

Role of Imaging in Diagnosis of Bisphosphonates-related Osteonecrosis of the Jaw: A Review

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Bisphosphonates are drugs used to inhibit osteoclast and decrease bone metabolism. They are mainly used to treat bone lesions associated with malignancy. The most recent complication of bisphosphonate treatment is osteonecrosis of the jaw associated with local risk factors, such as surgical dental procedure, and/or periodontal/periapical infections. Early diagnosis is the only key to preventing further progression of the lesion. This review paper highlights the different imaging modalities, which help in early diagnosis, and management of the lesion.

Keywords: Bisphosphonates, Imaging modalities, Multiple myeloma

INTRODUCTION

Osteonecrosis of the jaw is a well-recognized difficulty associated with bisphosphonates therapy. The first explanation of bisphosphonates-related osteonecrosis was given by Marx,¹ Migliorati,² and Wang *et al.*³ Intravenous bisphosphonates are mainly used for the management of conditions associated with cancer, such as hypercalcemia of malignancy, lytic lesions associated with multiple myeloma, and skeletal-related events due to bone metastases of solid tumors such as breast cancer, prostate cancer, and lung cancer. The primary purpose of bisphosphonate is to improve comorbid situations associated with cancer.⁴ Other common uses of bisphosphonates include osteoporosis,^{5,6} Paget's disease,⁷ and osteogenesis imperfecta.⁸ The latest term proposed by the American Association of Oral and Maxillofacial Surgeons is medication-related osteonecrosis of the jaw (MRONJ) as similar types of lesions are seen due to antiangiogenic drugs.⁹

The modified definition of MRONJ is:

1. Current or previous treatment with antiresorptive and/or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks, and

3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.⁹

Clinical Signs and Staging (Table 1)

The clinical stages of BRONJ are given by (Ruggiero *et al.*, 2009)⁹ and later used by American Association of Oral and Maxillofacial Surgeons (Table 1). The staging system helps to diagnose BRONJ cases and provide appropriate treatment to the patients.¹⁰

Imaging Findings

Imaging findings provide an important piece of information with respect to course and magnitude of BRONJ. Imaging modalities including periapical and panoramic radiographs, computed tomography (CT) scan, magnetic resonance imaging (MRI), and bone scans are helpful know the extent of the disease. The diagnostic techniques are also helpful differentially diagnose the lesion.¹¹ These radiographic features of BRONJ include bone sclerosis, cortical bone erosion, and formation of bone sequestrum, osteolysis, and persistent alveolar socket after tooth extraction, periosteal neoformation¹² thickening of the lamina dura, periradicular radiolucencies, and narrowing of the mandibular canal.¹³

Panoramic radiograph helps in overall assessment of entire jaw, and in revealing areas of bone destruction in all patients with symptomatic BRONJ. The osteolytic lesions show patchy radiolucent areas and sporadically radiopaque sequestra of necrotic bone.¹² Keeping in mind that 30-50% of mineral loss of bone should be present before its visualization on radiographs, it is usually difficult to interpret initial osteolytic lesions on panoramic radiograph.^{12,14} According to a study by Dore *et al.*,¹⁴ it

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Table 1: Current staging and treatment guidelines by American Association of Oral and Maxillofacial Surgeons on bisphosphonate-related osteonecrosis of the jaw⁹

At risk	<ul style="list-style-type: none"> • Asymptomatic • No necrotic bone present • History of treatment with oral or IV bisphosphonates 	
Stage 0	<ul style="list-style-type: none"> • No clinical evidence of necrotic bone • Nonspecific symptoms or clinical or radiographic findings present: <ul style="list-style-type: none"> Symptoms <ul style="list-style-type: none"> • Odontalgia not because of an odontogenic cause • Dull, aching bone pain • Sinus pain • Altered neurosensory function Clinical findings <ul style="list-style-type: none"> • Loosening of teeth not caused by periodontal disease • Periapical/periodontal fistula not associated with a necrotic pulp Radiographic findings <ul style="list-style-type: none"> • Alveolar bone loss/resorption not because of periodontal disease • Dense, woven, or persistent unremodelled bone in extraction socket • Thickening of the PDL • Narrowing of IA canal 	<ul style="list-style-type: none"> • Systemic management with pain medications, and/or antibiotics
Stage 1	<ul style="list-style-type: none"> • Exposed and necrotic bone present • Asymptomatic with no evidence of infection 	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education, and review of indications for continued bisphosphonate therapy
Stage 2	<ul style="list-style-type: none"> • Exposed and necrotic bone present • Pain and clinical evidence of infection 	<ul style="list-style-type: none"> • Oral antibacterial mouth rinse and pain control • Superficial debridement to relieve soft tissue irritation
Stage 3	<ul style="list-style-type: none"> • Exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral-antral/oral-nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor 	<ul style="list-style-type: none"> • Antibiotic therapy, and pain control • Surgical debridement/resection for longer term palliation of infection, and pain

