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Characteristic Multimodal Imaging of Medication-Related Osteonecrosis of the Jaw: Comparison Between Oral and Parenteral Routes of Medication Administration

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: To assess multimodal imaging features of medication-related osteonecrosis of the jaw (MRONJ) and to analyze the differences between oral and parenteral routes of medication administration. We retrospectively reviewed panoramic radiographs, CT, MRI, and bone scintigraphy of patients with MRONJ.

Material/Methods: A retrospective study was conducted in 16 patients with MRONJ who underwent panoramic radiography, CT, MRI, and bone scintigraphy. Statistical analysis for the comparison between routes of medication administration and multimodal imaging features was performed with the Pearson's χ^2 test.

Results: The percentage of cases with sequestrum separation was 25.0% (4/16 cases) on panoramic radiography and 81.3% (13/16 cases) on CT. The percentage of cases with periosteal bone proliferation on CT was 41.7% (5/12 cases) in the oral route of administration *vs.* 100% (4/4 cases) in the parenteral route of administration (p=0.042). The percentage of cases with spread of soft tissue inflammation to buccal and other spaces on CT and MRI was 33.3% (4/12 cases) in the oral route of administration *vs.* 100% (4/4 cases) in the parenteral route of administration (p=0.021).

Conclusions: The sequestrum separation on panoramic radiography in patients with MRONJ was unclear in comparison to CT. Furthermore, characteristic CT findings of patients with MRONJ in the parenteral administration group were periosteal bone proliferation and spread of soft tissue inflammation to buccal and other spaces.

MeSH Keywords: **Resonance Imaging • Mouth • Radiography • Tomography Scanners, X-Ray Computed**

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Background

Bisphosphonates are inhibitors of osteoclastic bone resorption. They are effective in treating osteoporosis and other metabolic bone diseases, and prevent skeletal events associated with metastatic neoplasms [1–5]. Although bisphosphonates are effective, they are also implicated in the development of medication-related osteonecrosis of the jaw (MRONJ) [6,7].

In recent years, many authors have reported that long-term use of bisphosphonates and other anti-resorptive medications, especially long-term high-dose intravenous bisphosphonates, may cause osteonecrosis of the jaws

Table 1. Characteristics of the patients with MRONJ.

Number of patients	Administration of medication		
	Oral (12)	Inject (4)	Total (16)
Age (years)			
Mean ±SD	81.3±5.4	61.0±10.6	76.2±11.2
Range	74–89	48–73	48–89
Sex			
Male	0	0	0
Female	12	4	16
Primary disease			
Osteoporosis	11	0	11
Rheumatism	1	0	1
Osseous metastases of breast cancer	0	4	4
Medication			
Alendronate	5	0	5
Risedronate	5	0	5
Minodronate	2	0	2
Zoledronate	0	3	3
Denosumab	0	1	1
Location of MRONJ			
Mandible	11	4	15
Maxilla	1	0	1
Staging of MRONJ			
Stage 1	0	0	0
Stage 2	0	0	0
Stage 3	10	3	13
Stage 4	2	1	3

MRONJ – medication-related osteonecrosis of the jaw; SD – standard deviation.

(MRONJ) [8]. Such patients are often referred to radiological institutes for the evaluation of bisphosphonate-induced changes in the jaws, and in order to exclude other diseases of the jaws, e.g., infected osteoradionecrosis or chronic osteomyelitis. Such an evaluation of the jaws is necessary before all orofacial procedure can be performed [9].

Panoramic radiography is one of the imaging modalities that is used most commonly by dentists and oral and maxillofacial surgeons because of their familiarity with this modality. Computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy offer a greater advantage compared with panoramic radiography as regards the evaluation of the jaws. Imaging of the jaws is important in the diagnosis and management of MRONJ. The aim of this study was to assess multimodal imaging features of medication-related osteonecrosis of the jaw (MRONJ) and to compare between oral and parenteral routes of medication administration, with the use of panoramic radiography, CT, MRI, and bone scintigraphy.

Material and Methods

Patients

This retrospective study was approved by the ethics committee of our institution. After providing written informed consent, 16 patients (0 male, 16 female; age 48–89 years, mean age 76.2 years) with MRONJ underwent panoramic radiography, CT, MRI, and bone scintigraphy in our university hospital from January 2012 to September 2016. The diagnosis of MRONJ was made according to the position papers of the American Association of Oral and Maxillofacial Surgery [10], as follows: (1) current or previous treatment with a bisphosphonate; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks; and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws. Furthermore, the histopathological diagnoses of MRONJ

Table 2. Multimodality imaging features of MRONJ with panoramic radiography, CT, MRI and bone scintigraphy.

