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Research Article

Panoramic Radiography Features of Medication-Related Osteonecrosis of the Jaws (MRONJ)

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The diagnosis of medication-related osteonecrosis of the jaws (MRONJ) relies on the application of the clinical criteria stated in the American Association of Oral and Maxillofacial Surgeons position paper. The role of diagnostic imaging in integrating MRONJ clinical assessment is still debated, as pathognomonic imaging features have not been yet recognized. The present study retrospectively evaluated the radiographic signs of MRONJ on panoramic radiography with the aim of describing the characteristics of the lesions at different stages of the disease. The presence of alterations of the lamina dura (thickening or loss), the persistence of the alveolar socket following tooth extraction, and bone alterations (including sequestrum, sclerosis, osteolysis, mandibular canal enhancement, pathologic fracture, sinus involvement, and periosteal reaction) were investigated. The occurrence of each radiographic sign was stratified depending on oral status, antiresorptive pharmacological treatment administered, and general health variables. A weak relationship between radiographic signs and disease stage was observed. Mandibular canal enhancement was associated with the advanced disease stage (p-value < 0.001). The distribution of the different radiographic features was not influenced by the underlying disease (osteoporosis or oncologic disease) treated with antiresorptive drugs. Bone sequestrum was more frequently encountered in the mandible. Panoramic radiography appears to be a valid support in the assessment of MRONJ lesions. The clinician should be aware of the signs associated with MRONJ occurrence in order to improve the diagnostic performance and provide adequate treatment.

1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is a pathologic condition associated with pharmacological treatment with antiresorptive and/or antiangiogenic therapy for the modulation of bone remodeling [1]. The pathogenesis of MRONJ remains unclear, although it appears that both antiresorptive and antiangiogenic drugs inhibit bone remodeling mediated by osteoclasts [2]. Moreover, it has been hypothesized that gene polymorphisms can have a role in promoting MRONJ onset [2, 3]. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper, the risk factors recognized to favor MRONJ development can be categorized as drug-related, demographic, local, and systemic or genetic factors [1]. At present, more than 25 risk factors, including dental extraction, periodontitis, chemotherapy, corticosteroid use, and smoking, have been claimed to have a role in MRONJ onset [4, 5].

MRONJ diagnosis is performed clinically through the assessment of the presence of necrotic bone, either exposed or probable through an intraoral/extraoral fistula, persisting for more than 8 weeks, in patients with a history of pharmacological treatment with antiresorptive or antiangiogenic agents, in the absence of previous head and neck radiation therapy or jaw metastases of other tumors [1]. The AAOMS classification recognizes four stages of the disease, with Stage 0 being characterized by a lack of necrotic bone exposure and Stages I–III presenting with exposed bone in the oral cavity [1]. Importantly, in Stage 0, pain and neurosensory alterations can be present, along with nonspecific radiographic findings, including bone resorption, osteosclerosis, thickening of the lamina dura, and persistence of the alveolar socket

after extraction [6]. Although the time of occurrence of radiographic bone alterations, their development depending on medication posology, and the related risk of MRONJ development are still debated, [5] diagnostic imaging plays an important role in the evaluation of suspected cases of MRONJ.

Panoramic radiography is the most frequently employed technique in dentistry due to its advantages in terms of reduced radiation dose and relatively low cost while providing a comprehensive overview of dental arches, maxillary and mandibular bones, and surrounding anatomic structures [7]. Overall, panoramic radiography has been reported to provide an immediate view of the lesion, although limitedly detecting early changes of bony structures and other detailed features of MRONJ, such as sinus communication and bone fragmentation [8].

The aim of the present study was to retrospectively identify and categorize the panoramic radiograph features of MRONJ lesions.

2. Materials and Methods

2.1. Study Design. This retrospective study was conducted on medical and dental records, clinical photographs, and panoramic radiographs of patients diagnosed with MRONJ and treated at the Unit of Dentistry and Oral Surgery, University Hospital of Pisa (Pisa, Italy) between 2017 and 2022. All patients signed an informed consent for anonymous data collection. The study was conducted in accordance with the principles stated in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University Hospital of Pisa.

