Resemblances and differences between osteoradionecrosis of the jaw and medication-related osteonecrosis of the jaw

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Abstract

Aim. The aim of this retrospective study was to identify the clinical, radiological, and histological characteristics of patients diagnosed with osteonecrosis of the jaw (ONJ) and treated at the Oral and Maxillo-Facial Surgery Clinic of the Emergency Clinical County Hospital of Targu Mures between 2017 and 2022. The study aimed to analyze correlations between patient characteristics, particularly their history of bone modifying agent use or local radiotherapy during cancer treatment, in order to identify specific patient profiles that could aid in evaluating treatment response and guide individualized treatment strategies.

Methods. Fifty-two patients diagnosed with ONJ were included in the study. The patients were divided into two groups based on their medical history: the bone modifying agent use group and the radiotherapy group. Clinical, radiological, and histological data were collected and analyzed. Statistical analysis, including p-values, was performed to compare patient characteristics between the two groups.

Results. Patients in the radiotherapy group were significantly older than those in the bone modifying agent use group (66 years vs. 56.9 years, p=0.001). There was a higher proportion of males in the radiotherapy group compared to the bone modifying agent use group (90% vs. 22%, p<0.001). Jaw involvement was more prevalent in the radiotherapy group compared to the bone modifying agent use group (95% vs. 66%, p=0.018). Histological analysis showed a similar frequency of Actinomyces species in both groups (50% vs. 34%, p=0.264).

Conclusions. The findings of this study suggest the existence of two distinct patient profiles based on their treatment history (bone modifying agent use vs. radiotherapy) in ONJ. Patients in the radiotherapy group were older, predominantly male, and exhibited a higher prevalence of jaw involvement. Histological analysis revealed no significant differences in Actinomyces species frequency between the two groups. These distinct patient profiles may indicate different responses to treatment, emphasizing the need for individualized treatment strategies tailored to specific patient characteristics. Further research is warranted to validate these findings and develop personalized approaches for managing ONJ.

Keywords: osteonecrosis of the jaw, osteoradionecrosis of the jaw, medication-related osteonecrosis of the jaw, treatment strategies

DOI: 10.15386/mpr-2610

Manuscript received: 25.01.2023
Received in revised form: 26.02.2023
Accepted: 13.03.2023

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Introduction

Osteomyelitis is a common bone disease of the maxillary and facial regions, with local factors like increased levels of oral bacteria and specific anatomical features like teeth and bone covered by a thin mucosa as causes of its high frequency. A history of topical radiotherapy or increased use of bone modification agents (BMA) is the main factor linked with the high incidence of osteomyelitis of the jaw (OMJ) [1]. The current literature on osteomyelitis is wide-ranged and numerous classifications have been proposed based on clinical and radiological aspects or etiological pathogenesis. These have generated a varied nomenclature which creates confusion and makes a comparison of the studies impossible. The Zurich classification for OMJ described by Baltensperger et al. [1] is currently the most widely used in practice. It proposes the use of clinical and radiological criteria to characterize the separate forms and is presented in table I. Secondary subclassifications are based on histological criteria, with the third criterion constituting etiological aspects that can guide individualized treatment.

Table I. Zurich classification of osteomyelitis of the jaw [1].

	Types of Osteomyelitis
1	Acute Osteomyelitis (AO)
2	Secondary Chronic Osteomyelitis (SCO)
3	Primary Chronic Osteomyelitis (PCO)

Several other staging systems were proposed based on clinical and radiological aspects, response to therapy, especially to hyperbaric oxygen therapy, length of bone exposure, or a combination of these criteria. The most recently published are the ones described by Schwartz et al. [2], Notani et al. [3], and Lyons et al. [4]. While the first two use only clinical criteria, the third one also proposed a staging system based on radiological aspects that can be useful in guiding treatment decisions. These staging proposals are summarized in tables II and III.

Although bisphosphonate-induced Osteonecrosis of the Jaw (ONJ) was first reported in 2004 [5], these drugs are still considered the gold standard of therapy in osteoporosis, while also being used for controlling skeletal manifestation in cancer patients. More recently, denosumab has been approved for the treatment of osteoporosis and metastatic bone diseases, with subsequent cases of ONJ relating to its use being reported, which were later defined as denosumab-related ONJ [6,7]. Another drug related to the appearance of osteonecrosis is sunitinib, a multi-targeted tyrosine kinase receptor inhibitor with a potent anti-tumor effect [8.9]. Subsequently, the notion of Medication-Related Osteonecrosis of the Jaw (MRONJ) was defined to include bisphosphonate, denosumab, or other antiresorptive or angiogenetic drugs causing this complication. The updated definition and classification of MRONJ proposed by the American Association of Oral and Maxillofacial Surgeons [10] are presented in table IV.

