Imaging modalities in medication-related osteonecrosis of the jaw: a literature review

• **Wellington Hideaki Yanaguizawa** Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, SP, Brazil • **Solange Kobayashi Velasco** Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, SP, Brazil • **Rodrigo Lima Petersen** Private Practice • **Fábio de Abreu Alves** Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, SP, Brazil • **Marcelo Gusmão Paraiso Cavalcanti** Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, SP, Brazil

ABSTRACT | Osteonecrosis occurs by cellular death of the bone tissue due to an irreversible external factor. This disorder may be clinically unidentified in the early stages and result in degradation of the bone architectural structure, leading to pain, bone destruction, and loss of function. Thus, imaging exams become relevant to the recognition and definition of the bone necroses. The aim of this study was to review the literature on imaging exams frequently used for the diagnosis and evaluation of patients undergoing drug therapies associated with osteonecrosis of the jaw, such as panoramic radiography, computed tomography, magnetic resonance imaging and bone scintigraphy.

DESCRIPTORS | Osteonecrosis; Panoramic Radiography; X-Ray Computed Tomography; Magnetic Resonance Imaging; Radionuclide Imaging.

RESUMO | **Modalidades de imagem na osteonecrose dos maxilares relacionada à medicamentos: revisão de literatura** • A osteonecrose ocorre pela morte celular do tecido ósseo devido a um fator externo irreversível. Esse distúrbio pode não ser clinicamente identificado nos estágios iniciais gerando quadros de dor, destruição da arquitetura óssea e perda de função. Assim, os exames de imagem se tornam relevantes para o reconhecimento e a definição das necroses ósseas. O objetivo deste estudo foi revisar a literatura a respeito das diferentes modalidades de exames de imagem frequentemente utilizados para diagnóstico e avaliação de pacientes submetidos a terapias medicamentosas associadas à osteonecrose dos maxilares, como a radiografia panorâmica, tomografia computadorizada, ressonância magnética e cintilografia óssea.

DESCRITORES | Osteonecrose; Radiografia Panorâmica; Tomografia Computadorizada; Ressonância Magnética; Medicina Nuclear.

CORRESPONDING AUTHOR | **Wellington Hideaki Yanaguizawa** School of Dentistry, University of São Paulo • **Av. Prof. Lineu Prestes, 2.227,** São Paulo, SP, Brazil • **05508-000** E-mail: wellingtonkibe@usp.br

• **Received** Dec.3, 2019 • **Accepted** Jan. 5, 2020.
• **DOI:** http://dx.doi.org/10.11606/issn.2357-8041.clrd.2020.164723

INTRODUCTION

Osteonecrosis – also known as avascular necrosis, ischemic necrosis or aseptic necrosis – is a pathological process caused by severe decrease in circulation in bone tissue resulting in the death of osteocytes and bone marrow cells. Osteonecrosis is not a disease-specific entity, but the common final course of many conditions leading to necrosis in any bone of the human body.[1]

In the maxillary region, osteonecrosis presents mainly as a result of two clinical situations: as a consequence of radiotherapy in the treatment of malignant neoplasms in head and neck regions, resulting in osteoradionecrosis, or as a side effect of drug therapy with antiangiogenic drugs, generating medication-related osteonecrosis of the jaw (MRONJ).[1,2] This is considered a rare but potentially severe adverse effect, and may affect the quality of life of these patients.[2]

The correct analysis of MRONJ through imaging exams is essential to investigate and assess this disease. Imaging exams provide information to outline the most favorable treatment plan for the patient.[3,4] Several studies exhibited MRONJ as incidental findings at different imaging exams, such as panoramic radiography (PR), computed tomography (CT), cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), and scintigraphy.[5–10] Thus, the purpose of this study was to present a literature review of different imaging exams that may be used to assess MRONJ patients.

MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

In 2003, the American surgeon Marx reported and described MRONJ[1]. The condition was first named "Bisphosphonates-related osteonecrosis of the jaw" (BRONJ) because of its relation to the use of the class of anti-resorptive drugs called bisphosphonates, both oral (alendronate, ibandronate and risedronate) and intravenous (pamidronate and zolendronic acid).[3,8] In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended the replacement of the term BRONJ for "Medication-related osteonecrosis of the jaw" (MRONJ), due to the increase in the number of cases of osteonecrosis of the jaws associated with other antiresorptive drugs, such as denosumab, and antiangiogenics, such as bevacizumab, sunitinib, sorafenib, imatinib and ziv-aflibercept, that is, not only bisphosphonates.[2,11–14]

These drugs have been used to control and treat many diseases, such as osteopenia and osteoporosis, hypercalcemia associated with bone metastasis of malignant neoplasms (especially multiple myeloma and metastatic bone cancer), fibrous dysplasia, Paget's disease, and imperfect osteogenesis.[13]

The clinical diagnosis of MRONJ was defined by the AAOMS following three mandatory conditions: presence of bone exposure area or persistent intra- or extra-oral fistula for eight weeks or more in patients without prior history of radiation therapy who were or are being treated with antiresorptive and/or antiangiogenic agents.

Epidemiology varies depending on the population and the study. According to Kim et al., about 0.1% of patients that receive the medication orally and 0.8 to 12% of patients that receive the medication intravenously may develop MRONJ.[14]

This type of osteonecrosis occurs most frequently associated with trauma, teeth extractions, implant surgery, and prostheses with stability or retention failures, associated to an infectious agent (periodontal or endodontic infection) or spontaneously.[6,15] Furthermore, factors such as the time of administration, dose and route of administration of these drugs are closely linked to the risk of developing MRONJ.[1,13]

Clinically, MRONJ affects the posterior mandible region, and may present local pain symptoms, areas of mucosal ulceration, purulent edema and secretions, tooth mobility, paraesthesia, and intra or extraoral fistulae.[13,14]

Treatment of osteonecrosis of maxillary bones is determined in consonance with the stage, severity of symptoms, functional impairment and general prognosis of the disease.[4] However, treatment protocols are still widely discussed, ranging between more conservative treatments with use of mouthwashes with chlorhexidine 0.12% in cases where bone exposure is asymptomatic (stage 1) or antibiotic therapy when there are reports of pain with bone exposure (stage 2), and more invasive procedures, such as debridement at the site of the lesion, or surgical resection of the affected area (stage 3).[15,16]

IMAGING MODALITIES

Radiographically, osteonecroses caused by different types of antiresorptive drugs are very similar. The nonspecificity of these images leads to diagnostic criteria that do not consider the radiographic characteristics only.[7,11,17] In addition, both methodologies and results in imaging studies among patients with MRONJ are greatly inconsistent, which has made it difficult to analyze the frequency of these radiographic findings.[3,5,6,10] Controversially, other studies have shown that imaging studies certainly have the potential to contribute significantly to both screening and initial diagnosis, as well as to the treatment and follow-up of these pathological processess.[5,8,18]

Panoramic radiography (PR)

PR is a radiographic exam widely used by professionals as initial assessment and follow-up of osteonecroses, since it provides a two-dimensional image involving all extension of both maxillary bones, as well as adjacent structures such as the nasal cavity and the maxillary sinuses, exposing the patient to a lower dose of radiation compared to three-dimensional exams.[9] However, because PR is a two-dimensional projection, it suffers limitations such as magnification, superposition and distortion of anatomical structures.[10] In cases where the lesions affect anterior regions, these lesions may be misdiagnosed due to the limitations of the examination.[9] Moreover, factors such as patient position and proper acquisition technique influence the quality of the PR image.[18]