2.2. Patient Data Collection. Information on gender, age, smoking habit, and the presence of comorbidities (hypertension, diabetes, cardiovascular disease, and hypercholesterolemia) were collected for all patients.

Data on antiresorptive therapy (AT) and the reason for administration were retrieved. The AT was classified depending on the type of medication administered (bisphosphonates or denosumab), length of therapy, and cumulative dose. The patients were classified as either affected by osteometabolic diseases (e.g., osteoporosis) or oncologic diseases, such as metastatic breast cancer, multiple myeloma, metastatic prostate cancer, metastatic lung cancer, and metastatic renal cancer. The therapeutic approach and treatment outcomes were also reported.

2.3. MRONJ Staging. MRONJ staging was performed clinically as reported in the AAOMS criteria [1]. All the patients with suspected MRONJ were clinically evaluated, and photographs of the lesion were taken. Panoramic radiograph was performed on the same day of the first clinical evaluation. Consistently with previous reports presented in the literature [8–10], the radiographic signs investigated included:

(i) Increased thickness of the lamina dura: an increase in the thickness of the normally thin lamina dura is associated with an enlargement of the periodontal ligament space (Figure 1).

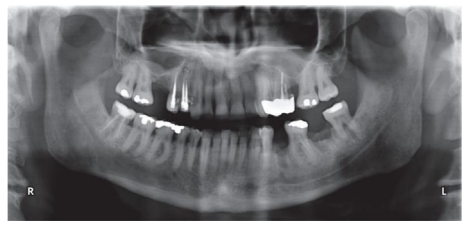

Figure 1: Increased thickness of the lamina dura: the normally thin layer of the lamina dura appears to have increased in thickness and is associated with periodontal ligament space enlargement in correspondence with tooth 3.6.

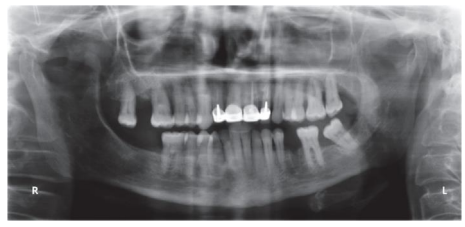

Figure 2: Persistence of alveolar socket: the presence of an unhealed socket 3 months following the extraction of tooth 3.5 can be observed. A lack of bone regeneration causes the typical empty socket aspect.

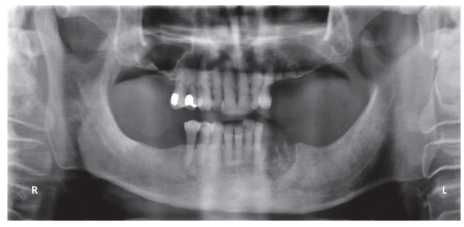

Figure 3: Sequestrum: bone sequestrum in the left mandible appears as an irregularly calcified area with both aspects of hypo and hypermineralization. A thin radiolucent rim around the sequestrum can be present.

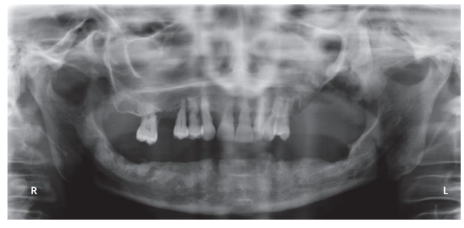

Figure 4: Sclerosis: increased and uneven bone mineralization can be observed in the right mandible.

(ii) Persistence of alveolar socket: the presence of an unhealed empty socket at 3 months following tooth extraction (Figure 2).

(iii) Sequestrum: area of increased bone density characterized by inhomogeneous mineralization with a peripheral radiolucent rim (Figure 3).

(iv) Sclerosis: focal area of markedly increased radiopacity (Figure 4).

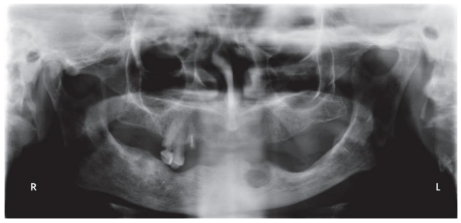

Figure 5: Osteolytic processes: osteolysis in the left mandible appearing as an irregular radiolucent area with ill-defined margins.