Imaging features	Administration of medication			P-value
	Oral	Inject	Total	
Panoramic radiography	12 patients	4 patients	16 patients	
Osteolytic changes of the jaws	12 (100%)	4 (100%)	16 (100%)	
Sclerotic lesions	12 (100%)	4 (100%)	16 (100%)	
Sequestrum separation	4 (33.3%)	0 (0%)	4 (25.0%)	0.182
CT images	12 patients	4 patients	16 patients	
Osteolytic changes of the jaws	12 (100%)	4 (100%)	16 (100%)	
Sclerotic lesions	12 (100%)	4 (100%)	16 (100%)	
Sequestrum separation	11 (91.7%)	2 (50.0%)	13 (81.3%)	0.064
Periosteal bone proliferation	5 (41.7%)	4 (100%)	9 (56.3%)	0.042*
External dental fistula	2 (16.7%)	1 (25.0%)	3 (18.8%)	0.712
Spread of soft tissue inflammation				
Buccal space	8 (66.7%)	0 (0%)	8 (50.0%)	
Buccal and other spaces	4 (33.3%)	4 (100%)	8 (50.0%)	0.021*
MR images	12 patients	4 patients	16 patients	
Special attention to intensity changes	12 (100%)	4 (100%)	16 (100%)	
Pathological gadolinium enhancement	12 (100%)	4 (100%)	16 (100%)	
Spread of soft tissue inflammation				
Buccal space	8 (66.7%)	0 (0%)	8 (50.0%)	
Buccal and other spaces	4 (33.3%)	4 (100%)	8 (50.0%)	0.021*
Bone scintigraphy	4 patients	1 patient	5 patients	
Increased uptake	4 (100%)	1 (100%)	5 (100%)	

* Significant difference ($p<0.05$).

were confirmed by surgery in all cases. Table 1 shows characteristics of the patients with MRONJ.

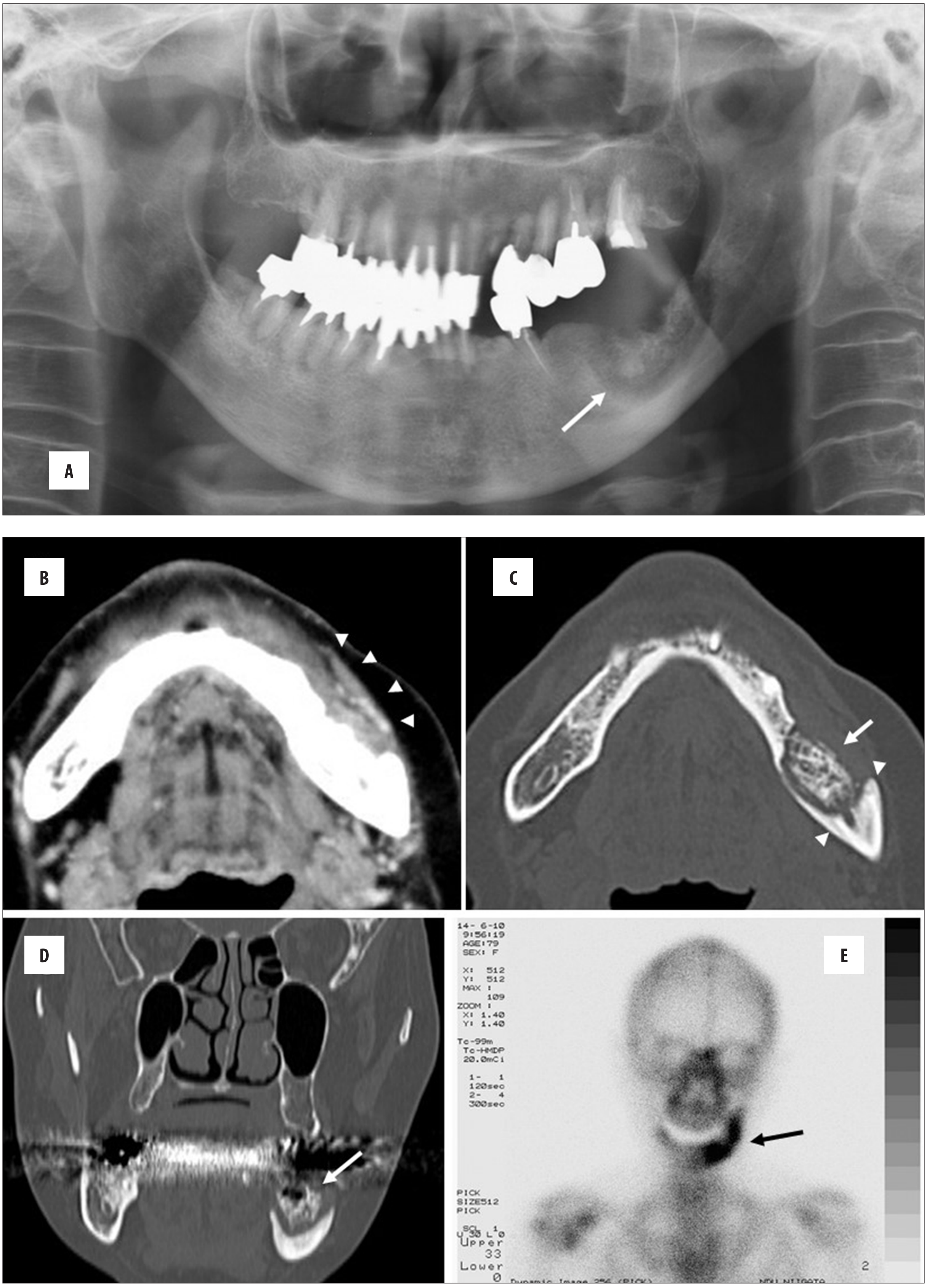
Image acquisition

Panoramic radiographs were performed with a panoramic machine (Veraviewepocs; J MORITA MFG, Kyoto, Japan) using the maxillofacial protocol of our hospital, as follows: tube voltage, 70 kV; tube current, 10 mA.

