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REVIEW ARTICLE

Do various imaging modalities provide potential early detection and diagnosis of medication-related osteonecrosis of the jaw? A review

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Objective: Patients with medication-related osteonecrosis of the jaw (MRONJ) often visit their dentists at advanced stages and subsequently require treatments that greatly affect quality of life. Currently, no clear diagnostic criteria exist to assess MRONJ, and the definitive diagnosis solely relies on clinical bone exposure. This ambiguity leads to a diagnostic delay, complications, and unnecessary burden. This article aims to identify imaging modalities' usage and findings of MRONJ to provide possible approaches for early detection.
Methods: Literature searches were conducted using PubMed, Web of Science, Scopus, and Cochrane Library to review all diagnostic imaging modalities for MRONJ.
Results: Panoramic radiography offers a fundamental understanding of the lesions. Imaging findings were comparable between non-exposed and exposed MRONJ, showing osteolysis, osteosclerosis, and thickened lamina dura. Mandibular cortex index Class II could be a potential early MRONJ indicator. While three-dimensional modalities, CT and CBCT, were able to show more features unique to MRONJ such as a solid type periosteal reaction, buccal predominance of cortical perforation, and bone-within-bone appearance. MRI signal intensities of vital bones are hypointense on T_1WI and hyperintense on T_2WI and STIR when necrotic bone shows hypointensity on all T_1WI, T_2WI, and STIR. Functional imaging is the most sensitive method but is usually performed in metastasis detection rather than being a diagnostic tool for early MRONJ.
Conclusion: Currently, MRONJ-*specific* imaging features cannot be firmly established. However, the current data are valuable as it may lead to a more efficient diagnostic procedure along with a more suitable selection of imaging modalities.
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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) was initially introduced as bisphosphonate-related osteonecrosis of the jaw (BRONJ) by Marx in 2003.[1] However, several articles have shown that bisphosphonates (BPs) are not the only agents causing osteonecrosis of the jaw (ONJ).[2–4] Many other antiresorptive agents (ARs), antiangiogenic agents (AAs), and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (*e.g.* denosumab) also induce osteonecrosis of the jaw. Consequently, in 2014, the term MRONJ was proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) to include all relevant medications.[5] In 2015, the term antiresorptive drug-related osteonecrosis of the jaw (ARONJ) was presented by the International Task Force on Osteonecrosis of the Jaw considering BPs and denosumab as ARs; however, a global consensus on the terminology has not been reached yet.[6] Throughout this article, MRONJ will be used when describing the related conditions.

Pain appears to be the most common symptom for MRONJ patients regardless of the exposure of bone.[7–9] MRONJ tends to occur mostly after dental extractions[5,7,8,10–12] and pre-existing inflammatory dental diseases.[5,7,8,13–15] However, MRONJ is believed to be triggered by an existing infection *resulting in* subsequent tooth extraction rather than the operative trauma from tooth extraction itself.[16–18] Periodontal disease is the second most common factor[12] with a possible linkage to MRONJ. There are reports of 15 or more missing teeth or advanced periodontal bone loss, signifying a high risk of developing MRONJ.[19,20] Medication-related osteonecrosis mostly takes place in the jaw with a mandibular predominance.[5,8,10,11] Contrastingly, the necrosis *outside* the jaw area (*e.g.* the auditory canal, femur, and tibia) has been reported with only a small number of cases.[21,22] This phenomenon is probably because of its high bone metabolism[23] from continuous mastication[24,25] resulting in a higher rate of bone remodeling, according to Wolff's law stating that remodeling occurs secondary to the forces applied to it.[26] Consequently, patients with high alveolar bone density might be increasingly at risk.[27] Besides, thin covering soft tissue is also susceptible to mucosal trauma and is therefore easily infected by the multispecies microbial ecosystem in the oral cavity.[28,29]

The current diagnostic criteria primarily rely on clinical manifestations without the integration of imaging modalities resulting in underdiagnosis of "non-exposed" or "Stage 0 MRONJ".[5] According to the International Task Force on Osteonecrosis of the Jaw,[6] Stage 0 was not included to avoid overdiagnosis from its non-specific symptoms similar to common dental diseases. However, this might inadvertently delay any proactive treatment that prevents disease progression. It is vital as roughly half of Stage 0 patients tend to develop advanced stages and end up with poorer prognosis.[9,30,31] Therefore, extra caution should be taken during diagnosis to provide the optimal approach for patients. Stage 0 comprised roughly 30% of MRONJ cases, and two-thirds of these cases tend to show radiological signs.[9] On top of that, MRONJ is a bony disease; therefore, diagnostic imaging modalities should be incorporated as standard diagnostic tools.

The current article presents a maxillofacial imaging evaluation from all aspects in the hope of creating useful guidance to aid in diagnosing the condition and raising awareness among dental practitioners to prevent disease progression.

Methods

Electronic literature searches were performed to identify current literature pertaining to available MRONJ diagnostic imaging modalities. The searches were conducted using Medical Subject Headings (MeSH Terms) and keywords in the MEDLINE database (PubMed), Web of Science, Scopus, and Cochrane library. Search terms are as follows: ("Bisphosphonate-Associated Osteonecrosis of the Jaw" [MeSH Terms] OR "MRONJ" [tw] OR "BRONJ" [tw] OR "Medication-related osteonecrosis of the jaw" [tw] OR "Bisphosphonate-related osteonecrosis of the Jaw" [tw] OR "Osteonecrosis/chemically induced" [MeSH Terms] OR "Jaw diseases/chemically induced" [MeSH Terms]) AND ("Diagnostic Imaging" [MeSH Terms] OR "Panoramic radiograph" [tw] OR "Cone-beam computed tomography" [tw] OR "Computed tomography" [tw] OR "Magnetic resonance imaging" [tw] OR "Functional imaging" [tw]). MeSH terms were used where the database supports.

The following criteria must be met.

(1) Reports of any studies were included.
(2) Only human studies were included.
(3) Only studies written in English were included.
(4) Studies unrelated to MRONJ, osteomyelitis, and osteonecrosis were excluded.
(5) Studies unrelated to imaging modalities were excluded.

After the final selection based on the above criteria, abstracts were read, and only full texts of relevant studies were retrieved. References from included articles and similar articles were also manually checked and included. The search strategy diagram in Figure 1 portrayed studies included in the article covering imaging techniques and features.