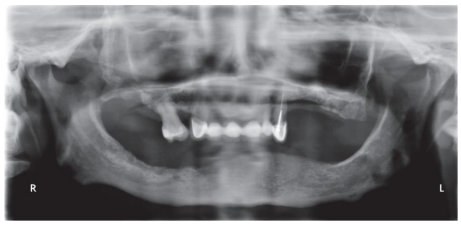

Figure 6: Differences in sclerosing: irregularities in bone mineralization with different bone densities of the alveolar margin compared with the mandibular bone can be seen in the right mandible.

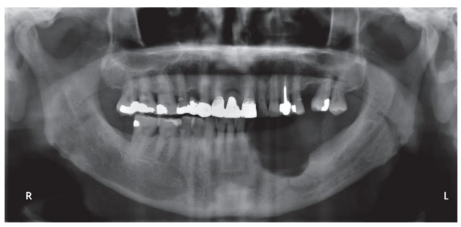

Figure 7: Enhancement of the mandibular canal: the mandibular canal may appear more evident in correspondence with a MRONJ lesion (left mandible) compared to the contralateral side.

(v) Osteolytic processes: the presence of a bony area characterized by increased radiolucency compared to surrounding bone tissue (Figure 5).

(vi) Differences in sclerosing: inhomogeneous bone density at the level of the alveolar margin compared with the mandibular and/or maxillary bone (Figure 6).

(vii) Enhancement of the mandibular canal: increased the enhancement of the border of the mandibular canal on the side affected (Figure 7).

(viii) Pathologic fracture: interruption of bone continuity characterized by uneven margins and bone remodeling on the edges of the fractured bone (Figure 8).

(ix) Sinus involvement: increased radiopacity of the maxillary sinus is often associated with oroantral communication at the level of the alveolar margin (Figure 9).

(x) Periosteal reaction: the presence of proliferative periostitis with the juxtaposition of newly formed bone at the level of the inferior mandibular border (Figure 10).

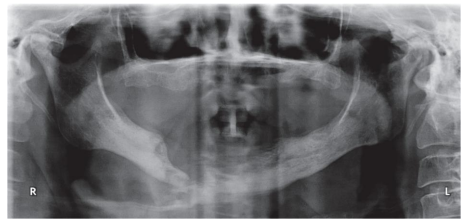

Figure 8: Pathologic fracture: MRONJ lesions can lead to bone density alterations extended to the body of the mandible, eventually causing spontaneous fractures characterized by irregular margins and uneven mineralization (right mandible).

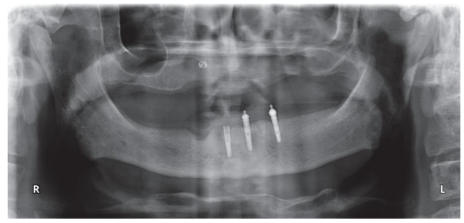

Figure 9: Sinus involvement: when localized in the maxillary bone, sinus involvement may be characterized by a loss of characterization of the alveolar margin and a continuity of the sinus with the oral cavity (left maxilla).

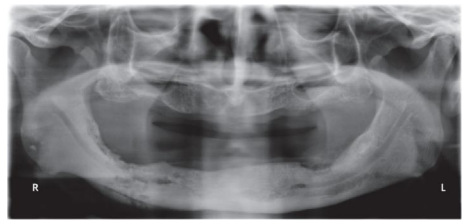

Figure 10: Periosteal reaction: periosteal reaction with proliferation can be present at the level of the inferior mandibular border in correspondence with MRONJ lesion (right mandible).

The sample was stratified depending on the stage of the disease, the localization of the MRONJ, and the underlying disease requiring the administration of antiresorptive/anti-angiogenic drugs.

The analysis of clinical photographs and diagnostic imaging datasets was performed by two calibrated examiners. The calibration process was carried out on 40 images that were not part of the study sample until a κ score > 0.8 was obtained.

