Imaging features of medicine-related osteonecrosis of the jaws: comparison between panoramic radiography and computed tomography

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Objective. The current staging system of medicine-related osteonecrosis of the jaws (MRONJ) assigns patients to different stages based on clinical manifestations. The extent of bone disease cannot be fully determined without radiologic evaluation. Missing radiologic information may lead to incorrect classification of MRONJ, resulting in poor outcomes of treatment. The objective of this study was to compare computed tomography (CT) and panoramic radiography (PR) features of MRONJ in different stages to achieve accurate staging on the basis of combined findings from clinical staging and imaging.
Study Design. A retrospective study was carried out to analyze the differences in the radiographic features of various clinical stages in MRONJ, as shown by PR and CT.
Results. Both PR and CT could detect the typical syndrome of osseous sclerosis in grade 0 and grade 1. For the patients of grade 2, more features were observed on CT, such as periosteal reaction, cortical perforation, and periosteal bone deposition. CT was also conducive to analyzing the degree of the maxillary lesion and soft tissue involvement as compared with PR.
Conclusions. This study showed that CT detects changes that may not be revealed by plain radiography in patients with MRONJ. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:e69-e76)

Bisphosphonates, as potent bone resorption inhibitors, have been used in clinics for nearly 30 years and are widely used to control diseases associated with bone turnovers, such as osteoporosis, Paget disease, and bone metastases (multiple myeloma, breast cancer, lung cancer, etc.).[1,2]

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 (medicine-related osteonecrosis of the jaws [MRONJ]), and the number of related case reports has increased gradually. Before patients present with any clinical symptoms of MRONJ (e.g., abscess, mucosal/gingival fistula, nonhealing postextraction socket, swelling, bone pain, trismus), the duration of progressive disease with these clinical symptoms usually lasts for a long time, during which time the patients either ignore the symptoms or have them treated as routine dental problems or discomfort, resulting in a serious decline in the quality of life.[3] The cumulative incidence of MRONJ reported in the literature is 0.8% to 18.5%, with the duration of bisphosphonate therapy at presentation ranging from 6 to 60 months or even longer.[4,5] The mandible was the site most frequently affected by MRONJ, and in the majority of cases (95%), MRONJ was induced by intravenous bisphosphonates.[6]

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The diagnosis of MRONJ needs to be made using a reliable staging system, followed by appropriate treatment planning based on its severity. Currently, the MRONJ staging system recommended by the American Association of Oral and Maxillofacial Surgery (AAOMS) is the one most widely used in clinics.[7,8] However, this system assigns patients to different stages based on clinical manifestations and does not include radiologic evaluation. The extent of bone involvement cannot be fully elucidated on the basis of superficial clinical manifestations, and conventional dental radiography is inadequate to correctly identify the extent of bone disease.[9] Thus, incomplete information may lead to incorrect classification of MRONJ, resulting in poor treatment outcome.

Panoramic radiography (PR) is one of the imaging modalities most commonly used by dentists and oral and maxillofacial surgeons because of their familiarity with this modality. Computed tomography (CT) offers a greater advantage compared with PR for observation of the jaws. The aim of this was to collect data with regard to patients with MRONJ admitted to our center, to summarize the typical imaging features seen in PR and CT, and to compare the abilities of these two

Statement of Clinical Relevance

This study showed that computed tomography detects changes that may not be revealed by plain radiography in patients with medicine-related osteonecrosis of the jaws.

modalities to identify specific early and late radiographic features and the extent of the lesion. We also hope to take advantage of the identification of these imaging features to set a reference index for staging of MRONJ and to improve efficacy of treatment.

MATERIALS AND METHODS

Study design

To address our research purpose, we designed and implemented a retrospective study of patients diagnosed with MRONJ related to antiresorptive therapy, who had been referred to the first author (Y.G., for his well-known expertise in treating such cases) from July 2011 to December 2015. The research was approved by the institutional biomedicine ethics committee of our hospital. The inclusion criteria for the study strictly followed the AAOMS definition of MRONJ to distinguish it from any other delayed healing conditions.[10] The following inclusion criteria had to be met: current or previous treatment with antiresorptive or antiangiogenic agents; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and which has persisted for longer than 8 weeks; no history of radiation therapy to the jaws or obvious metastatic disease to the jaws; and having undergone both CT and PR examination. Stage-specific treatment recommendations for management of MRONJ were consistent with the principles of Ruggiero et al.[1,10,11]