Panoramic radiography

In terms of MRONJ diagnosis, panoramic radiographs provide an immediate view of the lesions. Still, they cannot desirably perform in detecting early changes of

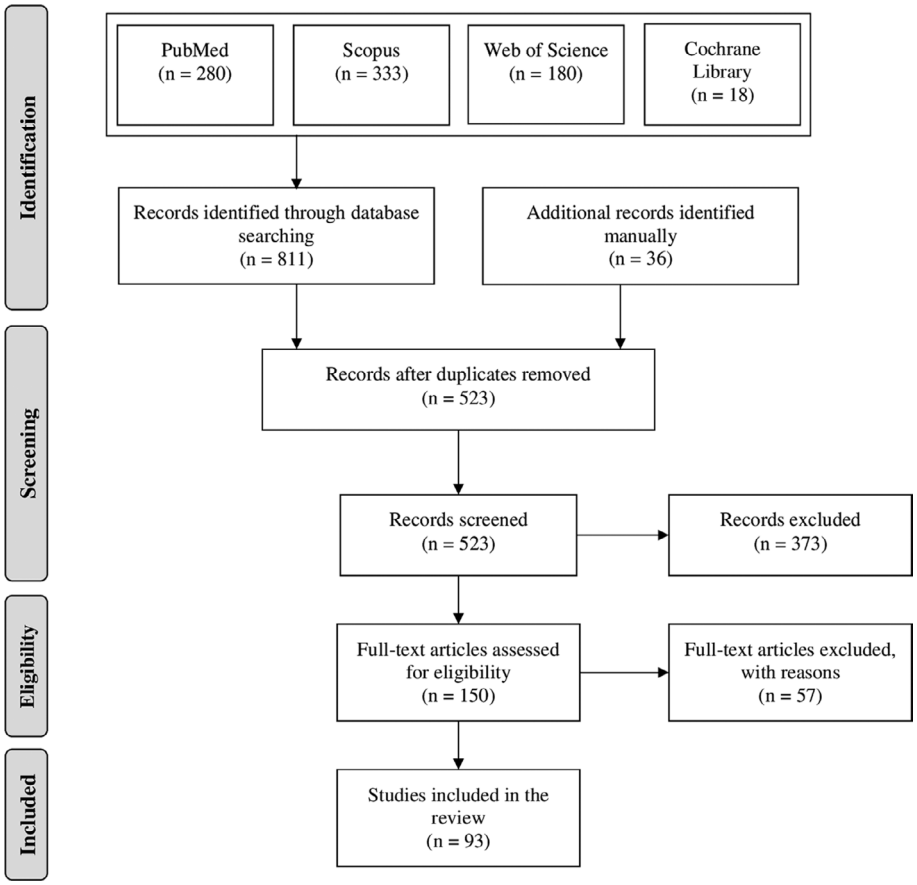

Figure 1 Diagram of the search strategy and study selection on MRONJ imaging techniques and features. MRONJ, medication-related osteonecrosis of the jaw.

bony structures and other detailed features of MRONJ such as sinus communication and bone fragmentation.[32] Panoramic radiography also has a lower ability to distinguish sequestrum from healthy bones.[33–35] When lesions are smaller than 1 cm, they can appear normal on panoramic radiographs.[35,36] Detecting bone changes can be late in plain radiographs because changes appear when the bone loses ~30–50% of its density. Furthermore, distortion due to motion artifacts and patient positioning are unpredictable. That is to say, the extent of the MRONJ lesion cannot be precisely determined. As a result, it causes a diagnostic delay and underestimation of the lesion compared with CT scans.[25,35,37–39] There is also a report that panoramic radiographs cannot be used for periodontal ligament (PDL) assessment in MRONJ patients.[40]

Panoramic imaging features of the non-exposed variant of MRONJ

The non-exposed variant or Stage 0 MRONJ can easily be confused with other common dental diseases, which are sometimes challenging to rule out, resulting in false-positive diagnoses.[5] Panoramic imaging features were systematically reviewed targeting Stage 0 MRONJ and found that PDL widening, lamina dura thickening, osteolysis, and diffused sclerosis were common findings.[41]

Şahin et al.[42] also assessed 66 panoramic radiographs of 28 and 38 cases of non-exposed and exposed MRONJ, respectively. The study was able to show that the most common panoramic features for non-exposed MRONJ were osteolysis, lamina dura thickening, and external oblique ridge enhancement (Figure 2). However, another study comprising 35 patients showed that osteolytic changes in Stage 0 were the only promising panoramic finding.[43]

A case–control study by Kubo et al.[39] showed that the sign of Class II mandibular cortex index (MCI), displaying semilunar defects/endosteal residues (Figure 3), was encountered more frequently at the unaffected sites of MRONJ patients (ONJ^+) compared to the BP-prescribed ONJ-negative group. Class II MCI might potentially be an MRONJ-developing factor with further investigation in a larger study. All features for non-exposed MRONJ are summarized in Table 1.

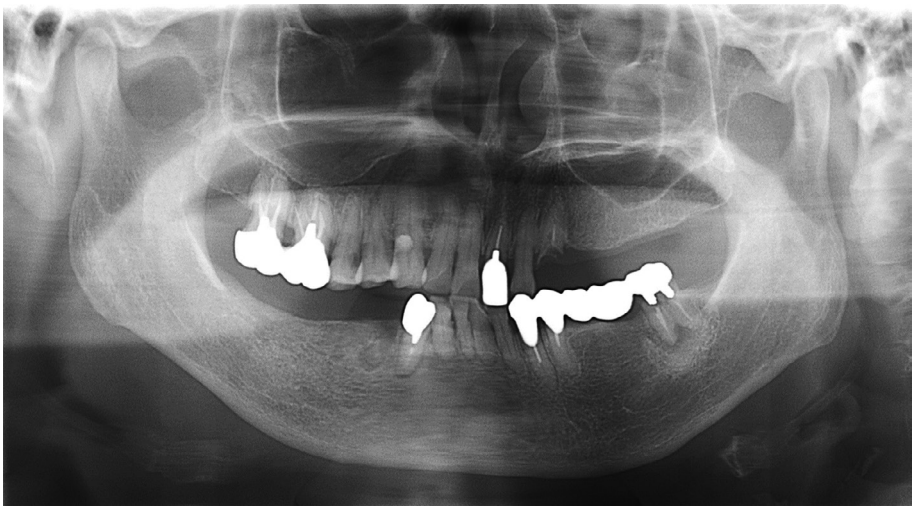

Figure 2 A 73-year-old female presented with pain and gingival swelling at the lower right first premolar region without bone exposure; Stage 0 MRONJ was then diagnosed. She had a history of breast cancer surgery for eight years and received zoledronate for three years. A panoramic radiograph shows partial bone osteolysis at the complaint site and osteosclerosis at the right mandible. MRONJ, medication-related osteonecrosis of the jaw.

Panoramic imaging features of the exposed variant of MRONJ

The most common findings of exposed MRONJ are osteolysis, osteosclerosis, mixed lytic/sclerotic lesions,[43–45] visible extraction socket, and sequestrum formation.[46]

Klingelhöffer et al.[47] reported in a case–control study of 36 MRONJ patients showing a statistically significant degree of six radiographic signs (osteosclerosis, visible alveolar socket, lamina dura thickening, enhancement mandibular canal, proliferative periosteal reaction, and cortical lysis) more than the control group. However, according to Suei's study,[45] the lamina dura thickening could also be seen in other osteomyelitis indicating that this may not have been a significant factor in his study. These changes were progressive and often encountered in serial imaging[25] (Figure 4).