Table II. Schwarz et al. and Notani et al. classification [2,3].

Stage 1	Stage 2	Stage 3
Minimal soft tissue ulceration and superficial necrosis in the cortical bone	Cortical bone and also a portion of the underlying medullary bone are necrotic, with stage IIa as minimal soft tissue ulceration and stage IIb as soft tissue necrosis and fistula	The full thickness of a segment of bone is involved, including the lower border
Grade 1	**Grade 2**	**Grade 3**
Osteoradionecrosis confined to the alveolar bone	Osteoradionecrosis limited to the alveolar bone and/or the mandible above the level of the mandibular alveolar canal	Osteoradionecrosis extends to the mandible under the level of the mandibular alveolar canal and a skin fistula and/or a pathological fracture is present

Table III. Lyons's classification of osteonecrosis of the jaw [4].

	Affected bone	Symptoms	Treatment recommendations
Stage 1	<2.5 cm	Asymptomatic	Medical therapy only
Stage 2	>2.5 cm	Pathological fracture or involvement of inferior dental nerve, or both	Medical therapy only unless there is dental sepsis
Stage 3	>2.5 cm	Symptomatic, but with no other features despite medical treatment	Consider debridement and local pedicled flap
Stage 4	>2.5 cm	Pathological fracture, involvement of inferior dental nerve, fistula, or a combination	Reconstruction with free flap

Table IV. Definition and staging of Medication-Related Osteonecrosis of the Jaw [10].

Definition (all criteria must be present)
1. Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistulaI in the maxillofacial region that has persisted for more than eight weeks
3. No history of radiation therapy to the jaws or metastatic disease to the jaws.
Staging
0. No clinical evidence of necrotic bone in patients who present with nonspecific symptoms or clinical and radiographic findings
1. Exposed and necrotic bone or fistula that probes to the bone in patients who are symptomatic and have no evidence of infection/ inflammation
2. Exposed and necrotic bone, or fistula that probes to the bone, with evidence of infection/inflammation
3. Exposed and necrotic bone or fistulae that probe to the bone, with evidence of infection, and one or more of the following:
• Exposed necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, or zygoma in the maxilla).
• Pathologic fracture.
• Extraoral fistula.
• Oral antral/oral-nasal communication.
• Osteolysis extending to the inferior border of the mandible or sinus floor, mandible, maxillary sinus, or zygoma in the maxilla).
• Pathologic fracture.
• Extraoral fistula.
• Oral antral/oral-nasal communication.
• Osteolysis extending to the inferior border of the mandible or sinus floor.

Risk factors for developing MRONJ include treatment with BMA (usually indicated for malignancy or osteoporosis), BMA type, dose, and timing of administration, local factors like previous radiotherapy, poor oral health, periodontal diseases that require dental surgery or extractions, various general medical conditions, and alcohol or tobacco addiction. Out of these, the use of BMA and radiotherapy appear to have the strongest association and are usually not found together in the same patient, but rather form two distinct groups of patients with somewhat different characteristics [11,12].

Osteoradionecrosis of the jaw (ORNJ) is a form of ONJ and is defined as exposed irradiated bone that fails to heal in 3 months without any evidence of persisting or recurrent tumors. Radiation-induced fibrosis, blood vessel destruction, and tissue hypoxia have been mentioned as possible mechanisms of pathogenesis [12,13]. Risk factors that can influence ORNJ are related to basic oncological disease (site and size of the tumor, surgical treatment performed or dose of radiotherapy), oral health (infection or dental surgery), general status (immune deficiencies and malnutrition or diabetes), and sociological factors (alcohol or tobacco abuse) [11]. Optimal treatment options for ORNJ are still debated in the literature. Hyperbaric oxygen therapy and drugs like pentoxifylline and vitamin E have been introduced to reduce radiation sclerosis and tissue hypoxia or damage caused by free radicals produced by inflammation [12]. Surgery is considered the best option in advanced stages to suppress osteoradionecrosis progression while the use of fluorescence-guided surgery can also improve results [14]. Prevention measures should be taken and any dental issue should be fixed before radiotherapy. Also, patients should be informed to maintain a good oral health in order to reduce the frequency and severity of ORNJ.