Image examination and observation

All 40 cases included had both CT and PR examination. All panoramic radiographs were unspecific conventional images. CT images were acquired with Bright Speed Elite Select (GE, Beijing, China), with interval slice thickness of 1.25 mm. Patients who had undergone CT within 6 months from onset of the clinical syndrome were included so that we had some agreement on the clinical signs and the CT findings. Both PR and CT were observed by two experienced radiologists (oral radiologist with at least 5 years work experience) to identify the imaging features. The obtained CT data were viewed on imaging workstation (Carestream DIMS 1.0; Carestream Health, Inc., Rochester, NY) layer by layer. The CT threshold was adjusted in the soft tissue window to see if there was soft tissue or maxillary sinus inflammation and to observe bone changes (e.g., osseous sclerosis, periosteal reaction, sequestrum separation) in the bone window and mandibular cortical bone perforation on a three-dimensional reconstruction of the CT image. Many changes in the jaw (e.g., lamina dura thickening, prominence of the inferior alveolar nerve canal, mandibular fractures) were seen on PR.

Table I. Patient data (N = 40 patients)

	No. of Patients
Types of Cancer	
Breast cancer	14
Multiple myeloma	10
Kidney cancer	8
Bladder cancer	3
Prostate cancer	2
Lung cancer	1
Esophageal cancer	1
Gastric cancer	1
Antiresorptive Therapy	
Duration of antiresorptive therapy before first visit (months), mean (range)	37.92 (10-96)
Types of Antiresorptive Therapy	
Zoledronate	18
Pamidronate	13
Zoledronate + pamidronate	9
Antiangiogenic agents	5
Time for Clinical Symptoms Before Treatment (months), Mean (range) Time	14.64 (2-96)
Trigger of BRONJ Lesions	
Extraction	30
Spontaneous	9
Infected dental implant	1
BRONJ Location	
Maxilla	12
Mandible	24
Both maxilla and mandible	4
BRONJ stage	
Grade 0	1
Grade 1	4
Grade 2	11
Grade 3	24
Treatment Methods	
Operative	25
Nonoperative	15

Data analysis

The primary outcome variables in the present study were the radiographic features, that is, osteosclerotic and soft tissue changes observed on PR and/or CT images. Other study variables recorded were demographic characteristics, including age, gender, cancer diagnosis, type of antiresorptive therapy, and predisposing factor for MRONJ onset (e.g., spontaneous, extraction, implant). Descriptive and nonparametric (Wilcoxon test) analyses were performed to compare the ability of the two methods to identify specific early and late features.

RESULTS

Clinical data

Forty patients (44 MRONJ lesions) who met the inclusion criteria were included in the study (Table I). Of the 40 patients, 18 were males, and 22 were females (average age 65.08 years; range 44-85 years). The three most common primary tumors were breast cancer (14), multiple myeloma (10), and kidney cancer (8). The