IV: Intravenous, IA: Inferior alveolar, PDL: Periodontal ligament

is difficult to differentiate necrotic areas from normal bone or osteolytic lesions from metastases on panoramic radiograph. Chiandussi *et al.*¹² dealt with the two basic problems while interpreting BRONJ cases using panoramic radiographs: (1) Inability to define margins between necrotic areas and healthy bone and (2) understanding the actual extent of the lesion because of the two-dimensional image of three-dimensional structures. The above problems were overcome using CT, and MRI as they both show images in all three planes (axial, sagittal, and coronal sections).

CT Findings

The initial BRONJ findings are focal sclerosis with a disorganized trabecular pattern and loss of corticomedullary differentiation.¹⁵ The advancement of the disease involves periosteal reaction and sequestrum formation.¹⁶ Bianchi *et al.*¹⁶ conducted a cluster analysis and grouped patients into four categories depending on their CT findings.

- No signs
- Included the presence of trabecular alteration and cortical bone erosion
- Included the findings for group B plus osteosclerosis and sequestration <15 mm
- Included the findings for group C and where the size of sequestration was larger than 15 mm.

The statistical analysis in their study concluded that the advancement of CT staging is directly related to a greater clinical extension of the lesion. The authors also suggested CT stages of 0, I, II, and III correspond to Group A to D as a possible imaging correlation to the clinical staging.¹⁶

Bisdas *et al.*¹⁵ in their study predominantly found osteolysis with the destruction of cortices followed by sclerosis with periosteal bone proliferation. They also observed the reduced size of marrow spaces.

Cone-beam CT (CBCT) Findings

CBCT involves relatively low cost and low radiation dose as compared to conventional CT scans at a high isotropic spatial resolution ranging from 0.4 mm to as low as 0.076 mm.¹⁷⁻²⁰ The dose of CBCT is 5-74 times that of a single film-based panoramic X-ray. Modifications in patient positioning (tilting the chin) and the use of thyroid collar can appreciably reduce the dose by up to 40%.^{21,22} The dose delivered by CBCT is 3 to 20% of a CT scan, which also depends on the equipment used, and the area scanned.²³ Guggenberger *et al.*^{24,45} suggested that CBCT may be able to detect initial bone changes, such as periosteal thickening, alteration in the trabecular pattern, cortical erosion, and changes in bone density before clinical evidence of necrotic bone.

Limitations of CBCT

1. The major limitation of CBCT is a large amount of scattered radiation due to large FOV that affects the image quality related to noise and contrast resolution.²⁰
2. CBCT use is limited to bone lesions because of its narrow soft tissue window. Thus, lesions which extend into soft tissues, involving cervical lymph nodes, nasal mucosa, and maxillary sinus cannot be interpreted appropriately on CBCT.¹¹

MRI Findings

The MRI is used to assess bone marrow, surrounding soft tissues, neurovascular bundles, and lymphadenopathy in BRONJ cases. On MRI, changes related to inflammatory fluid result in low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images.¹¹ The necrotic changes on MRI show a low-signal intensity surrounded by an increased signal intensity rim on both T1- and T2-weighted images.¹²