The most common images visualized in PR are radiopaque signs compatible with diffuse osteosclerosis and/or radiolucent signs compatible with osteolysis, present in the region of non-healed alveolus after tooth extractions.[9,19] PR has also been used in the assessment of increased trabecular bone density, thickening of the mandibular canal cortices and osteosclerosis of the sinus floor caused by medications.[12,20]

Some studies correlate the increase in the lamina dura thickness with the periodontal space around the teeth and the occurrence of MRONJ; however, recent studies show that PR is not precise to demonstrate changes in the width of the periodontal space.[21] Other two-dimensional examinations, such as periapical radiographs, exhibit images that allow a more detailed assessment of the thickening of the lamina dura, enlargement of the periodontal ligament and the density of the bone trabeculae, as well as information on carious lesions, periodontal or periapical disease, which are important factors to increase the risk of osteonecrosis.[8]

As the disease evolves, in stages 2 and 3, areas of bone with mottled appearance or bone sequestration and neoformation of periosteal bone, identical to those present in Garré's osteomyelitis, may also be identified in this type of examination.[5] According to Barragan et al.,[22] the PR revealed the osteolytic lesions of osteonecrosis associated with the use of bisphosphonates, but it was neither able to show the real total extent of the lesion nor more detailed information of the area of bone sequestration as shown by the three-dimensional examinations.[22]

At a later stage, MRONJ may behave in a destructive manner, leading to areas of pathological fractures and

cortical ruptures, but the PR examination may not reveal the lines of bone fracture and will not be able to reveal the involvement of the lingual and buccal cortices, making it impossible to correctly analyze the behavior of the lesion in relationship with adjacent structures.[23]

Radiographic findings of MRONJ found in PR are nonspecific, being more evident when a decrease of 30-50% in bone mineral density occurs, that is, when bone involvement is more significant due to buccal / lingual cortical thickness.[9,23] Thus, the differential radiographic diagnosis by PR includes several other sclerotic, osteolytic and mixed lesions, such as chronic osteomyelitis, osteoradionecrosis, metastases, among others.[5] If diagnostic information is ambiguous and further investigation of bone integrity is necessary, it is advisable to use three-dimensional examinations.

Computerized tomography (CT)

The high resolution of the helical computed tomography (CT) allows better assessment of the region affected by MRONJ, and it provides more information about cortical thickness, as well as involvement, bone marrow integrity, bone mineral density, relationship with the mandibular canal and other adjacent structures, irregularities of the alveolus after tooth extraction and the limits of bone sequestration.[24]

As well as PR, it is also possible to assess areas that are compatible with bone sclerosis, hypodense regions compatible with osteolysis, thickening of the lamina dura, periosteal reaction, bone sequestration and mandible fractures.[17]

Obinata et al. assessed the imaging features present in the MRONJ by comparing helical computed tomography (CT) and PR, and they found that CT provided more detailed information of osteolysis, osteosclerosis, bone sequestration, and periosteal reactions than in PR.[23]

Cone-Beam Computed Tomography (CBCT) is an advantageous option to assess the maxillofacial complex, since it emits less radiation and entails lower costs when compared to helical CT.[25] However, the non-differentiation among soft tissues is a disadvantage.

Torres et al. evaluated three measurement techniques of images obtained by CBCT and concluded that at the mandible, cortical bone quantitative evaluation is a valuable method to be applied as early diagnostic manifestation. These authors observed that in patients exposed to bisphosphonates, bone alterations such as increase in thickness and volume of cortical bone occur prior to bone exposure.[25] Another study assessed the bone marrow and also found a significant alteration in the initial cases of the disease (stage 0), being a possible simple predictive indicator of bone exposures, since the CT values were described as reliable indicators of the predisposition to the development of the osteonecrosis.[24]

The imaging characteristics present in the MRONJ, even with the aid of the CBCT, may present differential diagnosis with several other diseases; the images of mixed radiodensity and periosteal reaction (aspect of “onion skin”) are also typical in osteomyelitis.[26] Furthermore, MRONJ images may produce similar imaging aspects of metastatic lesions necrotic bone or areas submitted to radiation therapy in cancer patients. Those characteristics may generate confusion during the diagnosis process.[27]

