periosteal bone proliferation considering the higher sensitivity of CT in detecting osteolytic and sclerotic lesions in the jaw bones (113). According to study findings, lesions with higher periosteal bone growth on CT indicate MRONJ, whereas this characteristic is less common in ORNJ (78, 101, 108, 114). Additionally, the devitalized bone in the ORNJ diagnosis and the sclerosed bone in the RT field show bone that has lost vitality (101). Thus, CT appears to be a viable imaging modality for addressing ORNJ diagnostic tribulations. The ORNJ and MRONJ mysteries, which have comparable clinical manifestations, may be resolved with CT-based evaluations of the periosteal responses in RT locales. Neurological symptoms associated with advanced ORNJ may indicate MRONJ, primary or secondary malignancies, or both. To obtain a conclusive diagnosis in such circumstances, biopsies guided by PET and SPECT imaging are counseled (101). The diagnosis of inflammatory jaw diseases yields accurate results when CT analysis is supported by SPECT. According to Modabber et al., SPECT/CT has an 86% specificity value in the differential diagnosis of inflammatory jaw lesions like osteomyelitis, ORNJ, and MRONJ, a finding, which may guide the planned surgical procedures (115).

One more worrying occurrence is the emergence of a necrotic bone in cases with osteomyelitis. In contrast to osteomyelitis, which is likely to have both periosteal disruption and changes to the reactive bone formation, ORNJ has an enduring periosteum and no reactive bone. It is anticipated that the high therapeutic radiation doses delivered to the index ORNJ sites in the bone will result in much more severe symptoms and tissue damage than chronic osteomyelitis (116). MRI is the best imaging modality to evaluate soft tissues in the case of ORNJ owing to the absence of radiation exposure in MRI exams, despite the recommendation that CBCT evaluation of lesion details be performed (37, 117). Musha et al. stated that stage 1 of ORNJ had a median of 9 months (range, 1–44), for changes be seen on MRI, and that MRI could detect cases without symptoms such as pain (118). The superb ability of diagnosing ORNJ with MRI in the early stages without symptoms would be a huge benefit for its management.

CONCLUSION

In conclusion, choosing the best imaging modalities per the clinical characteristics of the patients may help to accurately depict the lesion and its bony or soft tissue extensions, thereby enabling the identification of ORNJ in HNC patients to solve the challenging diagnostic riddle. Comprehensive, multi-institutional, and prospective data scrutinizing all aspects of ORNJ is required. The evidence in the literature suggests that a combination of clinical findings, CT/MRI, and biopsy may enable the accurate diagnosis of ORNJ and its severity.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this manuscript.

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