An exposed MRONJ variant demonstrates both focal and diffused sclerosis but leans more toward diffused sclerosis, which can be differentiated from reactive sclerosis that is mainly localized.[25] Sequestra and

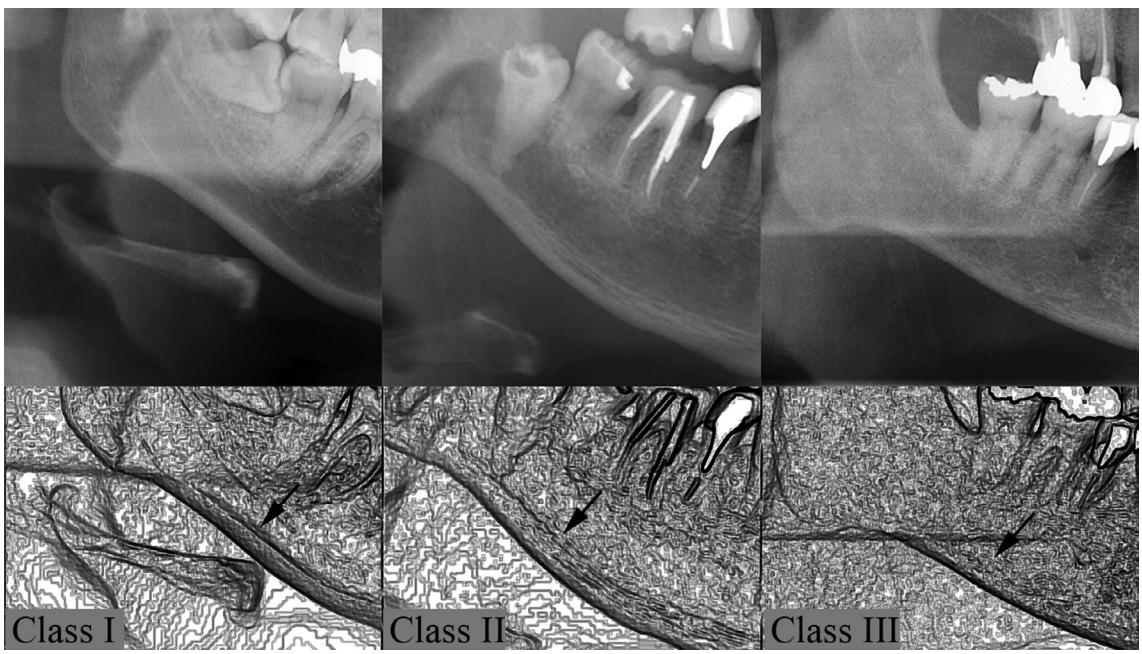

Figure 3 Cropped panoramic radiographs demonstrating three mandibular cortex index classes. **Class I:** Normal cortex with a continuous cortical outline **Class II:** Mild to moderately eroded cortex showing an interrupted cortical outline **Class III:** Severely eroded cortex containing a very ill-defined outline

Table 1 Panoramic features of non-exposed MRONJ

Author	Study design	Sample size	Imaging features
Moreno-Rabié et al.[41]	A systematic review	14 articles included	• Osteolysis[41–43]
Şahin et al.[42]	A case–control study	38 exposed MRONJ	• Lamina dura thickening[41,42]
		28 non-exposed MRONJ	• External oblique ridge enhancement[42]
Cardoso et al.[43]	Retrospective case series	35 patients	• PDL widening[41]
			• Diffuse sclerosis[41]
Kubo et al.[39]	A case–control study	24 MRONJ	• Class II MCI as a potential MRONJ predictor
		Two control groups:	
		1) 179 medicated non-MRONJ	
		2) 200 unmedicated	

MCI, mandibular cortex index; MRONJ, medication-related osteonecrosis of the jaw.

the prominent mandibular canal were significantly more featured in exposed than non-exposed MRONJ.[42]

Radiographic findings for Stages 1 and 2 are identical to Stage 0 but more pronounced.[42] Several authors have reported a concomitant relationship between clinical staging and the intensity of bone sclerosis, meaning that sclerosis would later intensify with an escalating degree of severity[25,43] (Figure 5). Lesions of Stages 1 and 2 are restricted to the alveolar area when Stage 3 is no longer limited to the alveolar bone area. In other words, osteolysis has already extended across the mandible to the inferior border and sinus floor, potentially causing a pathological fracture.[5]

Interestingly, one study investigated the relationship between radiographic findings and MRONJ staging. It was found that diffuse sclerosis and an enhanced osteosclerotic mandibular canal were associated with Stage 2, and cortical erosion and mandibular fractures were related to Stage 3. Nonetheless, this study's limitation was that only 4 out of 35 patients were diagnosed with Stage 3. Therefore, this small sample size may not reliably represent Stage 3's features.[43] Features for exposed MRONJ are summarized in Table 2.

Computed tomography (CT)

CT has been preferred as the standard imaging modality to detect osteolysis and osteosclerosis, which are the most common characteristics of MRONJ.[48] CT imaging encompasses a more extensive area than clinically observed bone exposure.[37] Therefore, it can optimally establish the extent of the lesion.[37,49] CT is superior to panoramic radiographs regarding MRONJ signs' detection such as trabecular bone density alteration and bone sequestrum.[35,37] It has been shown to offer a higher sensitivity of MRONJ detection at 96% compared to 54 and 92% of panoramic radiographs and MRI, respectively, in a clinical trial study of 28 MRONJ patients.[50] Hence, it is highly recommended for staging purposes.[49]

CT imaging features of MRONJ

Osseous sclerosis is the most common radiographic feature of MRONJ detectable in CT,[25,41,51] and its

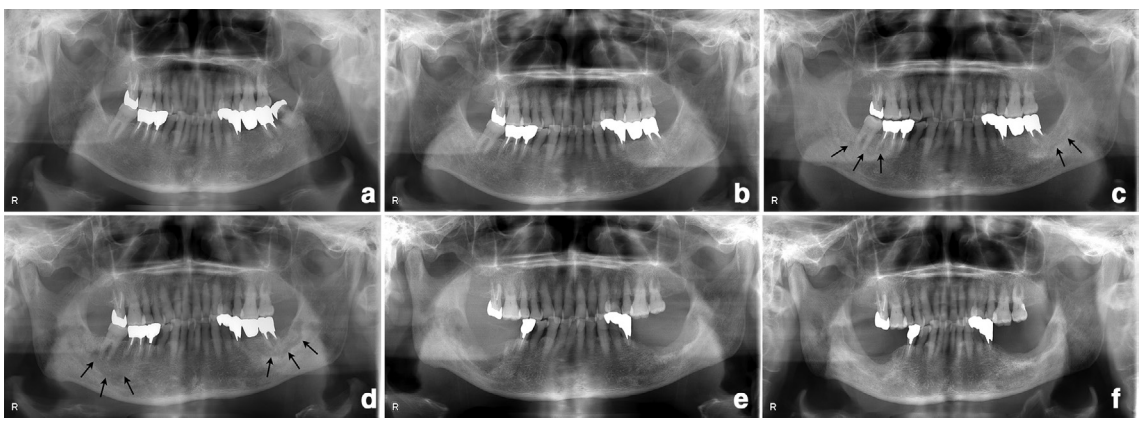

Figure 4 A series of panoramic images of a 68-year-old male MRONJ patient previously prescribed denosumab with a history of lung cancer and developed multiple bone metastases. Sequential panoramic images show: (**A**) Prior to denosumab administration. (**B**) Clinical bone exposure on both the left and right posterior mandible after nine months on denosumab without noticeable changes on panoramic radiographs. (**C**) Posterior mandibular ONJ-related radiolucent lesion seven months after denosumab cessation (arrows). (**D**) thirteen months after drug cessation showing more evident lesions at the same site (arrows) (**E**) one month after a surgical bone removal (one year and six months after drug cessation) (**F**) nine months after surgery. MRONJ, medication-related osteonecrosis of the jaw.