While curative therapies are harder to implement, preventing and maintaining a good quality of life by reducing symptomatology is an important treatment goal for MRONJ patients. Various treatment protocols have been proposed for every stage of osteonecrosis [15], from conservative treatment to minimally invasive surgical treatment, curettage, and local debridement [16]. Other more radical surgical treatment options include complete resection of necrotic bone, however, there is currently no consensus on an ideal treatment protocol for these patients. Thus, individualized treatment is likely the most useful approach, and to achieve this goal, it is important to identify different types of patients with concordant characteristics that can benefit from similar treatment approaches.

Our study aimed to identify the clinical, radiological, and histological characteristics of patients diagnosed with ONJ and analyze correlations between these characteristics to identify specific patient types that could provide useful in evaluating treatment response and further guide individualized treatment strategies.

Methods

We performed an observational retrospective study of consecutive patients diagnosed with ONJ admitted for

treatment to the Oral and Maxillo-Facial Surgery Clinic of the Emergency Clinical County Hospital of Targu Mures between 2017 and 2022. The diagnosis was made using the current definition based on specific signs and symptoms, clinical presentation, and a history of either local radiotherapy in the oral and maxillofacial territory or antiresorptive treatment for osteoporosis or for preventing skeletal manifestation in cancer treatments. Patients were excluded if they had missing data from their records. The selected patients were distributed into two groups depending on their history of either BMA use or local radiotherapy during cancer treatment. Data were extracted from patient records including clinical characteristics such as age, sex, involved regions, drug intake, medical history and histological analysis of biopsy specimens sampled during the surgical treatment. The data collected were further analyzed to identify normal distribution using the Kolmogorov-Smirnov test and different tests were used to compare the means for continuous variables depending on their distribution, such as the student's t-test for normally distributed variables and Mann-Whitney U test for non-normal distributions. Discrete variables were compared using the chi-squared test or Fisher's exact test when necessary. A p-value of <0.05 was considered significant. Statistical analysis was performed using SPSS v20 software (IBM, Armonk, NY, USA). The study followed the principles of the Declaration of Helsinki and ethical approval was obtained from the ethics committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Targu Mures, no. 1776/10.06.2022, and from the ethics committee of the Emergency Clinical County Hospital of Targu Mures, no. Ad. 1171/18.01.2022.

Results

Our study included 52 patients diagnosed with ONJ during the selected period, out of which 32 (62%) had a history of BMA use, in the form of bisphosphonates, and 20 (38%) had a history of radiotherapy. The overall mean age of the study population was 62.5 years and an almost equal proportion of both sexes was recorded (52% female). Regarding the patients from the BMA group, 44% had been prescribed the drugs as a treatment for bone metastases, while the remaining 56% had taken these BMA for other medical conditions. The most common site affected was the mandible (73% of patients) and several patients presented with a significant surgical complication in the form of a pathological fracture (23%). The histological analysis of the biopsy specimens revealed various findings, out of which the most common was the identification of Actinomyces species colonies, which were present in 40% of the patient samples. These characteristics are detailed in table V.

Table V. Patient characteristics.

Characteristic, unit	Value
Age, years	62.5±10.3
Sex	
Male, patients	25(48%)
Female, patients	27(52%)
Affected region	
Maxillary, patients	14(27%)
Mandibular, patients	38(73%)
Bisphosphonate use, patients	32(62%)
Indication for bone metastasis, patients	14(44%)
Indication for other bone diseases, patients	18(56%)
Previous radiotherapy, patients	20(38%)
Histological presence of Actinomyces species, patients	
Yes	21(40%)
No	31(60%)
Pathological fracture	
Yes	**12(23%)**
No	40(77%)

Values are expressed as numbers of patients (percent) or mean ± SD.

Table VI. Patient characteristics and comparisons between the groups.

Characteristic, unit	BMA patients (n=32)	Radiotherapy patients (n=20)	p-value
Age, years	66±10.4	56.9±7.1	0.001*
Sex			
Male, patients	7 (22%)	18 (90%)	<0.001*
Female, patients	25 (78%)	2 (10%)	
Affected region			
Maxillary, patients	11 (34%)	1 (5%)	0.018*
Mandibular, patients	21 (66%)	19 (95%)	
Histological presence of Actinomyces species, patients			
Yes	11 (34%)	10 (50%)	0.264
No	21 (66%)	10 (50%)	
Pathological fracture			
Yes	0 (0%)	12 (60%)	NA
No	32 (100%)	8 (40%)	

Values are expressed as numbers of patients (percent) or mean ± SD; p values with * are considered significant.