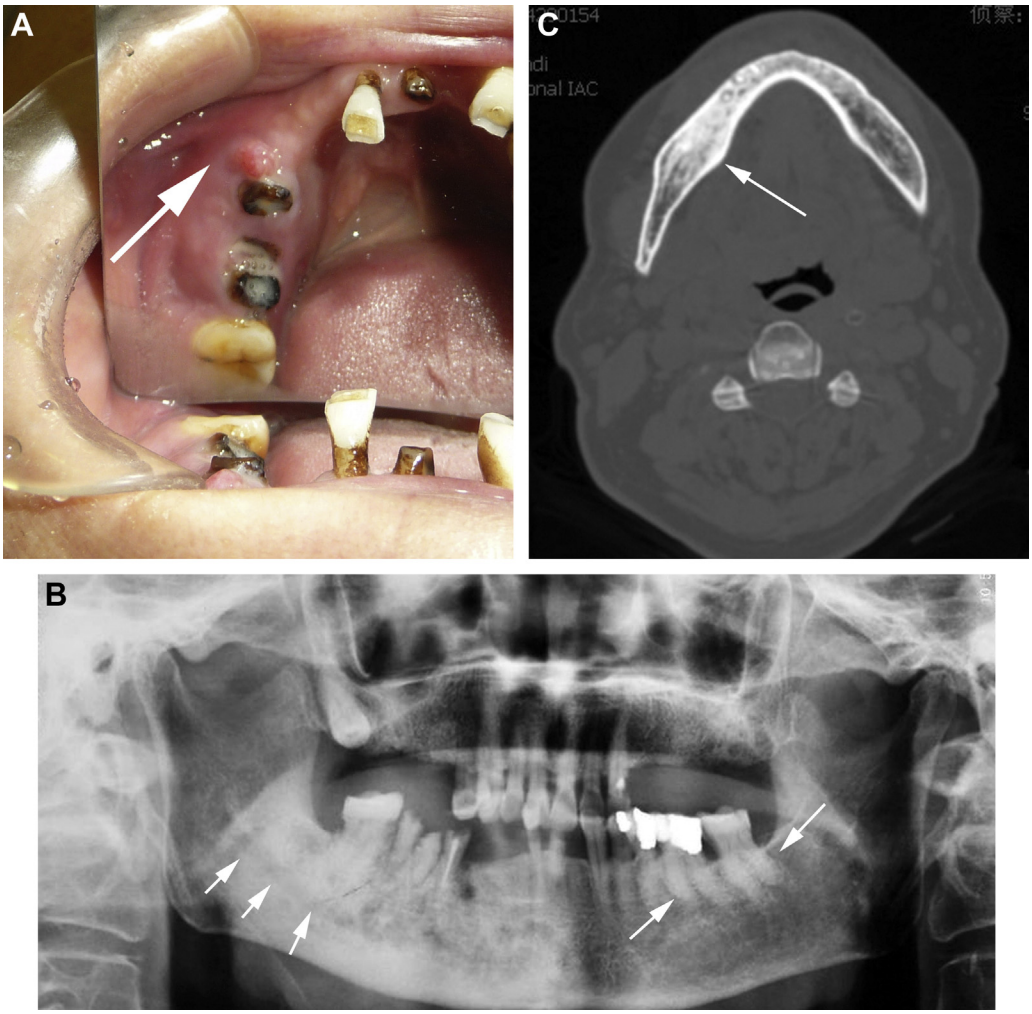

Fig. 1. Osteonecrosis of the right mandible in grade 1, case 25. **A**, Mucosal fistula that presented on the alveolar level of the right mandible adjacent to the second premolar tooth. **B**, Radiographic changes of serious lamina dura thickening and prominence of the inferior alveolar nerve canal on the posterior area of the right mandible on panoramic radiography (PR). **C**, Osseous sclerosis showed corresponding to exposed bone of the right posterior mandible on the axial section of computed tomography (CT).

cancer duration was 7.5 years (range 1-29 years), and the duration of bone metastasis was 5.05 years (range 1-13 years). There were 30 cases with a history of a trigger event (tooth extraction). Only four patients had a history of diabetes, and none of the patients in the study had a history of systematic and long-term use of steroids (e.g., dexamethasone, methylprednisolone). The average time of clinical symptoms (fistula, swelling, restricted opening), indicated as osteomyelitis, was 14.64 months (range 2-96 months). Further information about the patients with cancer, such as stage distribution and treatment methods, is shown in Table I.

Radiologic features and stage of MRONJ

On PR examination of the 28 mandibular osteonecrosis sites, lamina dura thickening was observed in 25 of 28 patients and prominence of the inferior alveolar canal in 23 of 28 patients (Figure 1). CT examination was able to show osseous sclerosis in all 28 patients with a statistically significant difference in showing the prominence of the inferior alveolar canal ($P < .03$). Neither PR nor CT showed any changes in the bony architecture on the non-osteonecrosis sites in the same patients.

The key manifestations of the middle stage (grade 2) were the periosteal reaction, cortical perforation, or periosteal bone addition (Figure 2). PR could only detect periosteal reaction in two of six cases compared with CT, which revealed periosteal reaction in all six cases. Periosteal bone deposition and cortical perforation were seen in 19 of 28 cases, whereas this feature could not be reported from a two-dimensional (PR) examination. These differences were statistically significant ($P \leq .05$).