CT imaging was performed with a 16-multidetector CT scanner (Aquilion TSX-101A; Toshiba Medical Systems, Otawara, Japan) using the maxillofacial protocol of our hospital, as follows: tube voltage, 120 kV; tube current, 300 mA; field of view, 240×240 mm; and rotation time, 0.5 s. The protocol consisted of axial acquisition (0.50 mm) with axial, coronal, and sagittal multiplanar reformation (MPR) images. The patients underwent contrast-enhanced CT (CECT) with nonionic iodine to assess head and neck lesions. One nonionic contrast agent was used, Iohexol 300 mgI/mL (Omunipaque 300 Syringe, Daiichi-Sankyo, Tokyo, Japan). The contrast agent was administered as an injection (100 mL), at a rate of 2.0 mL/s (Autoenhance A-250, Nemoto-Kyorindo, Tokyo, Japan).

The MR images (head coil, 1.5 Tesla MR unit; EXCELART Vantage MRT-2003; Toshiba Medical Systems, Otawara, Japan) included unenhanced axial T1 sequences [repetition time (TR) 660 ms, echo time (TE) 12 ms], T2-weightted sequences (TR 4000 ms, TE 120 ms), short TI inversion recovery sequences (TR 2500 ms, TE 15 ms, TI 190 ms), and coronal T1-weighted sequences. After injecting contrast medium (gadobutrol; Gadovist 1.0mol/L Syringe, Bayer, Osaka, Japan; 0.1 mL/kg), axial and coronal T1-weighted images (TR 660 ms, TE 12 ms) were acquired.

Four hours after injection, bone scintigraphy was performed with an SNC-5100R (Shimadzu, Kyoto, Japan) and a Scintipack 24000 (Shimadzu) with a 128×128 matrix. The images were recorded on a computer at 5 min/frame. The radiopharmaceutical used in this study was ^{99m}Tc-labeled hydroxymethylene diphosphonate (^{99m}Tc HMDP) (Nihon Medi-Physics, Tokyo, Japan). Each patient was administered the agent at a dose of 14.8 MBq/kg of body weight,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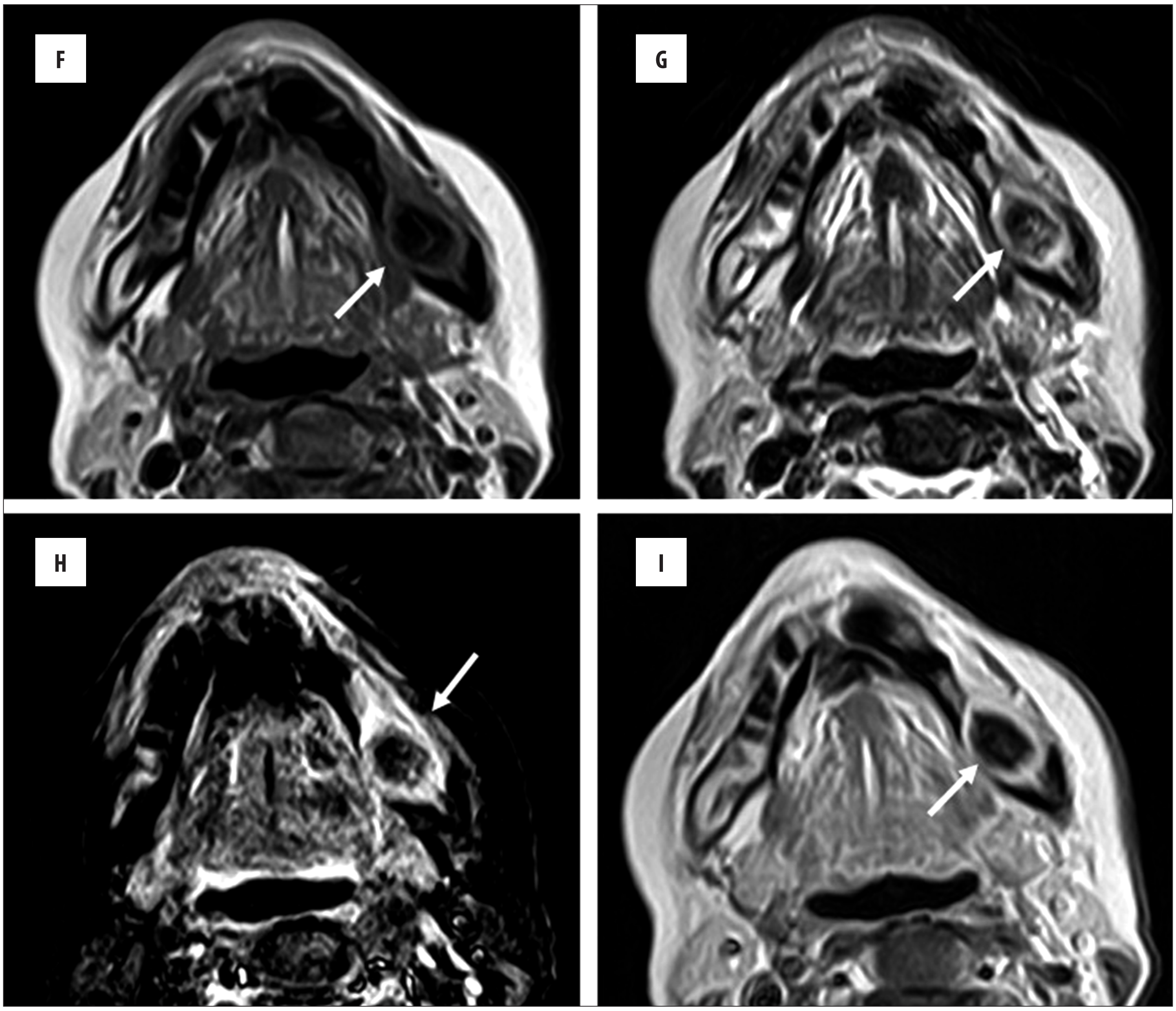