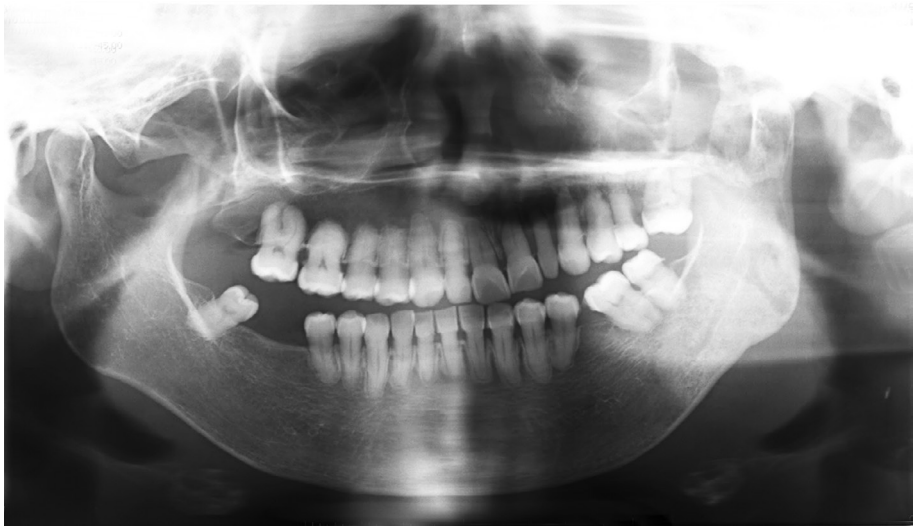

Figure 5 A panoramic radiograph of a 68-year-old male with lung cancer demonstrating thicker lamina dura after pamidronate and zoledronate administration for five and three years, respectively.

internal structure is mainly a mixture of sclerotic and lytic patterns.[52–54] Focal medullary sclerosis and the loss of corticomedullary junction on CT were found related to tooth loosening and delayed socket healing. These findings might constitute potentially early radiographic findings.[48,55] PDL widening and lamina dura thickening were listed as the initial signs of MRONJ.[5] However, according to Suei,[45] PDL widening was not observed in MRONJ cases; instead, it was more common in osteoradionecrosis (ORN).

The periosteal reaction was relatively uncommon, but it was rather seen in MRONJ than in ORN that caused by radiation arteritis.[45,56–60] A solid type reaction was reported in one study as a pathognomonic sign explicitly observed in MRONJ.[45] However, another study described periosteal bone formation to be more relevant to non-antiresorptive related osteomyelitis.[46] The presence of periosteal new bone was also related to a lower cure rate, especially in irregular-shaped reaction; this feature suggests complete resection of the lesions.[61–63]

Cortical perforations in MRONJ patients usually occur in both buccal and lingual cortical bone (Figure 6). If only one side is involved, it is more likely to be the buccal side.[52] Discontinuity of buccal and lingual mandibular cortex was observed in all cases where sequestrum was present.[53] In maxillary MRONJ, maxillary sinusitis signs are common[52,64–67] showing mucoperiosteal thickening, air-fluid levels, and fistula formation[35,37,64,68] (Figure 7).

Sequestrum formation is mostly a cancellous sequestrum; conversely, a cortical sequestrum is considerably rare but unique to MRONJ (only 12% of MRONJ cases) than other infectious bone diseases.[45] Another highly

Table 2 Panoramic features of exposed MRONJ

Author	Study design	Sample size	Imaging features
Şahin et al.[42]	A case–control study	38 exposed MRONJ 28 non-exposed MRONJ	• Diffused and focal sclerosis[25,42,43,47] • Mixed osteolysis and sclerosis[43–45]
Klingelhöffer et al.[47]	A case–control study (randomized, examiner-blinded)	36 MRONJ patients 24 medicated non-MRONJ 60 controls	• Prominent mandibular canal[42,43,47] • Sequestrum formation[42,46] • Visible extraction socket[46,47]
Shin et al.[46]	Comparative case series	161 medication-related patients 203 medication-unrelated patients	• Lamina dura thickening[47]; insignificant in another study[45] • Periosteal reaction[47]
Suei[45]	Comparative case series	25 patients	• Cortex disruption[47]
Marx et al.[44]	Retrospective case series	119 patients	
Phal et al.[25]	Retrospective case series	15 patients	
Cardoso et al.[43]	Retrospective case series	35 patients	
Ruggiero et al.[5]	Position paper		• Stage 1 and 2 – limited to alveolar bone • Stage 3 – beyond alveolar bone area

MRONJ, medication-related osteonecrosis of the jaw.

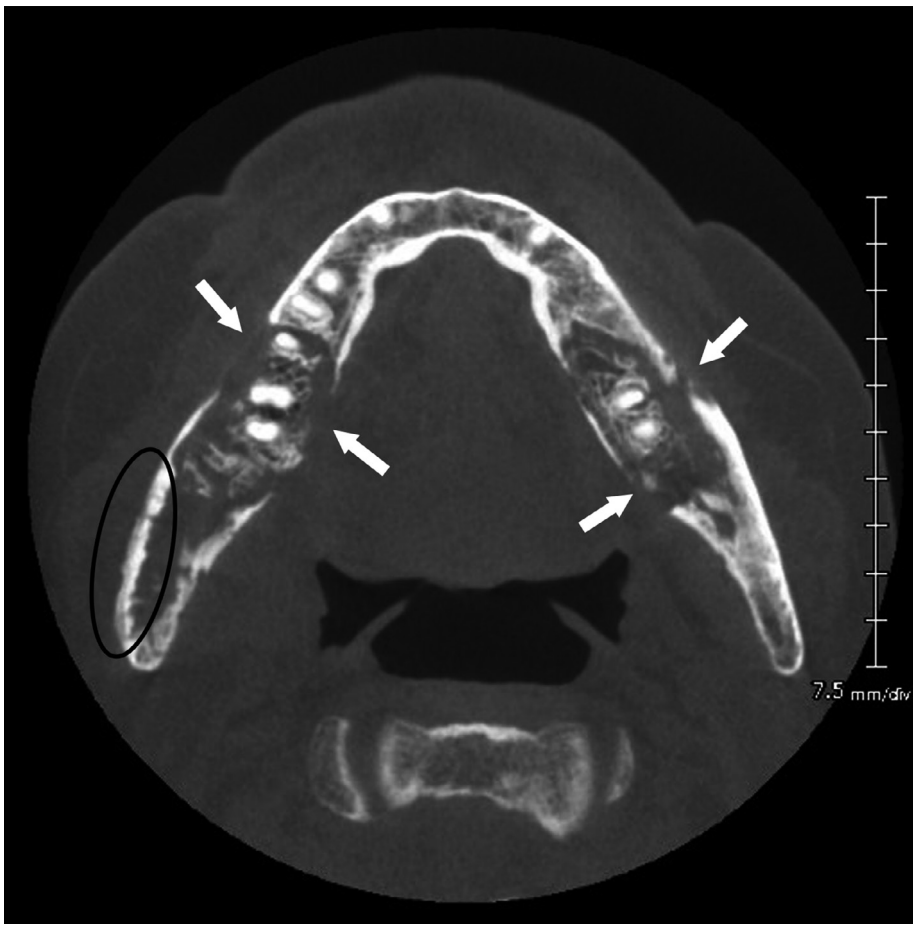

Figure 6 A 68-year-old male diagnosed with MRONJ with a history of lung cancer and developed bone metastasis. An axial CT image shows cancellous sequestra on both sides of the mandible with buccolingual cortical perforation (arrow). Periosteal reaction is also detected on the right posterior part of the buccal cortical bone (circle). MRONJ, medication-related osteonecrosis of the jaw.