Garcia-Ferrer *et al.*²⁶ studied MRI findings in 14 patients with clinically absent BRONJ lesions. In their study, they found viable bone areas as low-signal intensity on T1-weighted images, and high-signal intensities on T2-weighted images because of inflammatory fluid.^{26,27} Necrotic bone areas showed hypointense signals on both T1- and T2-weighted images.²⁶ Bedogni *et al.*²⁸ reported two patterns of BRONJ on MRI in 11 patients. These MRI patterns were in accordance with the histopathological features. In the first pattern, clinically evident exposed bone areas showed low signal intensity on both T1- and T2-weighted images, and inversion recovery images. These findings were indicative of low water content, and histopathologically osteoblasts, osteoclasts, and vessels were absent. In the areas of non-exposed bone, second pattern was observed. This area showed hypointensity on T1-weighted and hyperintensity on T2-weighted and inversion recovery images, suggesting high water content, and inflammation. The histopathology of non-exposed bone showed hypervascularity, hypercellularity, and osteogenesis.²⁸

Nuclear Bone Scanning

The three-phase bone scan screening modality is used to diagnose osteonecrosis.²⁹ The first phase is also called the nuclear angiogram or flow phase. In this Phase, 2-5 serial images are obtained during injection of the radiopharmaceutical agent. In second phase, the blood pool images are obtained within 5 minutes of injection. The pooling/flowing of blood increases in areas of inflammation because of capillaries dilatation. In the third phase, bone images are obtained after 3 h when urine excretion of radionuclide agent decreases in soft tissues.³⁰ The uptake of radiopharmaceutical agent (Tc99m) is dependent on

osteoblastic activity and skeletal vascularity. Bone scans are more sensitive than conventional radiography because it shows abnormal radionuclide uptake 10-14 days before significant bone mineral loss on conventional films.³⁰ Hence, early subclinical diseases such as osteomyelitis and osteonecrosis bones are easily detected.

Lapa *et al.*³¹ reported 32 patients with clinical symptoms of BRONJ who underwent three-phase bone scanning for diagnosis. The symptoms of BRONJ reported were exposed bone (81.3%), pain (31.3%), fistula (18.8%), and swelling (15.6%). The inclusion criteria were to complete a three-phase bone scan and additional single-photon emission computed tomography (SPECT) or SPECT/CT scans during the second and third phase. The procedure followed in their study was as follows: (1) The acquisition of image started immediately after IV injection of 520-750 MBq 99mTc-labeled MDP. Dynamic images of the head were obtained (dynamic first phase). (2) After 5 min of injection, the blood-pool images (second phase) were obtained using a 128 × 128 matrixes (for 5 min) and then, SPECT images were performed for 10 min. (3) A whole-body scintigraphy was performed 3 h after the injection, with static scanning at a speed of 15 cm/min, using a dual-head F camera followed by a dedicated scintigram of the head.

Scintigraphic Findings

The dynamic first phase was suspicious for ORNJ because it showed increased perfusion of the bone structure in 18/32 patients (56.3%). The positive blood-pool phase was observed in 25 patients (78.1%) and late phase in 27 patients (84.4%). The SPECT imaging in late phase was observed positive in all 32 patients. It improved the diagnostic accuracy in 5 patients, which did not show bone necrosis on planar scintigrams.

Raje *et al.*²⁷ reported fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, F-18 sodium fluoride (NaF)-PET/CT findings in 11 patients with multiple myeloma. NaF helps evaluate bone mineralization in the jaws because of its correlation to bone turnover, and mineralization. Patients were injected with fluorodeoxyglucose (FDG) PET/CT and NaF on different days to evaluate glucose metabolism and bone mineralization, respectively. Patients were informed to avoid physical exertion a day before the (FDG) PET/CT scan and fast for at least 6 h what? before the FDG injection. NaF PET/CT scan was taken without any patient preparation. After 60 min of radiopharmaceutical injection, whole-body PET/CT scan (focused on head and neck) was taken to evaluate other potential sites of disease.

Interpretation

The oral cavity was divided into four quadrants: Right and left maxilla, right and left mandible. The PET/CT scan

was interpreted by a nuclear medicine physician, who analyzed quantitative standardized uptake value (SUV) on the head and neck PET/CT images. The radiologist first stated whether each quadrant was definitely normal or abnormal for both modalities. They found total 17 clinically involved quadrants and the rest 27 were labeled as a control. All patients had undergone FDG-PET and NaF-PET scan except one who did not go for NaF-PET. They manually identified areas of increased FDG or NaF using a 70% threshold of the maximum uptake. For each affected site, a control (background) region was identified either on normal contralateral side or any other similar normal area in the case of bilateral disease. SUV was calculated by differences in patient weight and injected activity according to the following formula:

$$\text{SUV} = \frac{\text{Radioactive concentration (mCi / cc)} \times \text{patient weight (g)}}{\text{Injected dose(mCi)}}$$

The maximum SUV uptake (SUVmax) was calculated for each diseased and background region. Their ratio (lesion-to-background SUVmax) was also calculated to allow relative comparisons between FDG and NaF uptake and image contrast.