Figure 1. Multimodal imaging in a 79-year-old woman with osteoporosis who received oral alendronate. The patient presented with left mandibular pain. Panoramic radiography (**A**) shows osteolytic changes in the jaws and sclerotic lesions, however, sequestrum separation was unclear (arrow). Axial contrast-enhanced CT image (**B**) shows spread of soft tissue inflammation to buccal space (arrowheads). Axial (**C**) and coronal (**D**) bone tissue algorithm CT shows osteolytic changes in the jaws, sclerotic lesions, sequestrum separation (arrow), and periosteal bone proliferation (arrowheads). Bone scintigraphy (**E**) shows increased uptake (arrow). On MRI, axial T1-weighted image (T1WI) (**F**) revealed homogeneous, low-signal intensity with no hyperintensity, suggestive of sequestrum (arrow). Post-contrast T1WI (**I**) showed heterogeneous enhancement and a non-enhancing portion, suggestive of sequestrum (arrow). T2-weighted image (T2WI) (**G**) and short TI inversion recovery (STIR) (**H**) revealed heterogeneous, high-signal intensity with no hyperintensity and spread of soft tissue inflammation to buccal space (arrow).

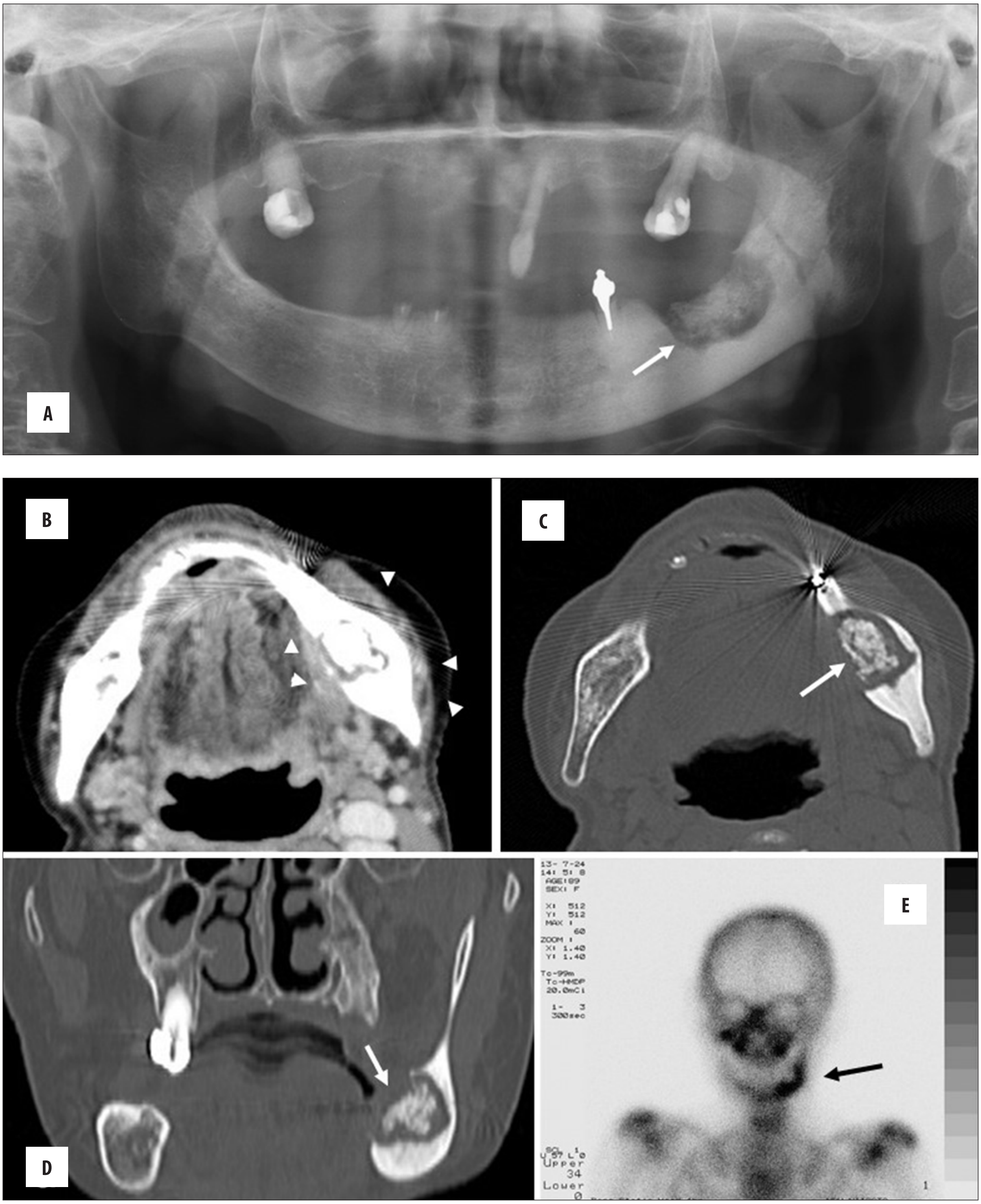
with a rapid intravenous injection. The stored data were displayed on a screen for analysis.