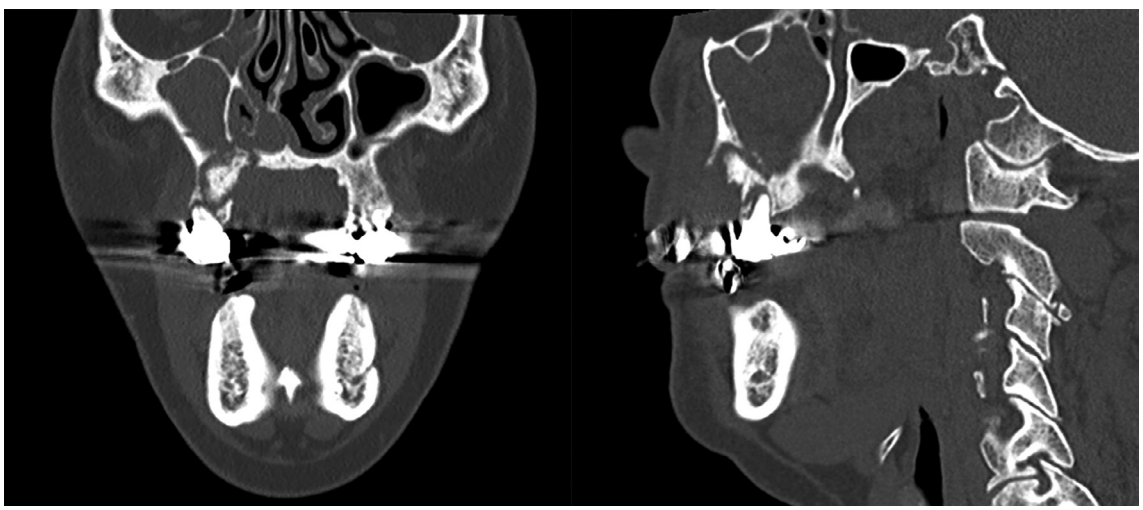

Figure 7 A 67-year-old male was diagnosed with Stage 1 MRONJ after the upper right first premolar extraction. He had a history of prostate cancer and prolonged use of zoledronate for five years and was during chemotherapy. The coronal and sagittal CT display a cortical sequestrum at the right maxilla with oronasal communication, and complete obliteration of the right maxillary sinus with high-density fluid is also observed. MRONJ, medication-related osteonecrosis of the jaw.

Table 3 CT features of MRONJ

Author	Study design	Sample size	Imaging features
Bagan et al.[51]	A case–control study	43 patients	• Osseous sclerosis with mixed internal structure (sclerosis and lysis)
		43 controls	
Moreno-Rabié et al.[41]	A systematic review	14 articles	
Popovic et al.[54]	Prospective case series	11 patients	
Baba et al.[52]	Retrospective case series	74 patients	
Elad et al.[53]	Retrospective case series	30 patients with CT	
Phal et al.[25]	Retrospective case series	5 of 15 patients with CT	
Bisdas et al.[48]	Prospective case series	32 patients	• Focal sclerosis and corticomedullary differentiation as possible early changes
Hutchinson et al.[55]	A retrospective cohort	30 patients	
Suei[45]	Comparative case series	23 of 25 patients with CT	• A solid type periosteal reaction (unique to MRONJ)
Baba et al.[52]	Retrospective case series	74 patients	• Buccolingual cortical perforation >Buccal cortical perforation >Lingual cortical perforation • Positive signs of sinusitis in affected maxilla • DRONJ >MRONJ (size of sequestrum)
Ueno et al.[56]	Comparative case series	17 of 18 patients with CT	• Distinct fractures > minute fractures
Fatterpekar et al.[69]	Retrospective case series	6 patients	• Bone-within-bone appearance

DRONJ, denosumab-related osteonecrosis of the jaw; MRONJ, medication-related osteonecrosis of the jaw.

suggestive characteristic of MRONJ was also described in the case series of six patients by Fatterpekar et al.[69] as a dense central sequestrum surrounded by osteolysis resulting in a bone-within-bone appearance. Sequestrum formation in denosumab-related osteonecrosis of the jaw (DRONJ) seems to be more frequent and more extensive[52] than MRONJ but often later detected at Stages 2 and 3.[70] Pathological fracture of MRONJ tends to be a distinct fracture rather than minute fragmentation in ORN.[56]

CT radiodensity has been used to evaluate cancellous bone. Still, no differences were revealed between exposed and non-exposed MRONJ, indicating that the bony structure may have altered even before bone exposure.[71,72] The CT value is also higher in the affected area (including Stage 0 MRONJ) than in the unaffected area.[41,71,73] CT signs of MRONJ recurrence, osteomyelitis resective margin, can be detected as early as 6 months following the surgical procedure before any clinical manifestations.[74] The summary of CT features is provided in Table 3.

Cone beam computed tomography (CBCT)

CBCT is recommended for assessing Stage 0 MRONJ[75,76] as it offers a higher spatial resolution than CT[77] with a smaller voxel size of 0.076 mm. In contrast, multidetector computed tomography (MDCT) provides around 0.35 mm considering its smallest voxel size.[78] Additionally, CBCT employs a more acceptable radiation dose and could be as minimal as 3 *Sv*.[79] As of its small field of view (FOV) makes it suitable for the evaluation of the alveolar bone area.[80] It offers superior detectability of sequestrum and bone fragmentation, bone quality, the extent of lesions, and many other features compared to panoramic radiographs.[10,32,81] Conversely, soft tissue structures will lack details and cannot be investigated.[82] According to Torres et al.,[83] CBCT delivers the optimal way to examine cortical bone compared to CT and MRI. Minimal changes such as linear sclerosis limited to alveolar margin and lamina dura can be detected, yet it demonstrates less extensive changes than positron emission tomography (PET)/CT and MRI.[84] In cases of suspected malignancy or metastasis, MDCT does provide more clinical benefits and should be selected as a method of choice.

CBCT imaging features of MRONJ

Common CBCT findings of MRONJ are thickening of the lamina dura, cortex irregularities, sclerosis, osteolysis, sequestrum, prominent mandibular canal, and subperiosteal bone formation.[10,85,86] However, thickened lamina dura and inferior alveolar canal prominence are thought to result from the medication itself.[5,6] According to a case–control study, cortical bone thickness, bone marrow changes, and cortical bone erosion detected by CBCT had been reported to be potential indicators of early changes of MRONJ[81,83,87] (Figure 8). Sequestrum noticed by CBCT in Stage 0 MRONJ patients may anticipate the forthcoming bone exposure.[88] Periosteal reaction is more common in higher stages.[86] Additional features seen on MDCT can also be viewed on CBCT with superior detailed display due to its higher resolution. CBCT features are listed in Table 4.