The FDG-PET and NaF-PET scan revealed abnormal focal uptake in 12 of 17 involved quadrants and 13 of 16 quadrants, respectively. The quadrants which showed increased uptake on both FDG- and NaF-PET, the NaF uptake was more intense and extensive by visual analysis. Of 27 clinically unaffected quadrants, two had focal abnormal tracer uptake on FDG-PET. Because one patient did not go for a NaF-PET scan, so out of 24 clinically unaffected quadrants three showed focal abnormal tracer uptake. The target-to-background ratio of SUVmax for the NaF-PET was significantly greater than FDG-PET. These findings led to the conclusion that NaF scan is significantly superior to FDG in the identification of osteonecrosis cases.

DISCUSSION

The main aim of using different imaging modalities is to early diagnose BRONJ cases, prevent further progression of the lesion and provide effective treatment to the patient. In subclinical stages, BRONJ can remain asymptomatic for a long period and can significantly affect outcome of the treatment. BRONJ cases are typically recognized by exposed bone. The bone exposure is usually secondary to infection or trauma to healthy tissues due to irregular bony surfaces. The patients on low doses of oral bisphosphonates without any clinical evidence of BRONJ do not need any auxiliary radiographic examination other than routine dental examination. The patients on

higher doses of oral bisphosphonates or on intravenous bisphosphonates with clinical symptoms are at increased risk.

These patients should undergo additional radiographic examination such as anatomic imaging (periapical or panoramic radiographs) or advanced imaging such as CT, CBCT, MRI, and bone scanning to delineate the lesion. As far as possible patients should be chosen clinically if they are not chosen clinically the rate of false positive radiographic findings are high. This is because it is difficult to differentiate BRONJ radiographically from acute or chronic osteomyelitis, benign or malignant tumors, as well as metastasis, infected osteoradionecrosis, and non-specific inflammatory disease. The panoramic radiograph gives a good overview of the oral cavity but it is always better to go for advanced imaging. CT and CBCT both provide a precise location, margins, dimensions, and proximity to vital structure of lesion. It also helps detect changes of cortical and trabecular architecture. If the clinician has to choose between these two modalities, it is wiser to advice small field of view CBCT with high resolution because it provides similar diagnostic information with less radiation dose. MRI is another advanced imaging modality that provides similar information about bony changes in BRONJ but superior in evaluating bone marrow and surrounding soft tissue changes. The initial MRI changes show hypointense bone marrow signals on T1-weighted images. T2-weighted and short T1-weighted inversion recovery sequence show hyperintense signals because of increased inflammatory fluid content. In advanced stages, exposed bone shows hypointense areas and unexposed bone shows hyperintense areas on T2-weighted image. The bony sequestrem exhibits hypointense center with hyperintense peripheral rim on T2-weighted images. The most sensitive method to diagnose bone necrosis is scintigraphy. Patients with metastatic disease taking bisphosphonates usually advised bone scanning as routine investigating procedure. The radiopharmaceutical (99Tcm-MDP, 18F-FDG, and F-18 NaF) agent used during bone scanning is related to bone metabolism and blood pooling. Hence, this procedure is called "functional imaging." The functional imaging is an important treatment modality because it helps differentiate between tumor infiltration of multiple myeloma and BRONJ. This characteristic omits the need of biopsy and therefore prevent further trauma due to biopsy in osteonecrotic lesions. SPECT and Fusion SPECT/CT are better than plain scintigraphy because it helps to precisely locate osteonecrotic lesions with surroundings area.

CONCLUSION

All the above-mentioned imaging modalities help in early diagnosis of BRONJ lesions. These radiographic imaging techniques have their own benefits and problems associated

with them. The clinician should rationalize every case before prescribing any radiographic technique on the basis of clinical features, local risk factors, and comorbidities, the presence of metastatic tumor and cost of imaging.

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