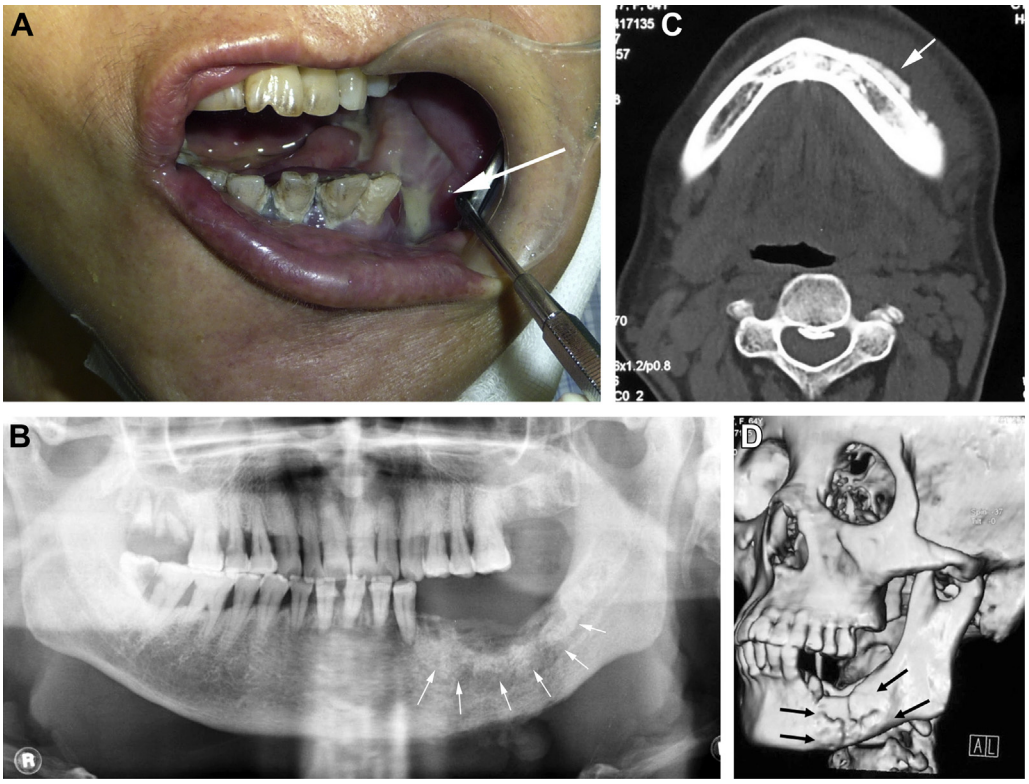

Fig. 2. Osteonecrosis of the right mandible in grade 2, case 31. **A**, Exposed bone with pus on the upward aspect of the left mandible adjacent to the first and second molar tooth. **B**, Mild bone loss with sclerosis surrounded on the distal aspect of the mandibular left canine. **C**, Saucerized radiolucency existed clearly corresponding to exposed bone of the left posterior mandible. **D**, Cortical perforation and periosteal bone deposition can be found in the three-dimensional reconstruction of computed tomography (CT).

In patients with advanced stage MRONJ (grade 3) who had mandibular fractures (5 of 28), both PR and CT could show the change in all five patients, but CT examination was able to also show soft tissue inflammation in tissues adjacent to the lesion in 11 of 28 patients (Figure 3).

In the diagnosis of 16 cases with MRONJ in the maxilla, CT had a distinct advantage compared with PR. Sequestrum formation and maxillary sinus inflammation were two main features revealed by CT in patients with grade 2 and 3 MRONJ, respectively, but could not be defined in PR examination in any patients in grade 2 (Figure 4). The results and values for significance of Wilcoxon nonparametric test are presented in Table II.

DISCUSSION

Research on MRONJ has been growing in recent years. The specific definition has been clarified, and it depends mainly on clinical findings. Patients also should have a history of use of bisphosphonates or other antiresorptive medication, without any clinical manifestation of tumor metastases.[12] The inclusion of pain in these clinical diagnostic criteria might cause some confusion; in our opinion, the presence or absence of pain does not necessarily indicate the stage or extent of bone involvement, since pain can be caused by various factors or can be totally absent at any or all stages other than at the very beginning (subclinical symptoms), when patients undergo tooth extraction for nonspecific diffuse pain resembling reversible or irreversible pulpitis without clinical evidence of carious lesion of the teeth in the region.

