Title

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Radiographic predictors of bone exposure in stage 0 MRONJ patients

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Abstract

Objective: To explore the radiographic appearance of stage 0 MRONJ and examine 5 radiographic parameters (trabecular sclerosis, cortical erosion, periosteal reaction, sequestration, crater-like defect) as predictors of progression to bone exposure.

Study design: 23 patients with history of antiresorptive therapy, no bone exposure and non-specific signs and symptoms were included. Intraoral photographs, panoramic and CBCT images at initial visit and follow-up intraoral photographs were reviewed. 3 patients had dental disease (D.D.), 10 stage 0 MRONJ patients did not progress to bone exposure (N.B.E.), and 10 patients progressed to bone exposure (B.E.). Radiographic parameters were scored as absent (0), localized (1) or extensive (2), and their sum formed the composite radiographic index (CRI).

Results: D.D. patients demonstrated minimal radiographic findings and their CRI was significantly lower than that of N.B.E. and B.E. patients. Additionally, B.E. patients demonstrated a higher radiographic index than N.B.E. patients. Intriguingly, sequestration was observed in the initial CBCT of 90% (9/10) of B.E. patients, whereas 80% of N.B.E. patients showed absence of sequestration at initial CBCT examination.

Conclusion: CBCT imaging can aid stage 0 vs dental disease diagnosis. Radiographic sequestration at initial presentation can serve as a predictor of future bone exposure in stage 0 MRONJ patients.

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Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is a significant adverse effect of antiresorptive and antiangiogenic medications prescribed to patients with osteoporosis or bone malignancies [1, 2]. Various pharmacological agents, such as bisphosphonates, denosumab (a RANKL inhibitor) or bevacizumab (a monoclonal antibody to VEGF) have been associated with the development of the disease [3-6]

MRONJ is defined as exposed bone in the oral cavity or bone that can be probed through an intraoral or extraoral fistula, which does not heal for 8 weeks, in a patient with a history of antiresorptive/antiangiogenic medication and no history of radiation therapy in the head and neck area. The most recent position paper by the American Association of Oral and Maxillofacial Surgeons (AAOMS) describes 4 stages of MRONJ (0-3), with stage 0 representing a non-exposed variant of the disease. Specifically, stage 0 refers to patients with no clinical evidence of exposed bone, but with presence of non-specific symptoms or abnormal clinical and radiographic findings [7]. Indeed, stage 0 MRONJ patients present with an intact mucosa and variable symptoms and signs, which poses a critical diagnostic dilemma.

A stage 0 MRONJ diagnosis may be reached after all other possible conditions, that could account for the patient's symptoms, have been ruled out. This diagnosis-by-exclusion approach increases the risk for over-diagnosis or under-diagnosis of patients with MRONJ [8-10]. Interestingly, 50% of patients with stage 0 MRONJ proceed to clinical bone exposure within 4-5 months after initial diagnosis [11]. However, prognostic markers, to distinguish patients who will progress to bone exposure from patients who will not progress, have not been established. Correct and early diagnosis of patients with stage 0 MRONJ and identification of parameters associated with development of bone exposure are of paramount importance in management.

Given the lack of sufficient characteristic clinical features of stage 0 MRONJ, thorough radiographic assessment can play a pivotal role in prompt diagnosis and correct management. Cone beam computed tomography can provide precise evaluation of osseous abnormalities [12-16]. However, a detailed assessment of the radiographic appearance of stage 0 patients has not been reported. Additionally, there are no radiographic markers of stage 0 MRONJ cases that predict progression to clinical bone exposure.

In this study, we have retrospectively assessed the CBCT scans of 23 patients with an initial clinical diagnosis of stage 0 MRONJ and have correlated their radiographic parameters with subsequent bone exposure.

Materials and Methods

Twenty-three patients with a history of exposure to bisphosphonates (BP), denosumab (Dmab) or both referred to the Oral and Maxillofacial Surgery Clinic at the UCLA School of Dentistry from general dentists between January 2013 to April 2015 were included in the study. Antiresorptive therapy had been administered to the patients to treat osteoporosis or several types of bone malignancy including multiple myeloma, metastatic breast, lung or

prostate cancer (Table 1). Approval of the study by the UCLA Institutional Review Board (IRB) was obtained. All procedures followed the guidelines of the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

None of the patients presented with bone exposure or fistula formation probing to bone at initial visit. Patient signs and symptomatology were non-specific including dull bone pain, altered neurosensory function, mucosal erythema or edema.