Image analysis

Two oral and maxillofacial radiologists, with over 20 years of experience, independently reviewed all images, and any discrepancies were resolved by consensus. The panoramic radiographs were reviewed with regard to osteolytic changes of the jaws, sclerotic lesions, and sequestrum separation. The acquired CT images were reviewed with regard to osteolytic changes of the jaws, sclerotic lesions, sequestrum separation, periosteal bone proliferation, external dental fistula, and spread of soft tissue inflammation (buccal, submandibular, sublingual, masticator, and parapharyngeal space). The MR images of the jaws were assessed with special attention to intensity changes of the cortical and subcortical bony structures, pathological gadolinium enhancement, and spread of soft tissue inflammation (buccal, submandibular, sublingual, masticator, and parapharyngeal space). Bone scintigraphy of the jaws was assessed with increased uptake.

Statistical analysis

Statistical analysis for the comparison between routes of administration and multimodal imaging features of panoramic radiography, CT, MRI, and bone scintigraphy was performed with the Pearson's χ^2 test. These analyses were performed with the IBM SPSS Statistics statistical package,



version 24 (IBM Japan, Tokyo, Japan). A P lower than 0.05 was considered as statistically significant.

Results

Table 2 shows multimodal imaging features of MRONJ that were seen on panoramic radiography, CT, MRI, and bone scintigraphy. All cases showed osteolytic changes in the jaws and sclerotic lesions on panoramic radiography and CT. The percentage of cases with sequestrum separation was 25.0% (4/16 cases) on panoramic radiography and 81.3% (13/16 cases) on CT.

Regarding the comparison between oral and parenteral routes of administering medication, the percentage of cases with periosteal bone proliferation on CT was 41.7% (5/12 cases) in the case of oral administration *vs.* 100% (4/4 cases) in the case of parenteral administration ($p=0.042$). All