Pichardo et al.[89] demonstrated, in the study of 17 DRONJ and 17 MRONJ cases, that sequestrum formation in DRONJ was 30% less detected compared to

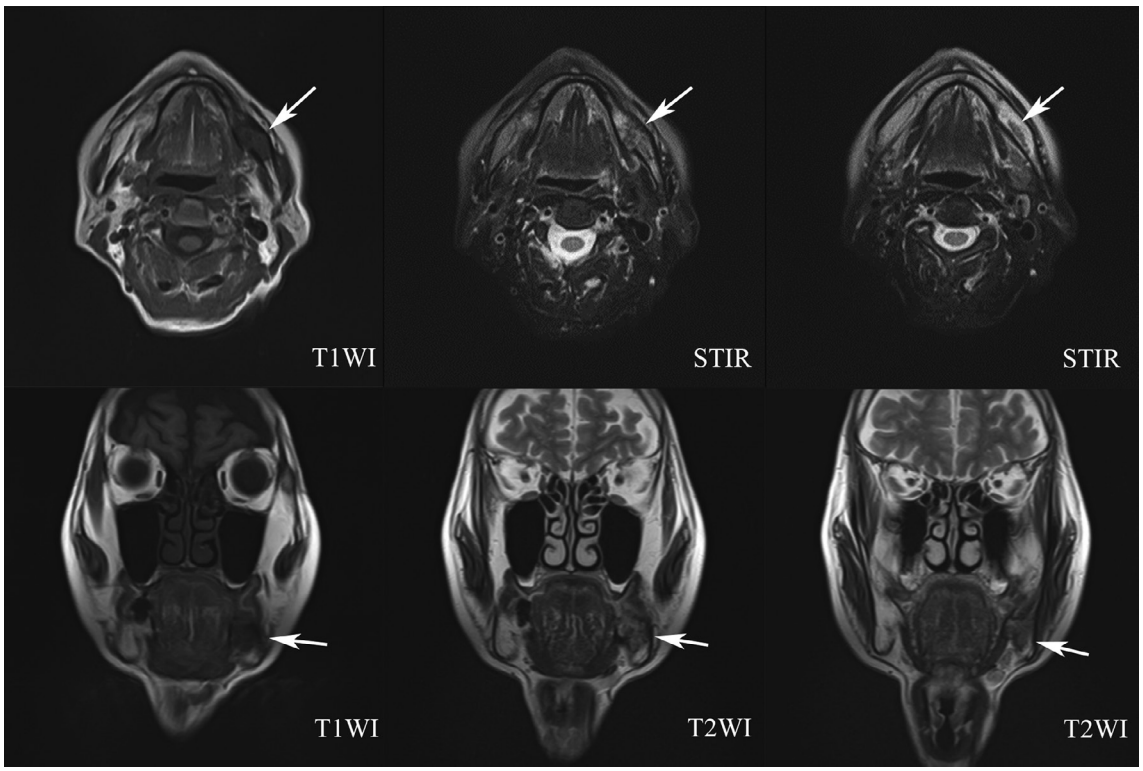

Figure 8 An 83-year-old male receiving ibandronate later developed purulent drainage after extracting the lower left first and second molar. The sagittal and coronal CBCT images demonstrate osteolytic bone marrow changes together with marrow coarsening in the left mandibular region. CBCT, cone beam CT.

MRONJ, but the size is usually more massive. The lysis of cortical borders in DRONJ is also 30% lower, which leads to a diagnostic delay and poorer anticipation of disease progression.

Magnetic resonance imaging (MRI)

MRI can detect bone marrow changes in the early stages[90] and once enhanced with a contrast agent, can show even more extensive changes than CBCT imaging and clinical examinations.[84] However, Stockmann et al.[50] stated that despite MRI's high detectability, the lesion's determination might still be limited to some extent. In a comparative study of 74 confirmed MRONJ patients, MRI showed more significant soft tissue swelling at 94% detection rate versus 80% on CT.[52] It was able to detect early osteomyelitis of Stage 0 MRONJ that were negative on CT.[91] A recent study by Huber et al.[92] retrospectively evaluated ultrashort echo time (UTE) MRI and CBCT for bone imaging in 19 MRONJ patients and found comparable results to CBCT imaging for both qualitative and quantitative parameters. However, interpretations of UTE MRI can be mistaken due to air artifacts resembling periosteal reaction and opposition.

MRI imaging features of MRONJ

According to the literature review (Table 5), Stage 0 MRONJ, bones are still viable without any bone exposure, displayed low intensity on T_1 weighted images

Table 4 CBCT features of MRONJ

Author	Study design	Sample size	Imaging features
Torres et al.[83]	A matched case–control study	12 patients 66 controls	• Bone marrow changes • Lysis of cortical bone. Potential early indicators for MRONJ
Ozcan et al.[81]	A case–control study	32 patients 32 controls	• Thicker cortical bone
Demir[85]	Retrospective case series	23 of 27 with CBCT	• Subperiosteal bone formation • Lamina dura thickening
Olutayo et al.[10]	Retrospective case series	22 patients	• Prominent mandibular canal • Other features conform to CT features

CBCT, cone beam CT; MRONJ, medication-related osteonecrosis of the jaw.

Table 5 MRI signal intensities on varying conditions

Author	Low *T*1WI	Low *T*2WI	Intermediate *T*2WI	High *T*1WI	High *T*2WI	High STIR	Low STIR	Conditions
Khan et al.[6]								Early (non- necrotic),
Bedogni et al.[37]								Unexposed areas,
Chiandussi et al.[38]	✓				✓	✓		Viable bones
Raje et al.[68]								
Khan et al.[6]								
Bedogni et al.[37]	✓	✓					✓	
Garcia-Ferrer et al.[93]	✓						✓	Necrosis,
Stockmann et al.[50]	✓							Exposed areas,
Krishnan et al.[94]								MRONJ
Hatakeyama et al.[95]								
Ueno et al.[56]	✓	✓	✓					
Ogura et al.[57]	✓					✓		
Arce et al.[96]								Necrotic bone (periphery)
Bisdas et al.[48]				✓	✓			
Wutzl et al.[97]								
Guggenberger et al.[84]	✓				✓			MRONJ Foci
Bisdas et al.[48]	✓	✓(center)			✓(rim)			Sequestrum
Garcia-Ferrer et al.[93]								

MRONJ, medication-related osteonecrosis of the jaw; STIR, short tau inversion recovery.

(T_1WI), and high intensity on both T_2 weighted images (T_2WI) and short tau inversion recovery (STIR) images indicating existing inflammation.[6,37,38,68] Once these bones become exposed or necrotic, the intensity becomes hypointense on T_1WI, T_2WI, and STIR, or sometimes intermediate intensity seen in some cases.[6,37,50,56,93–95] However, low intensity on T_1WI and high intensity on STIR has also been reported[57] (Figure 9). The necrotic bone periphery shows high intensity on T_2WI and contrast-enhanced T_1WI,[48,97] similar to MRONJ foci and sequestrum that had a hyperintense rim.[48,84,93] Strangely, abnormal MR signals of mandibular condyle on STIR were reported in 80% of the symptomatic side of MRONJ patients.[98] Cervical lymphadenopathies in ONJ are also common,[48] affecting mostly submandibular, submandibular angle, and jugulodigastric chains.[93]

Functional imaging (FI)

Bone scanning or bone scintigraphy is generally performed in tumor surveillance and metastasis detection. However, it is also valid for Stage 0 MRONJ detection[30,41,99] and is considered the most sensitive method.[38,96,100] Because the osteoblastic response due to γ-emitting radionuclides can be taken up 10–14 days before any significant radiographic changes can be detected.[101] Many studies have shown positive scintigraphy on MRONJ to be consistent with necrotic histologic appearance.[30,33,38,57,102,103] According to one retrospective study of 30 BP-treated cancer patients, bone scintigraphy for MRONJ prediction was assessed and produced 67% sensitivity and 79% specificity.[99]

The most common procedure is the Tc-99m MDP administered three-phase bone scan. The radionuclide is taken up at the site similar to the P-C-P bond of bisphosphonates,[80] though it only provides two-dimensional images.[104] Single-photon emission computed tomography (SPECT) imaging is then introduced. It collects data from various angles to form a three-dimensional image and is often integrated with a low dose CT (~0.5 mSv) for better anatomical localization (SPECT/CT).[33] SPECT/CT is more accurate than a surgical determination that often underestimates the lesion.[105] A previous study using SPECT/CT as a surgical guide found that 1 cm from the clean resected margin conformed to both histologic and scintigraphic appearance of MRONJ lesion.[106]

Artificial intelligence featuring the bone scan index (BSI) has recently been integrated into scintigraphy to improve detectability and reproducibility.[107] An abnormal uptake will be automatically compared throughout the body. The highest will represent that patient; as for the jaw, the representative area with the highest BSI will be labeled as $BSIJ_{max}$. This index is also accentuated in severe and apical periodontitis but still lower than in MRONJ.