2.4. MRONJ Treatment. MRONJ treatment was performed following the protocol previously described by Nisi et al. [11, 12]. Briefly, after the diagnosis of MRONJ, all patients were medically treated with a session of professional oral hygiene, together with reinforcement of oral hygiene instructions and a prescription of 2% chlorhexidine mouthwash to be used twice daily for 14 days. Patients were also given amoxicillin + clavulanic acid (2 g/day for 14 days) plus metronidazole (750 mg/day) and were clinically reevaluated 2 weeks later.

After medical treatment, resolution of the infection and pain relief were obtained, while signs of complete healing were not observed. A surgical approach was then performed. Pharmacological treatment included a standardized administration protocol of antibiotics, with the following scheme: 3 g of amoxicillin administrated preoperatively and 2 g/day for 2 weeks following surgery. In cases of allergy to penicillin, oral azithromycin (1 g/day) was administrated.

All surgical interventions were performed under local anesthesia following a standardized protocol by a single expert operator specialized in oral surgery. Surgical treatment included sequestrectomy, debridement of soft tissue, and curettage of bone. At the end of the surgical intervention, the closure of the surgical site was assured by suturing without mobilization of the flap with a resorbable/nonresorbable 5-0 suture thread; the removal of the visible suture was performed 14 days after surgery. Histology was performed on all removed bone samples.

Treatment outcome was deemed successful in cases of complete healing of MRONJ, described as the complete absence of exposed necrotic bone, residual mucosal defect, fistulas, and associated symptoms (swelling and pain) at the 6-month follow-up.

2.5. Statistical Analysis. Data were manually transferred from the clinical register to an Excel database created specifically for this study and proved for entry errors. All data are presented as mean and standard deviation unless otherwise specified. The unit of analysis was the patient. Categorical variables were analyzed with the χ^2 and McNemar tests. The Shapiro–Wilk test was used to check the normality of the data distribution.

3. Results

3.1. Patient Characteristics. In the period between 2017 and 2022, a total of 166 MRONJ diagnoses were retrieved from patient records. Sixteen patients were excluded due to incomplete documentation, and the remaining 150 records were analyzed for the study.

Of the 150 patient records, 96 (65.3%) belonged to female patients, with a mean age of 69 years (range 29–93). An underlying cancer diagnosis was present in 112 (74.7%) cases, while 38 (25.3%) patients were affected by osteoporosis. Breast cancer (40.2%) and multiple myeloma (21.4%) were the most recurring oncological diseases. Treatment with zoledronic acid was administered in 68.7% of patients for a mean time of 21.2 months (cumulative dose: 84.1 ± 39.4). Alendronic acid was prescribed in 20.7% of subjects, denosumab in 6% of cases, ibandronate in 4% of subjects, and 1 0.6% was treated with risedronate (Tables 1 and 2). The treatment regimen could not be retrieved for all patients, and data on the administration modality were not available.

3.2. MRONJ Lesions Characteristics. MRONJ lesions were categorized as Stage I in 2.7%, Stage II in 51.3%, and Stage III in 46% of cases. The lesions were localized to the mandible in 76.7% of cases. In 28.7% of patients, MRONJ without bone exposure was found. Dental extraction was recognized as the triggering factor for MRONJ development in 48.7% of patients, followed by problems with removable prostheses (16.7%) and periodontal/peri-implant infection (15.3%) (Table 3).

3.3. MRONJ Treatment Outcomes. Six months after conservative surgical therapy, a total of 115 lesions (76.4%) showed complete healing. Stratification per disease stage indicated complete healing and total resolution in all the four Stage I lesions. Complete healing was observed in 65 out of the

Table 1: Sample characteristics ($n = 150$ subjects).