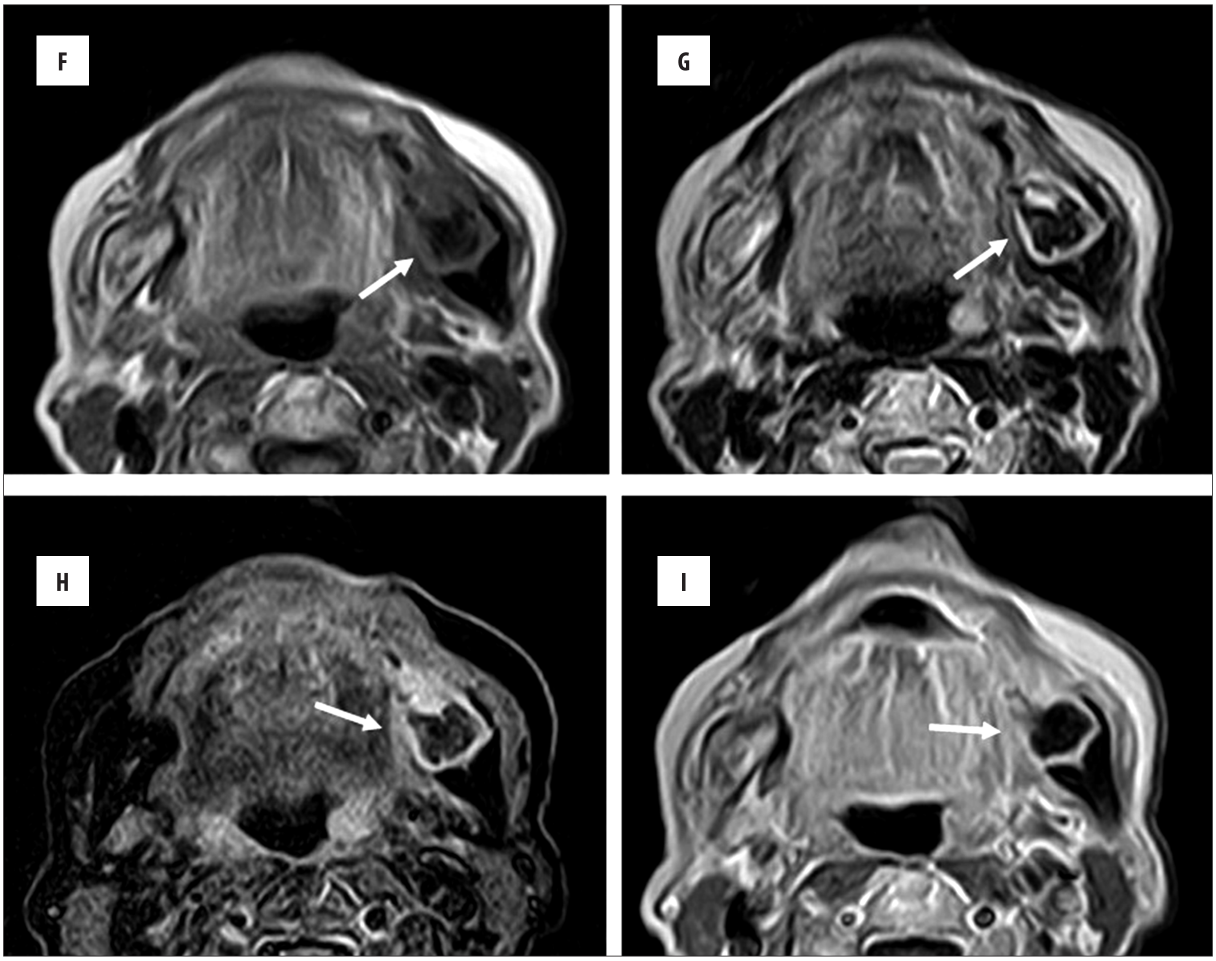


Figure 2. Multimodal imaging in an 89-year-old woman with osteoporosis who received oral alendronate. The patient presented with left mandibular pain. Panoramic radiography (**A**) shows osteolytic changes in the jaws, sclerotic lesions, and sequestrum separation (arrow). Axial contrast-enhanced CT image (**B**) shows spread of soft tissue inflammation to buccal, sublingual, and masticator spaces (arrowheads). Axial (**C**) and coronal (**D**) bone tissue algorithm CT shows osteolytic changes in the jaws, sclerotic lesions, sequestrum separation (arrow). Bone scintigraphy (**E**) shows increased uptake (arrow). On MRI, axial T1WI (**F**) revealed homogeneous, low-signal intensity with no hyperintensity, suggestive of sequestrum (arrow). Post-contrast T1WI (**I**) showed heterogeneous enhancement and a non-enhancing portion, suggestive of sequestrum (arrow). T2WI (**G**) and STIR (**H**) revealed heterogeneous, high-signal intensity with no hyperintensity and spread of soft tissue inflammation to buccal, sublingual, and masticator spaces (arrow).

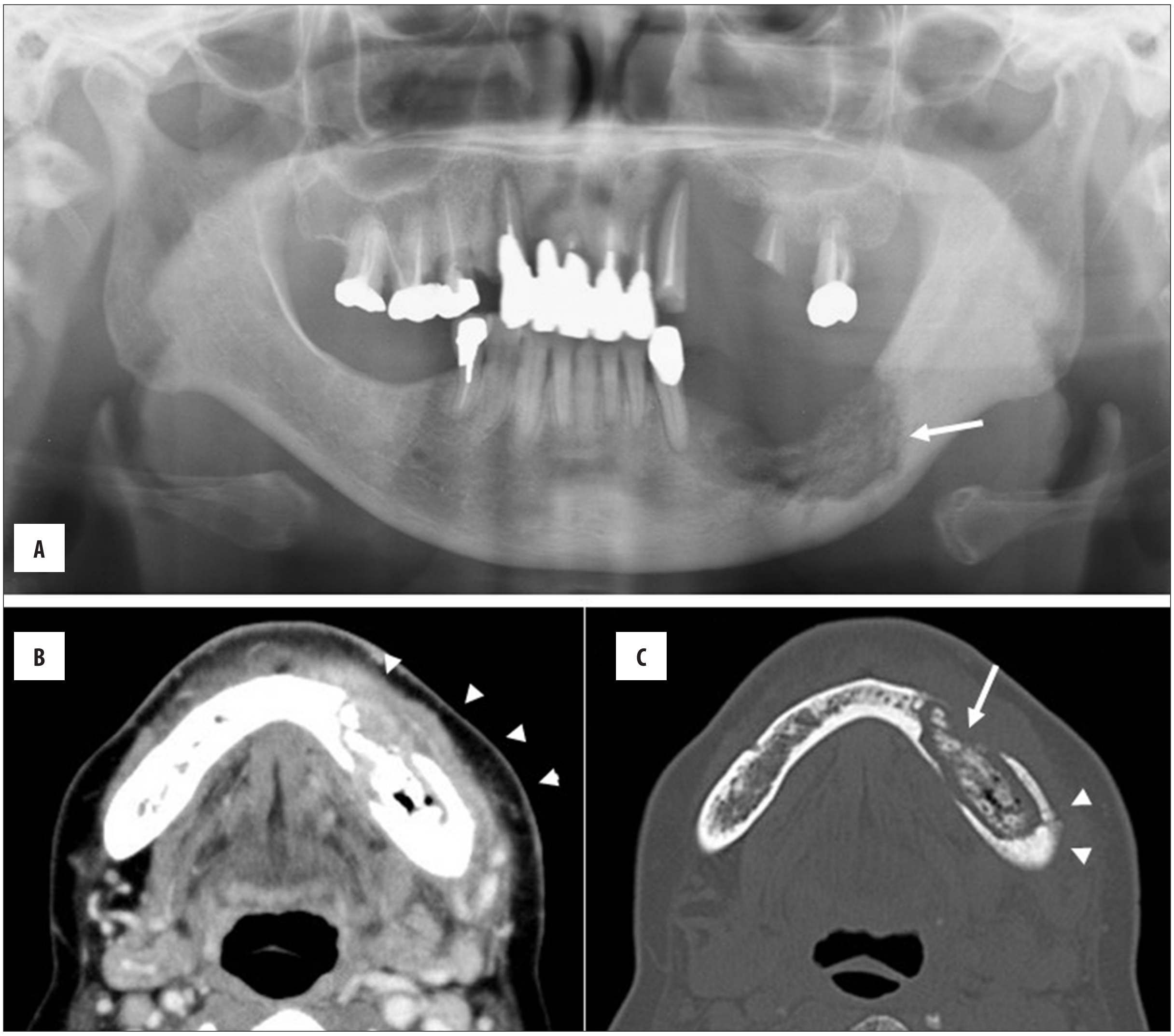
cases had intensity changes and pathological gadolinium enhancement on MRI. The percentage of cases with spread of soft tissue inflammation to buccal and other spaces on CT and MRI was 33.3% (4/12 cases) in the case of oral administration *vs.* 100% (4/4 cases) in the case of parenteral administration (p=0.021). All cases showed increased uptake on bone scintigraphy.