Patients were divided into two groups depending on their main risk factor, BMA use or previous radiotherapy. The patients in the radiotherapy group were significantly younger, 56.9 vs. 66 years, p= 0.001, more often male, 90 vs. 22%, p<0.001, and had more often mandibular lesions (95 vs. 66%, p=0.018) than the ones in the BMA use group. There was no significant difference regarding the presence of Actinomyces species in the histological specimens analyzed between the two groups (p=0.264). Regarding the presence of pathological fractures, all were observed in the radiotherapy group and comprised more than half of these patients (60%). The characteristics of the two groups and the comparisons between these are presented in table VI.

Discussion

The human bone is subjected to permanent remodeling, with osteoclasts constantly removing old bone and osteoblasts depositing a new bone matrix. The intervention of external or internal factors in this process can lead to altered bone healing and, through this, ONJ can appear. Among the causal factors for osteonecrosis in the oro-facial region is radiotherapy in patients with oral cavity cancers like lip, tongue, cheek, neck, or maxillary bone cancer. Another factor seems to be long-term therapy with BMA like bisphosphonates, denosumab, or other angiogenetic drugs used for osteoporosis, osteopenia, other bone diseases like Paget disease, and prevention of bone metastasis in oncological patients.

Our study looked at these two groups of patients and found that the incidence of MRONJ (62%) was almost double compared to ORNJ (38%), even though the average age of the oncological patients was lower. This is in line with current trends that report an increase in the incidence of the former, due to the implementation of new drugs, and a decrease in the occurrence of the latter, probably caused by improvements of radiotherapy techniques [17]. The use of antiresorptive medications has gained popularity in recent decades for the treatment of osteoporosis or other bone diseases and in the prevention of skeletal manifestation of the oncological patient (56% of our BMA patients were receiving BMA for prevention of metastasis). At the same time, the development of oncological treatment and more targeted radiological treatment can explain the reduction of ORNJ appearance. Although MRONJ has become more common due to the rising use of antiresorptive drugs, a distinction between different types of ONJ has not been clear and treatment strategies implemented after overt clinical signs like bone exposure occurrence can lead to a delayed diagnosis of MRONJ and difficult treatment.

The simple panoramic X-ray, which is very common in dental practice, is an essential diagnosis instrument for any bone disease like osteomyelitis, ORNJ or MRONJ. Of course, if more accurate information is needed, a three-dimensional imaging investigation like cone beam computer tomography (CBCT) is indicated and serves as a gold-standard in the diagnosis of oral and maxillofacial pathology. Radiologically, the appearance on the orthopantomogram or CBCT scan of ORNJ resembles conventional osteomyelitis with osteolysis and bony sequestrum. Often, moth-eaten bone appears on these films [18], and pathological fractures may appear. Bone modifying aspects can be present even from earlier stages in MRONJ patients, like changes in bone trabeculation, that evolve to the later stages when osteolysis extends to the sinus or inferior border of the mandible.

The radiologic aspects found in our study include simple osteolytic lesions (Figure 1), sclerotic lesions (Figure 2), or a mix of both, which is most frequent (Figure 3, 4). These characteristics were found similarly in both groups of MRONJ and ORNJ patients. Unhealed dental sockets or bone sequestrum (Figure 5) were observed especially in the medication-related group or in advanced stages and an impressive 23% of pathological fractures, with more than half of the radiotherapy patients presenting this kind of lesion (Figure 6). Bone sequestrum or pathological fractures can lead to severe oral feeding issues and loss of quality of life for patients. The most common site affected was the mandible (73% of patients), which was probably due to its relatively poor blood supply compared to the multiple arterial branches of the maxillary artery. This is in line with other published data that report this as the most common affected site for both MRONJ and ORNJ [18,19]. While our patients had only X-ray data available, further investigations like CBCT or magnetic resonance imaging could have provided more detailed information.