All cases included intraoral photographs, panoramic radiographs and CBCT scans at initial presentation and at least one follow-up clinical examination including intraoral photographs. Several patients had multiple follow-up visits, which included intraoral photographs. Follow-up periods ranged from 1 month to three years with an average of 10 months. All cases meeting the inclusion criteria were included in the study. For all patients, the 3D Accuitomo 170 scanner (J Morita USA, Irvine, CA) was used. The exposure factors were 90 kVp and 6 mA with a 17.5-sec exposure time, during 360° rotation (standard exposure settings). The field of view (FOV) was 6×6 cm with a 0.125 mm isometric voxel or 10×14 cm with a 0.25 mm isometric voxel.

Clinical examination was performed by an Oral and Maxillofacial Surgeon (TA) with experience in MRONJ cases. CBCT scans were evaluated by a senior Oral and Maxillofacial Radiology resident (AS) and a Board Certified Oral and Maxillofacial Radiologist with experience in MRONJ cases (ST). When consensus on the radiographic assessment was not reached, the opinion of ST was used. At the time of radiographic evaluation, radiologists were aware of the history of antiresorptive treatment, but were blinded to the clinical appearance, symptomatology, or eventual progression to bone exposure.

Five radiographic parameters in the area of interest were evaluated in all cases at initial presentation: trabecular sclerosis, cortical erosion, periosteal reaction, sequestration, and crater-like defect. The radiographic findings were classified as absent (value of 0) localized (involving the area of one tooth, value of 1) or extensive (exceeding the area of one tooth, value of 2). A composite radiographic index (CRI), which was the sum of the values for each of the five radiographic parameters was also used.

All patients were managed conservatively and were given emphasis on oral hygiene measures. No surgical intervention was performed in the oral region. Upon clinical follow-up, cases were evaluated for progression to clinical bone exposure (stage 1-3 MRONJ). All cases in which patients reported no symptomatology after dental retreatment were attributed to dental disease (D.D.). Cases in which patients reported persistent pain but no bone exposure were classified as stage 0 (N.B.E.). Cases with bone exposure (B.E.) were classified as stage 1, 2 or 3.

Statistics were performed with GraphPad Prism Software, (Inc. La Jolla, CA). Fischer’s exact test was used for qualitative data comparison. One-way ANOVA was used for quantitative data comparison. P values <0.05 were considered statistically significant.

Results

The majority of the patients included in our study were female (18/23). Antiresorptive therapy duration varied, with osteoporosis patients having the most prolonged treatment (mean of 6 years). Details about patient systemic disease, sex, age, type of antiresorptive medication and treatment duration are shown in Table 1.

Radiographic evaluation (Figure 1A, B) revealed extensive trabecular sclersis in 57% (13/23) of the patients and localized in 30% of the patients (7/23). Extensive cortical erosion was noted in 13% (3/23), and localized erosion was seen in 57% (13/23), of patients. Periosteal reaction was visualized in 5 patients, with 9% (2/23) characterized as extensive and 13% (3/23) as localized. Thirty-five percent (8/23) and 13% (3/23) of scans demonstrated extensive or localized sequestrum formation respectively. Lastly, an extensive crater-like defect was visualized in 13% (3/23) of scans, whereas a localized crater was noted in 57% (13/23).

We then explored how many of these patients progressed to stage 1-3 MRONJ by consulting our follow-up database. In 3/23 cases, patient symptomatology and clinical abnormalities ceased after dental treatment. These were therefore attributed to common dental disease (D.D.) instead of stage 0 MRONJ. Indeed, after endodontic retreatment and caries removal, erythema and swelling subsided and pain symptomatology was significantly reduced. (Table 2, Figure 2A, A1, A2).

In 10/23 cases, patients presented with persistent pain, abnormal clinical findings and no evidence of bone exposure on their follow-up sessions (Table 2, Figure 2B, B1, B2). These patients were classified as stage 0 MRONJ with no bone exposure (N.B.E.) and continued to be followed-up.