Variables	Outcome
Gender (*n*, (%))	
Female	98 (65.3%)
Age (years)	
Mean	69
Standard deviation	8.6
Median	70.5
Range	29–93
Comorbidities (*n*, (%))	
Smoking	44 (29.3%)
Hypertension	59 (39.3%)
Cardiovascular disease	18 (12%)
Diabetes	17 (11.3%)
Hypercholesterolemia	14 (9.3%)
Underlying disease (*n*, (%))	
Oncologic disease	112 (74.7%)
Metastatic breast cancer	45
Multiple myeloma	24
Metastatic prostate cancer	22
Metastatic lung cancer	13
Metastatic renal cancer	5
Other	3
Osteoporosis	38 (25.3%)

Table 2: Pharmacologic variables ($n = 150$ subjects).

Variables	Outcome
Zoledronate (*n*, (%))	103 (68.7%)
Length of therapy (months, ±SD)	21.2 ± 10.1
Cumulative dose (mg, ±SD)	84.1 ± 39.4
Alendronate (*n*, (%))	31 (20.7%)
Length of therapy (weeks, ±SD)	499.4 ± 313.2
Cumulative dose (mg, ±SD)	25,976.8 ± 13,218.9
Denosumab (*n*, (%))	9 (6%)
Length of therapy (months)	11.4 ± 6.4
Cumulative dose (mg, ±SD)	1,271.1 ± 688.4
Ibandronate (*n*, (%))	6 (4%)
Length of therapy (months)	83 ± 64.7
Cumulative dose (mg, ±SD)	12,450 ± 970
Risedronate (*n*, (%))	1 (0.6%)
Length of therapy (day)	100
Cumulative dose (mg, ±SD)	500

Table 3: MRONJ characteristics ($n = 150$ lesions).

Variables	Descriptive statistics
Clinical variables (n, (%))	
Localization	
Mandible	115 (76.7%)
III Quadrant	67
IV Quadrant	48
Maxilla	35 (23.3%)
I Quadrant	13
II Quadrant	22
Bone exposure	107 (71.3%)
Suppuration	146 (97.3%)
Pain	146 (97.3%)
Paresthesia	48 (32%)
Extraoral fistula	18 (12%)
Oroantral communication	17 (11.3%)
Mandibular fracture	7 (4.7%)
AAOMS stage 2014 (n, (%))	
Stage I	4 (2.7%)
Stage II	77 (51.3%)
Stage III	69 (46%)
Local risk factor	
Tooth extraction	73 (48.7%)
Prosthesis	25 (16.7%)
Periodontal/peri-implant infection	23 (15.3%)
Odontogenic infection	18 (12%)
Other	11 (7.3%)

77 Stage II lesions (84.4%) and in 46 of the 69 Stage III lesions (66.7%). The remaining 35 lesions showing no improvement following surgery were reevaluated, and a second surgery was performed at 6 months. Complete resolution was observed following reintervention in all cases.

3.4. Radiographic Findings. The most frequently occurring radiographic signs were osteolysis (64.6%), bone sequestrum (31.3%), and enhancement of the mandibular canal (30.6%) (Table 4).

In Stage I MRONJ, osteolysis, bone sequestrum, and sclerosis were observed. Stage II was characterized by osteolysis, persistence of the alveolar socket, and bone sequestrum. In Stage III, osteolysis, mandibular canal enhancement, and bone sclerosis were observed (Table 5). Pathologic bone fracture, maxillary sinus involvement, and periosteal reaction were present only in Stage III patients.

Considering the relationship between the radiographic findings and MRONJ staging, there was a significant difference in the following findings: enhancement of the mandibular canal ($p < 0.01$), sclerosis ($p = 0.006$), osteolytic process ($p = 0.014$), and periosteal reaction ($p = 0.017$).

The development of bone sequestrum was significantly higher in cancer patients. No statistical differences were observed between osteometabolic disease-affected patients versus cancer patients in terms of the presence of osteolysis ($p = 0.135$), enhancement of the mandibular canal ($p = 0.612$), sclerosis ($p = 0.224$), and persistence of alveolar socket ($p = 0.126$) (Table 6). Bone sequestrum ($p < 0.01$) and osteolysis ($p = 0.007$) were significantly higher in lesions with mandibular localization (Table 7).

Table 4: Occurrence of radiographic signs assessed on panoramic radiographs ($n = 150$ lesions).