Magnetic Resonance Imaging (MRI)

As with CT, magnetic resonance imaging can also be used to analyze the local characteristics and extent of osteonecrosis, as well as soft tissue involvement.[8] Studies have shown that MRI can determine MRONJ involvement with more details when compared with CT scans.[18]

MRI can also be used in association with an intravenous contrast solution to assess the quality of the bone marrow, obtaining positive results in the diagnosis of initial lesions.[26] Gadolinium contrast reveals a low signal in the images of T1 and T2,

suggesting a tissue of low water content, explained by the fact that the pattern of the necrotic bone has shortage of cells and vessels; besides, it allows the differentiation between areas of bone sequestrum and hyperemia. Gadolinium contrast presents higher concentration in the latter.[7]

However, because it is a high-cost and difficult-to-access exam, radiographs and CBCT remain the most commonly used imaging exams for bone assessment and follow-up of osteonecroses.

Bone scintigraphy

Bone scintigraphy is an examination capable of detecting even small areas of bone necrosis by radioisotope uptake by exhibiting marking areas in the periphery and low radioactive uptake in the center, probably due to the lower osteoblastic activity and absence of blood supply in the area due to cell necrosis.[28] As a result, this is the most sensitive test for the detection of subclinical lesions and initial stages in maxillary bones.[15]

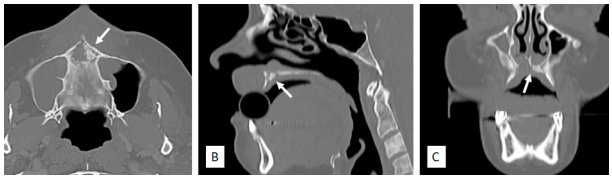

Figure 1 | Axial (A), Sagittal (B) and Coronal (C) planes on Computed Tomography images of a MRONJ case involving palatine bone (arrows).

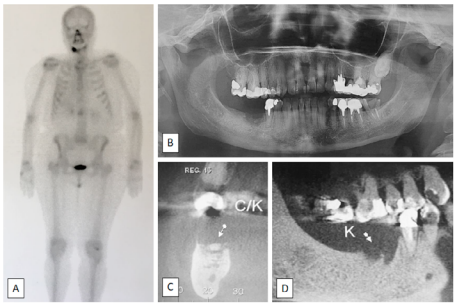

Figure 2 | Bone scintigraphy (A), Panoramic (B), coronal (C) and sagittal radiograph (D), and Cone-Beam Computed Tomography images (K arrow = bone resorption, C arrow = bone sequestrum) of a MRONJ case.

However, because it is an image examination of the whole skeleton, its resolution turns out to be of poor quality; in addition, the markers bind mainly in cells of greater metabolic activity. This aspect leads to a poor imaging differentiation among osteonecroses, tumors, bone metastases, osteomyelitis or bone inflammatory process, thus indicating that this examination modality has low specificity.[26]

CONCLUSIONS

MRONJ is usually diagnosed late, presenting bone exposure in the oral cavity and a combination of different types of imaging tests such as panoramic radiography, computed tomography, magnetic resonance imaging and bone scintigraphy may be relevant to identify these osteonecroses in the jaws. The costs of these methods vary greatly, as well as their accuracy and the information they provide. PR, CT and MRI are considered important examinations in the general evaluation of the lesions, the latter two being important in assessing the limits of the disease. MRI, as well as BS, may be useful in detecting subclinical osteonecrosis when the bone is not exposed. However, BS has no specificity and low resolution.