The diagnosis of MRONJ is largely dependent on the corresponding clinical manifestations and a history of use of bisphosphonates or other antiresorptive medications in the absence of obvious signs of metastasis; hence biopsies can be limited to the cases in which the possibility of metastasis has to be excluded, as this will help reluctant clinicians who wish to avoid problems of wound healing related to biopsies.[13,14]

To design the appropriate treatment plan, the extent of disease should be determined as soon as the diagnosis of MRONJ is established. Currently, the most widely used system is the AAOMS system, which is based on clinical manifestations but does not include evaluation of bone involvement. For early lesions,

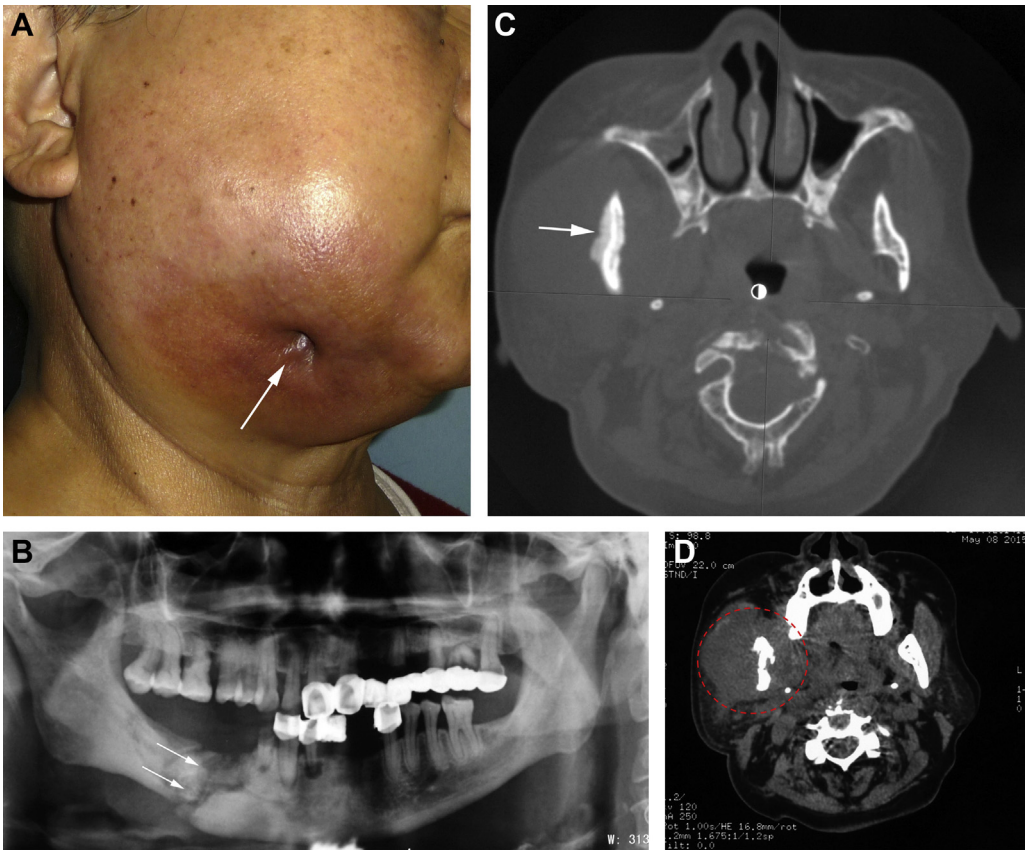

Fig. 3. Osteonecrosis of the right mandible in grade 3, case 37. **A**, Skin fistula and tissue swelling on the right cheek. **B**, Mandibular fracture could be found on right mandible body. **C**, Obvious periosteal reaction can be observed on the right mandible. **D**, Serious soft tissue inflammation presented in the space of masseter and medial pterygoid muscle.

conservative treatment is recommended, and advanced diseases will require elaborate surgical treatment; thus, we should be able to correctly classify the cases into early and late stages and determine the extent of bone and soft tissue involvement. When the patient presents with a small fistula and extensive bone involvement, the condition can easily be mistaken for an early lesion of MRONJ based solely on clinical symptom, thereby losing the golden time of treatment. This retrospective study was hence designed to determine the diagnostic efficacy of the two most commonly used radiographic methods: PR and CT.