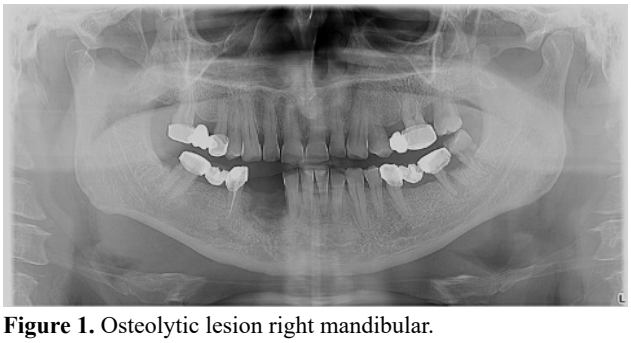

Figure 1. Osteolytic lesion right mandibular.

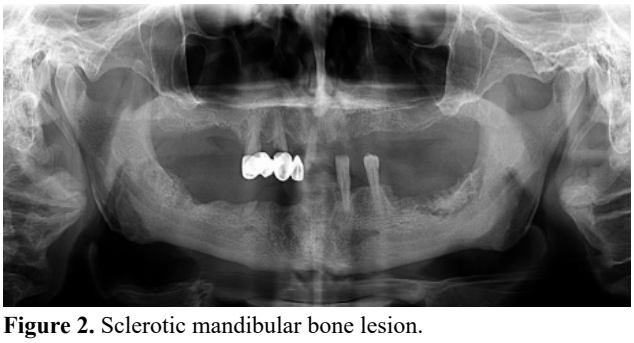

Figure 2. Sclerotic mandibular bone lesion.

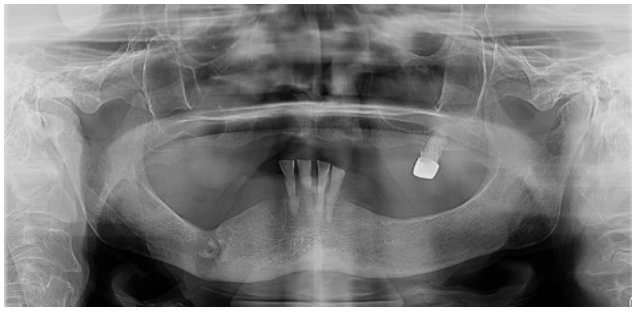

Figure 3. Sclerotic and osteolytic lesions.

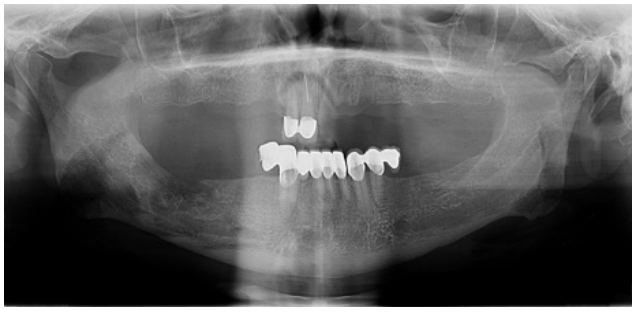

Figure 4. Mixed bone lesion.

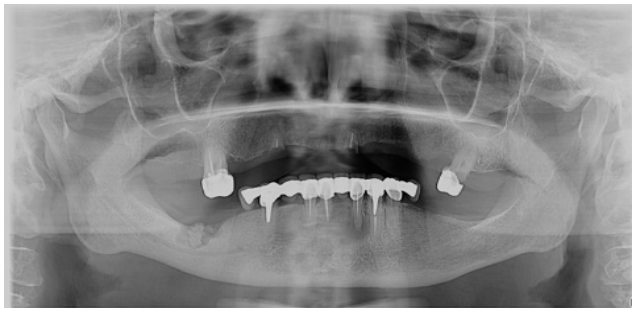

Figure 5. Bone sequestrum.

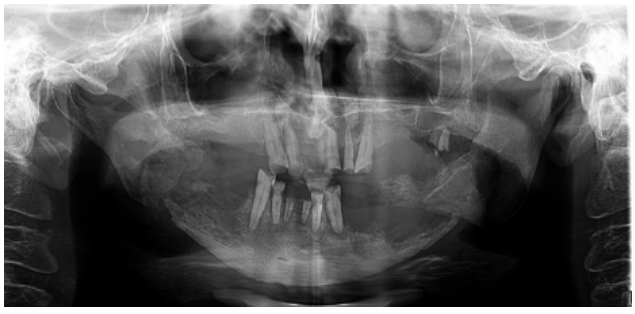

Figure 6. Pathological bone fracture.