Variables	Descriptive statistics
Thickened lamina dura	6 (4%)
Loss of lamina dura	0
Persistence of alveolar socket	40 (26.7%)
Sequestrum	47 (31.3%)
Sclerosis	41 (27.3%)
Osteolytic process	97 (64.7%)
Differences in sclerosing	26 (17.3%)
Enhancement of the mandibular canal	46 (30.7%)
Pathologic fracture	8 (5.3%)
Oblique line	1 (0.6%)
Sinus involvement	7 (4.7%)
Periosteal reaction	8 (5.3%)

4. Discussion

According to the present results, the most frequently encountered imaging features of MRONJ include the presence of osteolysis, the development of bone sequestrum, and the enhancement of the mandibular canal, followed by osteosclerosis and the persistence of postextractive alveolar socket. Indeed, the variability in MRONJ presentation may concur with an intrinsic difficulty in imaging interpretation. Nevertheless, radiographic features vary depending on the stage, with more severe complications occurring in Stage III patients. The role of traumatic events, such as dental extractions, repeated trauma from the inadequate removable prosthesis, and periodontal/peri-implant disease, appears extremely relevant as a triggering for MRONJ development.

Although the AAOMS classifies MRONJ on the basis of clinical features, it has been claimed that in cases of unexposed MRONJ, a diagnostic delay can occur [13]. Moreover, MRONJ clinical manifestations, including bone exposure, infection, fistulae, mucosal erythema, and purulent drainage, do not always reflect the true extent of the disease [14]. From this perspective, the adjunct of diagnostic imaging appears of utmost importance in further characterizing and staging MRONJ lesions.

Interestingly, different imaging techniques have been evaluated in the diagnosis of MRONJ [13]. Panoramic radiography appears undoubtedly as the first imaging step toward an initial understanding of the lesion. Among the characteristics which can be detected on panoramic radiographs, the development of osteolysis and/or osteosclerosis, and a thickening of the lamina dura have been consistently reported both in nonexposed and exposed MRONJ [13]. Moreover, it appears that the lack of bone repair with the persistence of postextractive alveolar socket, the development of a thickened lamina dura, and the presence of focal osteosclerosis could be classified as early radiographic

Table 5: Occurrence of radiographic signs assessed on panoramic radiographs depending on AAOMS stage.

Variables	Stage I	Stage II	Stage III	χ^2	p
Thickened lamina dura	0	4	2	1.069	0.785
Persistence of alveolar socket	1	23	16	2.845	0.416
Sequestrum	2	21	24	4.555	0.207
Sclerosis	2	11	28	12.324	0.006
Osteolytic process	6	38	53	10.572	0.014
Differences in sclerosing	1	7	18	7.326	0.062
Mandibular canal enhancement	1	10	35	25.435	<0.001
Pathologic fracture	0	0	6	7.537	0.05
Sinus involvement	0	0	7	8.854	0.03
Periosteal reaction	0	0	8	10.191	0.017

Table 6: Occurrence of radiographic signs assessed on panoramic radiographs depending on underlying disease.

Variables	Osteoporosis	Oncologic disease	χ^2	p
Thickened lamina dura	2	4	0.142	0.706
Persistence of alveolar socket	7	33	2.344	0.126
Sequestrum	18	29	4.7355	0.030
Sclerosis	8	33	1.477	0.224
Osteolytic process	22	75	2.231	0.135
Differences in sclerosing	4	22	2.047	0.152
Mandibular canal enhancement	11	35	0.257	0.612
Pathologic fracture	1	5	0.320	0.572
Sinus involvement	1	6	0.576	0.448
Periosteal reaction	0	8	3.073	0.08

Table 7: Occurrence of radiographic signs assessed on panoramic radiographs depending on affected site.