In 10/23 cases, patients presented with clinical bone exposure (B.E.) and various degrees of inflammation/infection of the surrounding soft tissue upon first revisit. Three patients progressed to stage 1 MRONJ, 5 patients to stage 2 MRONJ, whereas 2 patients demonstrated extra-oral fistula formation and were classified as stage 3 (Table 2, Figure 2C, C1, C2). Three female patients had been treated for osteoporosis, and 7 (3 male and 4 female) patients had been treated for bone malignancies. The time interval between first presentation and progression to bone exposure was on average 3.9 months with a standard deviation of 2.6 months. The individual time interval between initial visit and bone exposure for all patients is reported in Supplemental Table 1.

Patients who were categorized as dental disease (D.D.) cases, demonstrated minimal radiographic findings upon initial presentation and their CRI was strongly statistically significantly lower than N.B.E. and B. E. patients ($p<0.05$ and $p<0.001$ respectively). Additionally, B.E. patients had a statistically significantly higher composite radiographic index in comparison to N.B.E. patients ($p<0.05$, Table 2).

Next, we tested whether any of the radiographic parameters could serve as predictors for future progression to bone exposure in stage 0 patients. Trabecular sclerosis was seen in all B.E. and N.B.E. patients and the extent of sclerotic changes was very similar between the

two groups. No statistical significance of the presence of cortical erosion, periosteal reaction or crater-like defect was noted between the two groups (Figure 3).

Of note, 90% (9/10) of patients who progressed to bone exposure presented with radiographic signs of sequestration (6/10 extensive and 3/10 localized) in their initial CBCT scan. Only one patient who progressed to clinical bone exposure did not present with radiographic sequestration in the initial CBCT scan. In the stage 0 MRONJ group with N.B.E, 80% (8/10) showed absence of sequestrum formation in their initial radiographic examination. The incidence of radiographic sequestration between the B.E. and N.B.E. groups was statistically significant ($p<0.01$, Figure 3).

Discussion

Stage 0 is characterized as a non-exposed variant of MRONJ and presents with nonspecific clinical signs, symptoms and radiographic features. The absence of specific clinical traits often creates a diagnostic challenge for clinicians [17] In these cases, radiographic evaluation is a valuable tool towards a correct diagnosis as well as the estimation of the extent of osseous changes.

In a recent study, which included six patients from the population of the current manuscript, we reported that CBCT offers a more thorough diagnostic assessment in comparison to panoramic radiographs in cases of suspected stage 0 MRONJ and alters the diagnostic thinking efficacy and management of patients with suspected stage 0 MRONJ [17] Indeed, diagnosticians can more readily appreciate cortical and trabecular variations as well as osseous changes in the buccolingual dimension utilizing a three-dimensional scan [18-21]. In our current study, we only included patients that underwent both panoramic and CBCT scanning at the time of the initial visit.

Even though the importance of radiographic assessment in the diagnosis of stage 0 MRONJ has been emphasized [7], the radiographic findings that might be present in these patients have not been described in detail. For example, periosteal reaction and sequestrum formation are not reported as abnormal findings in stage 0 MRONJ patients in the AAOMS position paper [7]. Here, we assessed the radiographic appearance of stage 0 patients by assessing the presence and the extent of 5 radiographic parameters (trabecular sclerosis, cortical erosion, periosteal reaction, sequestration, and crater-like defect). These radiographic parameters were previously described in MRONJ patients with clinical bone exposure. Lamina dura thickening is another radiographic feature reported in MRONJ cases [22, 23]. In our experience, thickened lamina dura is not a common radiographic finding and can affect areas of the dentition not associated with symptomatology or bone exposure. Importantly, in the current study, a considerable proportion of our patients were edentulous at the site of interest, making it impossible to discern lamina dura boundaries.

Our subjects were mostly female. This is mainly attributed to the all-female osteoporotic patients, who comprised almost half of the patient population (11/23). Nearly all patients were in the 6^{th} to 8^{th} decade of age with an average of 70 years. This was due to the manifestation of systemic diseases treated with antiresorptives (osteoporosis, metastatic

cancer, multiple myeloma) tending to occur later in life [24-27] An exception was a 30-year old male patient with sacrum sarcoma that was treated with denosumab. No patients were taking antiangiogenic medication, probably due to the lower incidence of MRONJ in this group of patients when compared to bisphosphonate and denosumab-treated patients and to the small number of patients in our study [7, 28, 29].