From a histological point of view, all MRONJ is described as non-vital bone and resorption lacunae, with or without embedded osteoclasts [20]. When present, osteoclasts can be found in a floating position [21] with signs of soft tissue inflammation (Figure 7, 8). Bacterial infections are common findings, with many different types involved, like Actinomyces species. In our study, there was no significant difference regarding the presence of this bacterial strain in the histological specimens of the two groups, with a 34% incidence in the MRONJ group and 50% in the ORNJ one. These figures are lower than those reported by other studies that vary from 96.4% to 63.3% [22]. This difference could be explained by the reduced detection sensibility of our method, histological examination (Figure 9, 10), as opposed to the one used in other studies, PCR, which unfortunately was not available in our study. Moreover, the hematoxylin-eosin stain used in our study also provides a lower specificity for the detection of Actinomyces species, thus additional stains like by periodic-acid Schiff (PAS), Gram and Grocott's methenamine silver stain (GMS) have been proposed to increase it [22], which were also unavailable. Modern microbiological investigations like Matrix-Assisted Laser Desorption/Ionization–Time of Flight can lead to faster identification of bacterial colonization and help treatment guidance and decrease antibacterial resistance to antibiotics [23].

Histological aspects of ORNJ (Figure 11, 12) are the same as osteomyelitis and three phases can be observed, an initial pre-fibrotic phase with inflammatory response, a second constitutive organized phase with disorganization of extracellular matrix, and a third fibro atrophic phase when tissue remodeling occurs [21]. Gross et al. [24] found similar expression patterns for dendritic cell-specific transmembrane proteins in MRONJ and ORNJ specimens, although giant, hyper-nucleated osteoclasts were found only in the former specimens.

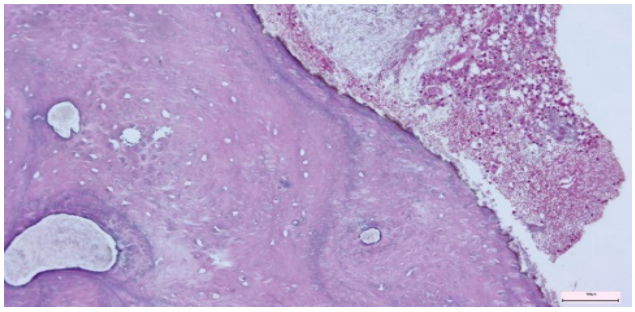

Figure 7. Patient with a history of bone modifying agent use - nonviable bone without osteocytes.

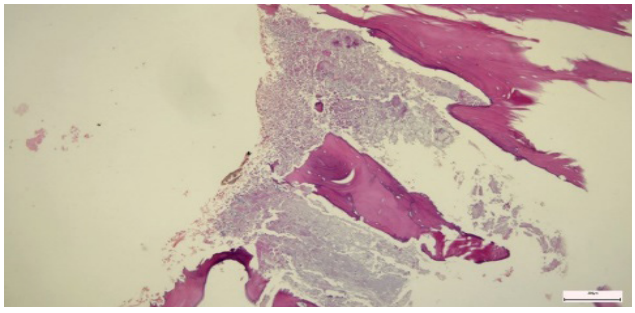

Figure 8. Patient with a history of bone modifying agent use – non-viable fragmented bone with bacterial colonies.

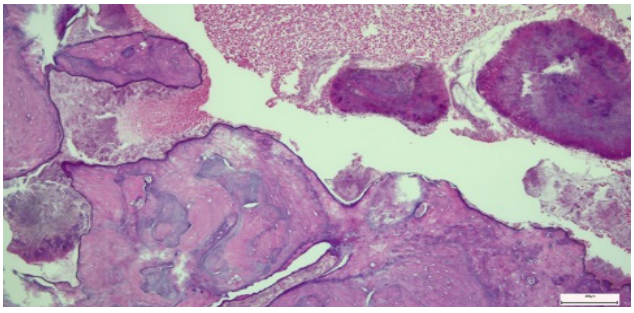

Figure 9. Patient with a history of bone modifying agent use - nonviable bone with actinomyces colonies.