Through analysis of patient data from different stages, we found that patients in grade 0 and grade 1 had major changes, such as osseous sclerosis, mainly caused by structural changes after bisphosphonates deposition in trabecular bone. A similar finding was reported by Aftimos et al., who stated that bones show empty lacunae and calcified matrix/osteoporotic change with or without bacterial invasion.[12] By observing mandibular lesions, useful clues can be found by using these two diagnostic modalities. We found that with PR it is very easy to determine the region of mandibular bone involvement. The majority of patients' lesions occurred in the molar region (25 of 28), involving the anterior teeth area (4 of 28) and the mandibular ascending ramus area (6 of 28), and only one case had involvement of the anterior teeth area alone.

The early typical syndrome of MRONJ is obvious on observation both on CT (osseous sclerosis) and PR (lamina dura thickening and prominence of the inferior alveolar nerve canal) (see Figure 1). However, PR is not sensitive for the evaluation of the medullary bone, maxillary sinus, and soft tissue involvement; these findings are similar to the studies by Bedogni et al. and Hamada et al.[9,15] A group of experts from Italy has found that it is easy to underestimate the disease condition of MRONJ by using PR and hence recommended that classification of osteomyelitis stage should be done with CT as well.[9]

In patients with grade 2 MRONJ, a number of features can be better observed on CT, such as periosteal reaction (6 of 6 on CT examination; 2 of 6 on PR examination.), cortical perforation, and periosteal bone deposition (see Figure 2). Further observation by sectional image or three-dimensional