Figures 1–3 show multimodal imaging in 3 cases with MRONJ on panoramic radiography, CT, MRI, and bone scintigraphy.

Discussion

Bisphosphonates are frequently used for the treatment of osseous metastases and osteoporosis. The incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) or MRONJ is dependent on a number of factors including the type of bisphosphonate used (zoledronic acid and pamidronate disodium carry the highest risk), the route of administration (the intravenous route carries a higher risk), the dose, and possibly the duration of therapy [1]. However, detailed studies comparing the imaging characteristics of MRONJ have not yet been performed [6]. The authors assessed multimodal imaging features of MRONJ with panoramic radiography, CT, MRI, and bone scintigraphy, especially as regards the comparison between oral and parenteral routes of administering medications. This study indicated that the sequestrum separation on panoramic radiography in patients with MRONJ was unclear in comparison to CT. Furthermore, characteristic CT and MRI findings of patients with MRONJ in the parenteral group included periosteal bone proliferation and spread of soft tissue inflammation to buccal and other spaces.

Conventional anatomic imaging, including periapical radiographs and panoramic x-rays, allow for quick visualization of the areas of concern, but one must keep in mind the lag



between bone changes and the appearance of radiographic findings, which could be up to 2 weeks [2]. Ruggiero [7] showed that the radiographic features of MRONJ remain relatively nonspecific. Regarding panoramic radiography of MRONJ, Klingelhöffer et al. [11] indicated that panoramic radiographs of patients undergoing antiresorptive therapy with manifested osteonecrosis more frequently showed changes in the bone structure. Ozcan et al. [12] suggested that the osseous changes associated with BRONJ in the mandible, which includes the cortical and spongious bones, do not reflect the external morphology of the mandible on panoramic images. Torres et al. [13] suggested that mandibular inferior cortical bone thickness in patients using bisphosphonates was detected on panoramic radiographs, and represented a potentially useful tool for the detection of dimensional changes associated with bisphosphonate therapy. In this study, we demonstrate that the sequestrum separation that can be seen on panoramic radiography in patients with MRONJ is unclear in comparison to CT.

CT helps to identify findings difficult to discern on plain radiographs and also provides three-dimensional information and better delineation of the extent of the lesions [2]. Regarding CT of MRONJ, Bisdas et al. [9] showed that CT images showed predominantly osteolytic lesions and sclerotic regions in the jaws with or without periosteal bone proliferation. Krishnan et al. [1] showed that, on CT, sclerosis, subtle lucencies of the periodontal ligament, cortex and around the apices of the teeth (in the early stage), osteolytic bone lesions, cortical disruption, and frank bone fragmentation (in the later stages) were observed. Guo et al. [8] showed that both panoramic radiography and CT could detect the typical syndrome of osseous sclerosis in MRONJ, Stage 0 and 1, and in patients with BRONJ, Stage 2. More features were observed on CT, such as periosteal reaction, cortical perforation, and periosteal bone deposition. Imai et al. [14] showed that the measurement of CT values may be useful for diagnosis and early detection of BRONJ. Ruggiero [7] showed that the CT findings of MRONJ are nonspecific, but this modality is significantly more sensitive to changes in bone mineralization and therefore is more likely to demonstrate areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and the presence of reactive periosteal bone. In this study, we noted that characteristic CT findings of MRONJ in patients in the parenteral groups included periosteal bone proliferation and spread of soft tissue inflammation to buccal and other spaces.