Variables	Maxilla	Mandible	χ^2	p
Thickened lamina dura	1	5	0.155	0.694
Persistence of alveolar socket	12	28	1.355	0.244
Sequestrum	2	45	13.926	<0.001
Sclerosis	11	30	0.385	0.535
Osteolytic process	16	81	10.572	0.007
Differences in sclerosing	7	19	0.227	0.34
Periosteal reaction	0	8	2.572	0.109

features of preclinical MRONJ [13]. However, it should be noted that the radiographic findings, which can be observed in Stages I–III MRONJ have also been described in Stage 0 disease as a consequence of AT [7, 15]. Therefore, the reasons behind the occurrence of bone changes with necrosis development and their link with the type and dosage of antiresorptive drugs administered need further investigation, also by taking into account the basic condition of the patient [10].

In our sample, pharmacological and clinical variables related to MRONJ development were assessed. MRONJ was mostly observed in females (65.3%) and patients affected by oncologic disease (74.7%). This finding is consistent with previous reports in the literature, indicating a predominancy of MRONJ development in females and oncologic patients presenting earlier stage disease [6]. Panoramic imaging revealed the presence of sclerosis, osteolysis, enhancement of the mandibular canal, and periosteal reaction as the most common signs, while sinus involvement and pathological fractures were observed only in cases of Stage III disease. Overall, a greater number of radiographic alterations was observed with the increasing MRONJ stage, although only the presence of sequestrum was significantly higher in Stages II–III. Mandibular localization was predominant for MRONJ development, consistently with previous reports [16].

The role of diagnostic imaging is gaining increasing importance in the presurgical planning and management of several oral diseases due to the possibility to achieve additional information to integrate clinical assessment [17, 18]. Among the techniques, panoramic radiography is the examination of choice for screening and comprehensively evaluating dento-periodontal health [19]. In cases of suspected MRONJ, this technique can identify some of the signs of the disease, including poor/nonhealing extraction sockets, sclerosis, sequestrum, pathological fractures, osteolytic areas, lamina dura thickening, widening of the periodontal ligament space and periosteal reaction [19]. Although providing an overview of the MRONJ lesion, its actual extent can be underestimated [20]. Therefore, three-dimensional diagnostic imaging techniques are often required to further assess MRONJ characteristics. Computed tomography (CT), either cone beam CT (CBCT) or multislice CT (MSCT), can support MRONJ assessment through the evaluation of several

radiographic signs of bone remodeling, such as cortex irregularities and subperiosteal bone formation [21]. While CBCT provides higher spatial resolution at a significantly lower radiation dose, MSCT appears extremely valuable in cases of soft tissue involvement [11, 22, 23]. Both techniques provide three-dimensional datasets which can be further processed to improve lesions visualization [17]. Nevertheless, the increased radiation dose and the actual diagnostic and therapeutic benefit deriving from the performance of CT should always be taken into account prior to prescribing additional examinations.

Although early bone changes have been related to AT, it appears still unclear the timing of bone changes, their relationship to the administration of antiresorptive drugs, the basic condition of the patient, and the development of necrosis [24]. Indeed, advanced MRONJ stages are related to a higher number of bone alterations [25].

It appears worth mentioning that the present data give insight into the radiographic signs associated with MRONJ, potentially improving clinicians' awareness regarding the importance of correct imaging interpretation. This study calls for the development of a more structured assessment of panoramic radiographs in patients at risk of MRONJ and advocates for increasing attention to initial radiographic signs, as our data confirm that early diagnosis of MRONJ at the initial stages of the disease is associated with improved prognosis and surgical treatment outcomes.

The present study has some limitations. First, the retrospective design of the study hindered the evaluation of additional clinical parameters, such as plaque score and periodontal status, as well as antiresorptive drug administration modality. The comparison with a control group treated with antiresorptive drugs and without a diagnosis of MRONJ could have provided a more accurate assessment of the modifications occurring in the course of AT and could potentially have allowed the performance of power analysis. Moreover, the three-dimensional imaging features of MRONJ were not evaluated. Finally, MRONJ treatment was not described, and follow-up was not reported. Nevertheless, the current results support the role of panoramic radiography as a useful tool in MRONJ diagnostic work-up, consistently with the current literature. Further studies, potentially with larger samples and involving a control group, are recommended to increase the awareness of MRONJ recognition among practitioners.

Data Availability

Data are available on request from the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The present version of the manuscript has been read and approved by all named authors.

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