ACKNOWLEDGEMENT

The authors are grateful to Dr. Valéria Tognato for providing them with the scintigraphy's case images.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Fondi C, Franchi A. Definition of bone necrosis by the pathologist. Clin Cases Miner Bone Metab. 2007;4(1):21-6.
2. Ruggiero SL, Dodson TB, Fantasia J, Goddday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw-2014 Update. J Oral Maxillofac Surg. 2014;72(10):1938-56. doi: https://doi.org/10.1016/j.joms.2014.04.031

3. Wilde F, Heufelder M, Lorenz K, Liese J, Helmrich J, Schramm A, et al. Prevalence of cone beam computed tomography imaging findings according to the clinical stage of bisphosphonate-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(6):804-11. doi: https://doi.org/10.1016/j.oooo.2012.08.458
4. Miyashita H, Shiba H, Kawana H, Nakahara T. Clinical utility of three-dimensional SPECT/CT imaging as a guide for the resection of medication-related osteonecrosis of the jaw. Int J Oral Maxillofac Surg. 2015;44(9):1106-9. doi: https://doi.org/10.1016/j.ijom.2015.05.002
5. Phal PM, Myall RWT, Assael LA, Weissman JL. Iumaging findings of bisphosphonate-associated osteonecrosis of the jaws. Am J Neuroradiol. 2007;28(6):1139-45. doi: https://doi.org/10.3174/ajnr.A0518
6. Guggenberger R, Fischer DR, Metzler P, Andreisek G, Nanz D, Jacobsen C, et al. Bisphosphonate-induced osteonecrosis of the jaw: Comparison of disease extent on contrast-enhanced MR imaging, [18F] fluoride PET/CT, and conebeam CT imaging. Am J Neuroradiol. 2013;34(6):1242-1247. doi: https://doi.org/10.3174/ajnr.A3355
7. Berg BI, Mueller AA, Augello M, Berg S, Jaquiéry C. Imaging in patients with Bisphosphonate-Associated Osteonecrosis of the Jaws (MRONJ). Dent J. 2016;4(3):29. doi: https://doi.org/10.3390/dj4030029
8. Arce K, Assael LA, Weissman JL, Markiewicz MR. Imaging findings in bisphosphonate-related osteonecrosis of jaws. J Oral Maxillofac Surg. 2009;67(5 Suppl.):75-84. doi: https://doi.org/10.1016/j.joms.2008.12.002
9. Treister N, Sheehy N, Bae EH, Friedland B, Lerman M, Woo S. Dental panoramic radiographic evaluation in bisphosphonate-associated osteonecrosis of the jaws. Oral Dis. 2009;15(1):88-92. doi:https://doi.org/10.1111/j.1601-0825.2008.01494.x
10. Guo Y, Wang D, Wang Y, Peng X, Guo C. Imaging features of medicine-related osteonecrosis of the jaws: comparison between panoramic radiography and computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):e69-e76. doi: https://doi.org/10.1016/j.oooo.2016.04.007
11. Klingelhoffer C, Klingelhoffer M, Muller S, Ettl T, Wahlmann U. Can dental panoramic radiographic findings serve as indicators for the development of medication-related osteonecrosis of the jaw? Dentomaxillofacial Radiol. 2016;45(5). doi: https://doi.org/10.1259/dmfr.20160065
12. Taniguchi T, Ariji Y, Nozawa M, Naioth M, Kuroiwa Y, Kurita K, et al. Computed tomographic assessment of early changes of the mandible in bisphosphonate-treated patients. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(3):362-72. doi: https://doi.org/10.1016/j.oooo.2016.06.002
13. Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al. Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. J Bone Miner Metab. 2017;35(1):6-19. doi: https://doi.org/10.1007/s00774-016-0810-7
14. Kim KM, Rhee Y, Kwon Y, Kwon TG, Lee JK, Kim DY. medication related osteonecrosis of the jaw: 2015 Position Statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons. J Bone Metab. 2015;22:151-65. doi: https://doi.org/10.11005/jbm.2015.22.4.151
15. Vassiliou V, Tselis N, Kardamakis D. Osteonecrosis of the jaws: Clinicopathologic and radiologic characteristics, preventive and therapeutic strategies. Strahlenther Onkol. 2010;186(7):367-373. doi: https://doi.org/10.1007/s00066-010-2066-9
16. Pautke C, Bauer F, Otto S, Tischer T, Steiner T, Weitz J, et al. Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: First clinical results of a prospective pilot study. J Oral Maxillofac Surg. 2011;69(1):84-91. doi: https://doi.org/10.1016/j.joms.2010.07.014
17. Bedogni A, Fedele S, Bedogni G, Scoletta M, Favia G, Colella G, et al. Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease. Br J Oral Maxillofac Surg. 2014;52(7):603-8. doi: https://doi.org/10.1016/j.bjoms.2014.04.009
18. Leite AF, Ogata FS, Melo NS, Figueiredo PT. Imaging findings of bisphosphonate-related osteonecrosis of the jaws: a critical review of the quantitative studies. Int J Dent. 2014;2014. doi: https://doi.org/10.1155/2014/784348
19. Khan AA, Morrison A, Hanley DA, Felsenborg D, McCuley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. J Bone Miner Res. 2015;30(1):3-23. doi: https://doi.org/10.1002/jbmr.2405
20. Motta ACF, Macedo LD, Santos GG, Gerreiro CT, Ferrari T, Oliveira TF, et al. Quantitative ultrasound at the hand phalanges in patients with bisphosphonate-related osteonecrosis of the jaws. Braz Oral Res. 2015;29(1):1-9. doi: https://doi.org/10.1590/1807-3107BOR-2015.vol29.0106
21. Assaf AT, Amberg V, Smeets R, Wikner J, Hanken H, Semmusch J, et al. Evaluation of periodontal space widening in patients with antiresorptive drug-related osteonecrosis of the jaws (ARONJ) on panoramic radiographs. Anticancer Res. 2018;38(9):5305-14. doi: https://doi.org/10.21873/anticanres.12857
22. Barragan-Adjemian C, Lausten L, Ang DB, Johnson M, Katz J, Bonewald LF. Bisphosphonate-related osteonecrosis of