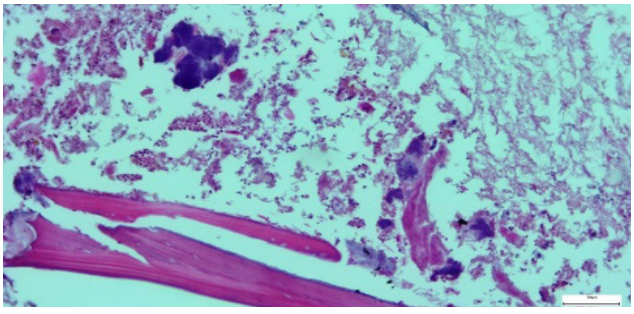

Figure 10. Radiotherapy patient - non-viable bone with actinomyces colonies and inflammatory cells.

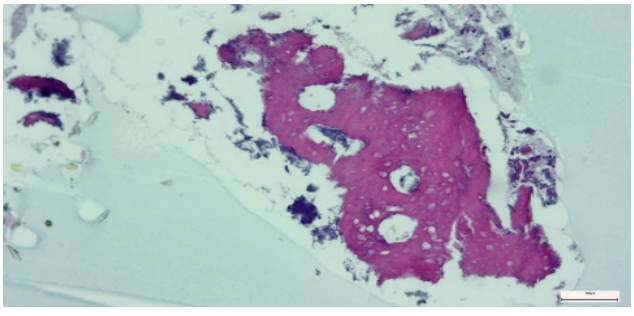

Figure 11. Radiotherapy patient – non-viable bone.

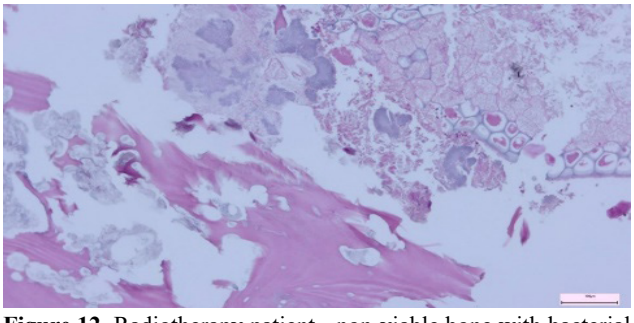

Figure 12. Radiotherapy patient - non-viable bone with bacterial colonies and vegetal fragments.

Indistinct from the cause of osteonecrosis, local radiotherapy or BMA use, treatment of patients with ONJ is still very challenging, thus we cannot talk about curing, but only of improving the patients' quality of life through symptom reduction. New strategies should be designed in order to improve the prevention of osteonecrosis and an individualized treatment strategy should be developed. More attention should be given to newer therapies for osteoporosis or skeletal manifestation like denosumab, sunitinib, and not only to bisphosphonates because of the increased risk of developing MRONJ associated with their use. Because oral health can influence the appearance of ORNJ and MRONJ, a multidisciplinary approach should be mandatory, which includes the dentist and dental hygienist. The initial clinical signs should prompt a recommendation for performing a panoramic X-ray, which can help in identifying the patients at risk for developing ONJ. They should be included in a special follow-up program and, once ONJ has been installed, a regular check-up including a minimum of a panoramic X-ray may lead to new information regarding ONJ development even in asymptomatic patients.

BMA prescribers, like endocrinologists, oncologists, rheumatologists, and other specialties should inform their patients regarding the risk of developing ONJ, and dental check-ups should be recommended before initializing BMA treatment [25]. Also, patients should focus on preventive dental care and any oral disease should be treated and a good oral status must be obtained before initializing radiotherapy or BMA, while invasive dental surgery should only be reserved for teeth with no chance of salvaging.

Conclusions

Patients diagnosed with ONJ caused by local radiotherapy or BMA use present different characteristics, with the former being older, more often male, and with a higher rate of involvement of the mandible. Typical X-ray and histological findings, alongside Actinomyces species infections, are common between both groups. The differences observed between the two groups outline two different patient profiles that can present different responses to treatment, therefore an individualized strategy should be developed based on these aspects. Any disease process must first be diagnosed before it can be treated effectively, thus these findings can serve to better define this disease and guide additional research on the imaging predictors that can be seen before the development of ONJ. A multidisciplinary treatment approach should be mandatory and include the dentist. Initial dental checkups and further follow-ups can improve the prevention of both ORNJ and MRONJ and the quality of life of these patients.

Institutional Review Board Statement

The study followed the principles of the Declaration of Helsinki and ethical approval was obtained from the ethics committee of the "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Targu Mures, no. 1776/10.06.2022, and from the ethics committee of the Emergency Clinical County Hospital of Targu Mures, no. Ad. 1171/18.01.2022.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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