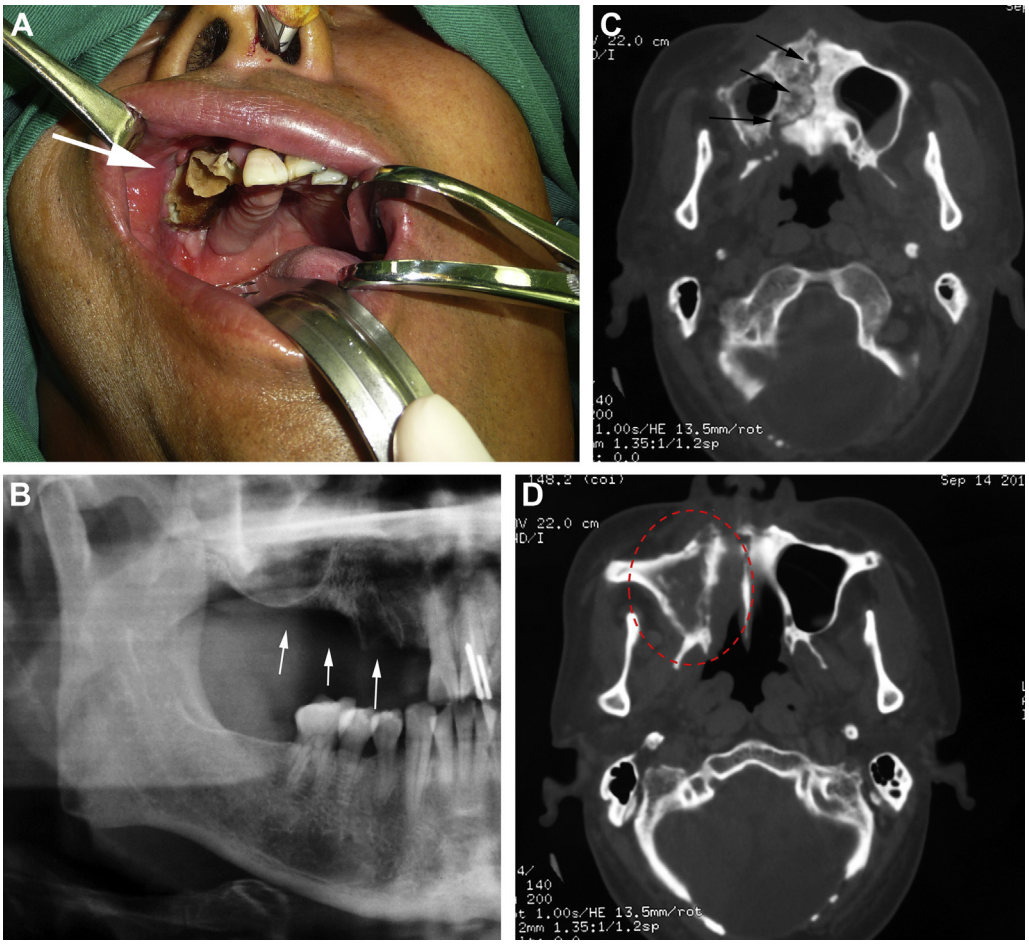

Fig. 4. Osteonecrosis of the right maxilla in grade 3, case 40. **A**, Exposed bone on the posterior area of the right maxilla. **B**, Panoramic radiography (PR) can only display the reduced bone density of right maxilla, but it is difficult to obtain more information because of the interference of the maxillary sinus and pharynx. **C**, Sequestrum formed along the midline and posterior border of right maxilla on axial section of computed tomography (CT). **D**, Inflammation can be found in the right maxillary sinus and nose cavity.

reconstruction of cortical perforation and periosteal bone deposition (3 of 6) may be developed as the disease progresses, but these features are not easy to find on PR (0 of 6).

In patients with grade 3 MRONJ, mandibular fracture can be observed on both PR and CT. However, CT is also conducive to analyzing the degree of medullary bone involvement, to determine the extent of osteotomy required. In addition, CT helps analyze the extent of soft tissue inflammation. In the case of the mandible with long-term soft tissue inflammation, both the involved soft tissue and bone need to be removed (see Figure 3). The determination of these surgical options is dependent on preoperative analysis of soft tissue involvement.[16]

Because of the interference of the maxillary sinus and the pharynx, PR is not ideal for observation of the maxilla. Sequestrum formation and maxillary sinus inflammation were two main presentations of MRONJ in maxillary bone, which could be detected easily on CT. On PR, only three cases presented a clear diagnosis. In patients without oroantral fistula, maxillary sinus inflammation was seen in the majority of cases. Sequestrum can also be found on CT but rarely on PR (see Figure 4).

According to our analysis, the roles of CT and panoramic tomography were inconsistent in patients with MRONJ at different stages. More useful information and a more accurate evaluation of the patient's condition can be obtained with CT. MRONJ is an evolving disease, and thus, complete and accurate diagnostic information is important in clinical decision making; therefore, we recommended CT as a staging reference.[17,18]

The radiographic features observed on CT scans, such as periosteal reaction, cortical perforation,

Table II. The imaging features of PR and CT in different stages of BRONJ

Variable	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*	*P value*
Mandible (n = 28)	1	4	6	17	
Osseous Sclerosis					
PR					
Lamina dura thickening (n = 25)	1	3	4	17	.16
Prominence of the inferior alveolar nerve canal (n = 23)	1	1	6	15	.03
CT (n = 28)	1	4	6	17	
Periosteal Reaction					<.01
PR	0	0	2	4	
CT	0	1	6	17	
Periosteal Bone Deposition and Cortical Perforation					<.01
PR	0	0	0	0	
CT	0	0	3	16	
Mandibular Fractures					1
PR	0	0	0	5	
CT	0	0	0	5	
Soft-Tissue Inflammation					.01
PR	0	0	0	0	
CT	0	0	0	11	
Maxilla (n = 16)	0	1	3	12	
Maxillary Sinus Inflammation					<.01
PR (n = 16)	0	0	0	3	
CT (n = 16)	0	0	3	10	
Sequestrum Formation					.004
PR (n = 16)	0	0	0	1	
CT (n = 16)	0	0	2	5	.01

CT, computed tomography; *MRNOJ,* medicine-related necrosis of the jaw; *PR,* panoramic radiography.

periosteal bone deposition, mandibular fractures, and soft tissue inflammation, are phenomena that are closely related to disease severity.

CONCLUSIONS

Both CT and PR play an important role in the diagnosis and treatment planning of MRONJ. PR is only sensitive to the gross involvement of bones, which usually presents in the advanced stages, whereas CT (axial and three-dimensional reconstruction) is sensitive to the initial development of the disease process and hence may help identify the same in very early stages. CT also plays an important role in the advanced stage of MRONJ in defining soft tissue involvement and maxillary sinus involvement. We hope that further work will combine findings from clinical staging and CT imaging to develop a more effective staging system to help in early diagnosis and efficient treatment of MRONJ.

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