PET/CT provides improved spatial resolution using positron-emitting radiotracers such as ^{18}F-sodium fluoride (NaF) and ^{18}F-fluorodeoxyglucose (FDG). NaF is more sensitive than FDG as it detects at the site where the osteoblastic activity occurs. While FDG acts as a glucose analog in glucose metabolism, which reflects the inflammatory process and shows up slightly slower on FI.[108,109] However, FDG performs well at detecting bone infection and determining the severity or stages of the diseases.[14]

A potential early detection using maximum standardized uptake value (SUV_{max}) from FDG-PET analysis has also been proposed. The value is usually higher in those who have been prescribed antiresorptive agents and patients with a dental infection.[110]

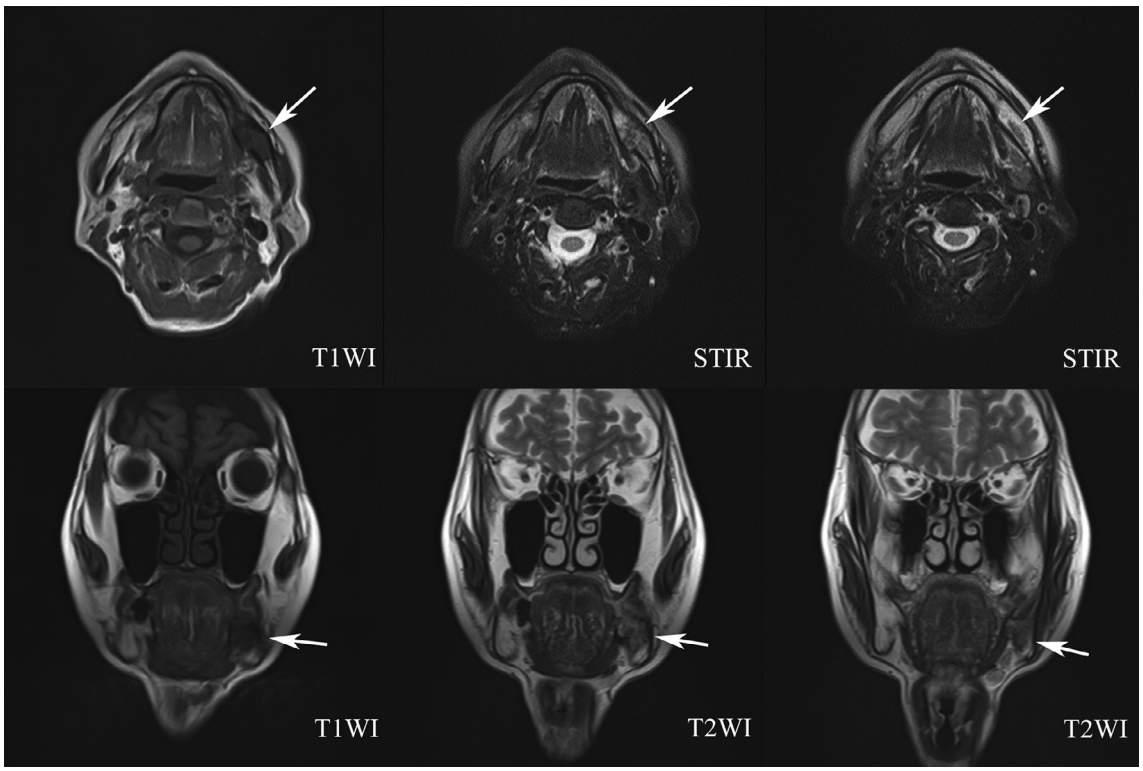

Figure 9 An 83-year-old female MRONJ patient presented with sinus drainage at the lower left second molar after extraction, with a history of taking alendronate. MRONJ, medication-related osteonecrosis of the jaw; STIR, short tau inversion recovery.

Axial MRI images demonstrate hypo-intensity on T_1WI and intermediate- to high intensity on STIR likely indicating the bone's viability (first row). Coronal MRI images show hypointensity on T_1WI and low to intermediate intensity on T_2WI (second row) likely indicating necrosis. According to Table 5, this patient in serial MRI imaging shows a mixture of necrosis and viability at the alveolar bone and inferior alveolar border, respectively.

The combination of functional imaging and CBCT has been reported aiding surgical resection and improving demarcation of MRONJ lesions. In order to lower the morbidity from resective procedures, remaining viable bones should be preserved.[111] However, bone vitality cannot be detected by a low-dose CT taken during functional imaging, since they are not reliable enough for diagnostic interpretation.[112] Therefore, CBCT is integrated into FI modalities (FI/CBCT) specific to bone remodeling (*i.e.,* MDP-SPECT or NaF-PET) and inflammatory activity (*i.e.* FDG-PET).

Functional imaging features of MRONJ

The index $BSIJ_{max}$ was reported to be a potential MRONJ prognostic tool when used three months before the disease progression to Stage 2, according to a retrospective evaluation of 44 cancer patients. The cut-off points were 0.09% in the maxilla and 0.06% in the mandible. The sensitivity and specificity were 88 and 96% in the maxilla, 64 and 89% in the mandible. These could be beneficial for early MRONJ prediction.[113]

According to three studies, the averages of SUV_{max} in MRONJ lesions were reported at the value of 7.5 ± 2.9 (10 patients),[68] 6.4 ± 2.1 (12 patients),[110] and 6.59 (23 patients)[114] (Figure 10). FDG cannot distinguish between inflammation and oncogenic tumors, thereby introducing the necessity for malignant specific tracers such as Tc-99m-sestamibi. An area with an uptake on FDG PET/CT but negative for Tc-99m-sestamibi would help support the diagnosis of MRONJ.[115]

The interpretation of combined FI/CBCT in necrotic regions was reported as negative on FDG-PET or SPECT imaging. However, the actual MRONJ outline includes both necrotic (FDG-PET negative) and inflammatory zone (FDG-PET positive). The vital region and reactive bone (SPECT or NaF-PET positive) shall be excluded and preserved. These findings were confirmed and harmonious with histopathological examinations.[111] Potential indicators from functional imaging are summarized in Table 6.