the jaw: model and diagnosis with cone beam computerized tomography. Cells Tissues Organs. 2008;189(1-4):284-8. doi: https://doi.org/10.1159/000151451

23. Obinata K, Shirai S, Ito H, Nakamura M, Carrozzo M, Macleod I, et al. Image findings of bisphosphonate related osteonecrosis of jaws comparing with osteoradionecrosis. Dentomaxillofac Radiol. 2017;46(5):20160281. doi: https://doi.org/10.1259/dmfr.20160281
24. Hamada H, Matsuo A, Koizumi T, Satomi T, Chikazu D. A simple evaluation method for early detection of bisphosphonate-related osteonecrosis of the mandible using computed tomography. J Craniomaxillofac Surg. 2014;42(6):924-9. doi: https://doi.org/10.1016/j.jcms.2014.01.012
25. Torres SR, Chen CSK, Leroux BG, Lee PP, Hollender LG, Santos EC, et al. Mandibular cortical bone evaluation on cone beam computed tomography images of patients with bisphosphonate-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(5):695-703. doi: https://doi.org/10.1016/j.0000.2011.11.011
26. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. Dentomaxillofac Radiol. 2006;35(4):236-43. doi: https://doi.org/ 10.1259/dmfr/27458726
27. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008;83(9):1032-45. doi: https://doi.org/10.4065/83.9.1032
28. Dore F, Filippi L, Biasotto M, Chiandussi S, Cavalli F, Di Lenarda R. Bone scintigraphy and SPECT/CT of bisphosphonate-induced osteonecrosis of the jaw. J Nucl Med. 2008;50(1):30-5. doi: https://doi.org/10.2967/jnumed.107.048785