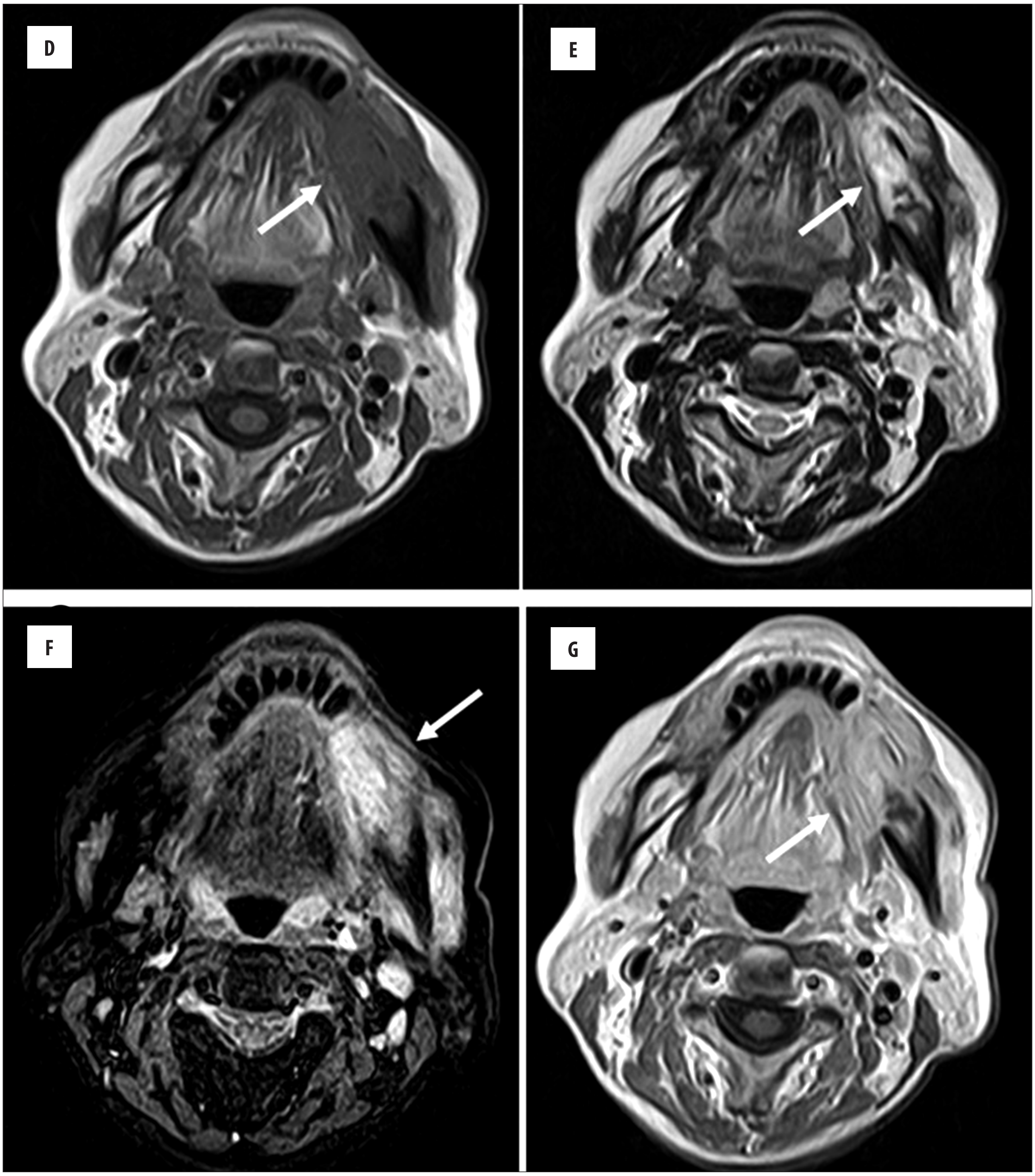


Figure 3. Multimodal imaging in a 58-year-old woman with osseous metastases of breast cancer who received parenteral zoledronate. The patient presented with left mandibular pain. Panoramic radiography (**A**) shows osteolytic changes in the jaws and sclerotic lesions, however, sequestrum separation was unclear (arrow). Axial contrast-enhanced CT image (**B**) shows spread of soft tissue inflammation to buccal, submandibular, and masticator spaces (arrowheads). Axial bone tissue algorithm CT (**C**) shows osteolytic changes in the jaws, sclerotic lesions, sequestrum separation (arrow), and periosteal bone proliferation (arrowheads). On MRI, axial T1WI (**D**) revealed homogeneous, low-signal intensity with no hyperintensity, suggestive of sequestrum (arrow). Post-contrast T1WI (**G**) showed heterogeneous enhancement and a non-enhancing portion, suggestive of sequestrum (arrow). T2WI (**E**) and STIR (**F**) revealed heterogeneous, high-signal intensity with no hyperintensity and spread of soft tissue inflammation to buccal and masticator spaces (arrow).

MRI is able to demonstrate bone marrow changes associated with edema or inflammation that result from an increase in water content, replacing the normal fatty marrow [2]. Regarding MRI of MRONJ, Bisdas et al. [9] indicated that the T1-weighted MRI signal was hypointense, the T2-weighted MRI signal was hypointense on the affected side, and pathological gadolinium enhancement was observed in the neighboring soft tissues, including the masticator space. Krishnan et al. [1] showed that the earliest MRI finding was the loss of the normal T1 hyperintensity of fatty marrow in the mandible and maxilla, and the MRI findings of more advanced BRONJ included bone destruction, soft tissue edema and enhancement, inferior alveolar nerve thickening, and pterygoid muscle swelling and enhancement. In this study, we noted that MRONJ cases had intensity changes and pathological gadolinium enhancement on MRI.

^{99m}Tc HMDP uptake in the bone is dependent on osteoblastic activity and skeletal vascularity [2]. Regarding bone scintigraphy of MRONJ, Krishnan et al. [1] indicated that bone scintigraphy showed increased uptake early in the disease. Hayama et al. [15] showed that dynamic analyses with a multicompartment model may help evaluate bone disorders in BRONJ. In this study, we show that MRONJ cases had increased uptake on bone scintigraphy.

This study had possible methodologic limitations. Potential selection bias cannot be excluded. Our sample was small, because relatively few patients have this rare disease.

Conclusions

In our study, the sequestrum separation on panoramic radiography in patients with MRONJ was unclear in comparison to CT. Furthermore, characteristic CT findings of MRONJ in patients in the parenteral group included periosteal bone proliferation and spread of soft tissue inflammation to buccal and other spaces. The results of the study present the multimodal imaging features of MRONJ. These findings can be helpful for diagnosis and management of MRONJ.

Conflict of interest

The authors declare that they have no conflict of interest.

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