Discussion

The diagnostic criteria based on frank bone exposure of MRONJ should be revised because it leads to a delay in diagnosis.[31] As it is a disease of the jawbone, many studies reported that the necrotic area in the radiograph is more extensive than the clinical presentation.[37,116] Therefore, it is undeniable that imaging modalities are

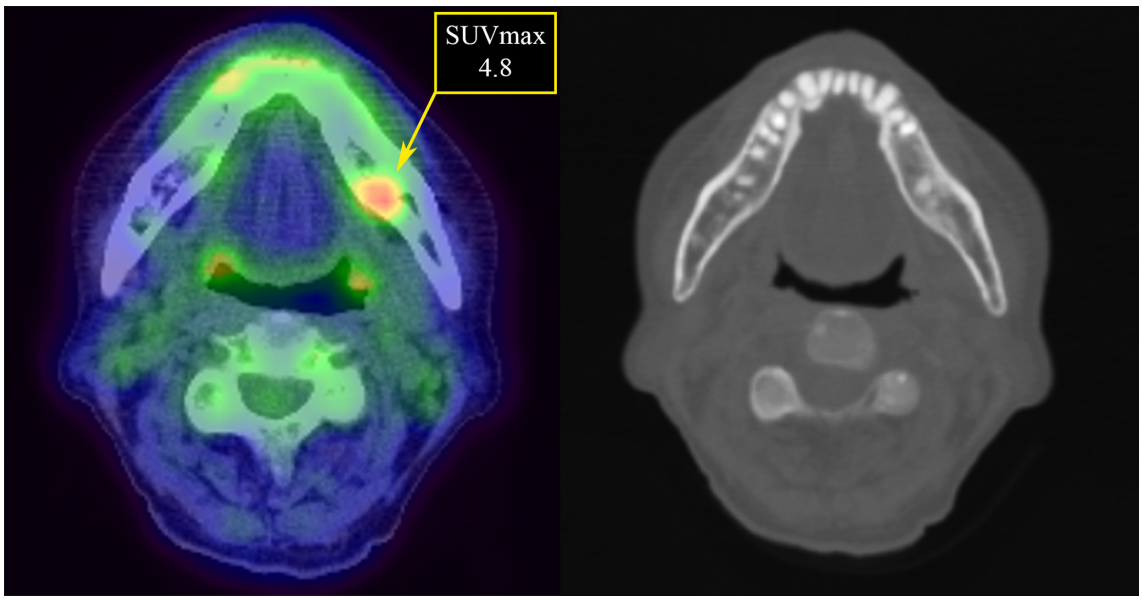

Figure 10 A 68-year-old male with Stage 0 MRONJ with a history of lung cancer and multiple metastases. FDG PET/CT images of the patient show an increased uptake at 4.8 of SUV_{max} at the left mandibular area indicating underlying inflammation or a potential site for developing MRONJ. In this case, clinical bone exposure occurred one month after FDG PET/CT examination. FDG, fludeoxyglucose; MRONJ,medication-related osteonecrosis of the jaw; PET, positron emission tomography;SUV_{max}, maximum standardized uptake value.

essential and shall be mandatory for MRONJ investigation. Nonetheless, no consensus regarding the imaging technique of choice has been determined for patient assessment.

Numerous imaging modalities have mainly served the purpose of preoperative, disease extent, and MRONJ-related complication evaluations. From an aspect of early detection, the awareness is still low; it has not been performed on a routine basis before bone exposure occurs. Among various interventions, panoramic radiography is the most common due to its instant overview of the lesions, low radiation exposure, and lower cost. Even though it provides gross details and potential sites of the affected area, the lesion's extent is often underestimated.[25,37] MRONJ features are non-specific; however, included pieces of the literature demonstrated osteolysis in Stage 0 MRONJ[41–43] rather than a mixture of osteolysis and sclerosis in exposed MRONJ.[43–45] Class II MCI could potentially be a future predictor of MRONJ progression, but the conclusion cannot be drawn as sample sizes were small and the *p*-value was at borderline.[39] Owing to its limitation of inability to give a thorough investigation of lesions, advanced imaging methods are usually required to achieve more accurate three-dimensional information.[50]

CBCT and CT have been shown to enhance the investigation of fine details and the lesions' extent, superior to panoramic radiographs.[25,32] CBCT permits better spatial resolution than CT; in turn, it cannot evaluate CT value and soft tissues.[77] They share most of the radiographic findings, but none of these features are pathognomonic for MRONJ. Some changes are considerably challenging to indicate, such as cortex thickening and corticomedullary differentiation, since no comparative standard values and baseline information have been designated.

Table 6 Potential indicators from functional imaging

Author	Study design	Sample size	Imaging features
Watanabe et al.[113]	Retrospective case series	44 patients	• $BSIJ_{max}$ with cut-off points of 0.09 in maxilla, 0.06 in mandible
Fleisher et al.[114]	Retrospective case series	23 patients	• SUV_{max} = 6.59 (standard deviation not available)
Watanabe et al.[110]	Retrospective case series	12 patients	• SUV_{max} = 6.4±2.1
Raje et al.[68]	Retrospective case series	10 patients	• SUV_{max} = 7.5±2.9
Catalano et al.[115]	Retrospective case series	4 patients	• FDG-PET positive, Tc-99m-sestamibi negative indicate MRONJ
Subramanian et al.[111]	Case reports	2 patients	FI/CBCT features of MRONJ outline • Include necrotic area (FDG-PET/ SPECT negative) • Include current inflammation (FDG-PET positive) • Exclude vital and reactive area (SPECT, NAF-PET positive)

CBCT, cone beam CT; FDG, flurodeoxyglucose; FI, functional imaging ; MRONJ, medication-related osteonecrosis of the jaw; PET, positron emission tomography; SPECT, single photon emission tomography; SUV_{max}, maximum standardized uptake value.

MRI help detect early marrow changes and soft tissue swelling when CBCT and CT cannot provide enough details.[52,84] MRI signal intensities for MRONJ seem to have consistent results from the information we have reviewed. Stage 0 demonstrated hypointensity on T_1WI, hyperintensity on T_2WI and STIR. The necrotic bone showed hypointensity on all T_1WI, T_2WI, and STIR (Table 5). As a reminder, MRI information is sometimes available from previously underwent brain MRI examinations; we recommend checking patient history before initiating any adjunctive investigations.[30,94]

FI is usually performed in metastatic cancer patients, and Stage 0 MRONJ is rather a result of a incidental finding. According to this review, the index $BSIJ_{max}$ and the value SUV_{max} could predict MRONJ progression factors with further study (Table 6). Even though this is considered the most sensitive technique for early lesions,[38,96,100] it has not gained popularity as a standard diagnostic tool for MRONJ because of its high-cost and low specificity.

This article's limitation is that many literatures are retrospective without prospective assessment of the patients. Follow-ups or periodic imaging examination are required to give a definite conclusion of MRONJ findings.[9] Additionally, sample sizes in many studies were considerably small without control groups, so it could not draw the conclusions whether the effects were from a medication itself or other underlying diseases.

Another limitation is that the topic is broad, but studies regarding the subject are limited. The diagnostic criteria used in some articles were not clear, and staging was not fully elucidated. Moreover, this review is not a systematic review, but the literature search and data extraction were processed both systematically and manually. It does not conform to the PRISMA-P protocol because it cannot be achieved due to lack of supported evidences.

In conclusion, pathognomonic imaging features for MRONJ cannot currently be established yet; however, the current information can be helpful for early detection when integrating multiple approaches of imaging techniques, especially three-dimensional modalities. As stated above, no consensus on which modalities should be used. Therefore, dental practitioners should always be aware not to overlook small or hidden changes and diligently select appropriate imaging modalities concerning patients' conditions and benefits to avoid over investigation and unnecessary interventions. We recommend a baseline and periodic follow-ups in order to be proactive to patients' conditions and to be able to provide an early definite diagnosis.

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