Over- or under-diagnosis of stage 0 MRONJ may have severe adverse effects on patients' oral and skeletal health. Indeed, over-diagnosis of MRONJ may lead to detrimental outcomes, if discontinuation of antiresorptive treatment is elected [1, 30,31]. Alternatively, under-diagnosing a patient with stage 0 MRONJ, as having common dental disease or other conditions, such as referred neuropathic pain, might lead to inappropriate and delayed treatment and might increase the possibility of developing clinical bone exposure. Proper diagnosis of stage 0 MRONJ can allow for management of local instigating factors, possible antibiotic treatment and more frequent follow-up visits [7].

Interestingly, 3 of 23 (13%) patients were initially diagnosed with stage 0 MRONJ but were subsequently classified as having common dental disease. The relatively low percentage of over-diagnosis in our study could be attributed to the accumulated considerable clinical expertise in managing MRONJ by the Oral and Maxillofacial Surgeons in our institution, as well as to the comprehensive radiographic assessment of all MRONJ patients that includes panoramic and CBCT imaging. The presence of these three patients, however, allowed us to explore whether radiographic findings could assist in further distinguishing patients with common dental disease from patients with stage 0 MRONJ. We observed that an overall absence of trabecular sclerosis, cortical erosion, periosteal reaction, sequestration and crater-like defect disfavors the diagnosis of stage 0 MRONJ and supports the diagnosis of dental disease in dentate patients. Since CBCT examination can aid in the diagnosis of challenging cases of dental disease, where identifying the source of symptomatology can often be ambiguous [32, 33] a detailed radiographic assessment utilizing CBCT technology should be considered in symptomatic patients on antiresorptives [17].

Half (10/20) of the stage 0 MRONJ patients progressed to frank bone exposure within 1-7 months. The percentage of progression to clinical bone exposure and time interval from initial diagnosis are in agreement with the report by Fedele et al investigating bone exposure progression in patients initially presenting with stage 0 MRONJ [11].

Patients who subsequently developed bone exposure had a higher composite radiographic index in comparison to the patients who remained in stage 0. This suggests that a detailed radiographic evaluation not only aids in the differential diagnosis of conditions that present with similar symptomatology, but could assist in the identification of patients with stage 0 MRONJ that might progress to clinical bone exposure. To further investigate whether a specific radiographic parameter(s) had a bigger contribution in the differentiation between B.E. vs. N.B.E. patients, we compared the presence of each radiographic parameter in these two groups. We observed that the discrepancy in the composite radiographic index was mostly attributable to the different incidence of sequestration. In fact, presence of sequestration in the initial CBCT scan was a strong predictor for bone exposure in 9 out of 10 patients. In contrast, sequestration was seen only in 2 out of 10 patients who did not

develop clinical exposure. These findings indicate that radiographic sequestration may serve as a reliable predictor of future bone exposure in stage 0 MRONJ patients.

Sequestration is characterized by devitalized bone separated from the surrounding bony tissue with inflamed granulation tissue. With time, epithelial rimming occurs around the detached necrotic bone, which subsequently exfoliates through the soft tissue or may lead to the formation of a sinus tract [34, 35]. This process of necrotic bone rejection could underlie the subsequent bone exposure observed in stage 0 MRONJ patients who present with radiographic sequestration. Furthermore, the high incidence of bone exposure development in patients with radiographic sequestration (9/11 or 82%) suggests that surgical removal of the sequestered bone should be considered in the management of these patients in an effort to decrease transition to clinical exposure. Importantly, only one of 9 patients without sequestration developed clinical exposure. Thus, absence of sequestration could be a positive radiographic indicator of favorable clinical outcome and could influence treatment planning towards a more conservative vs. surgical approach.

We recognize some limitations to our study. First, a relatively small number of patients were included, due to the rare incidence of stage 0 MRONJ. A few patients originally diagnosed as stage 0 MRONJ were subsequently classified as having common dental disease rather than MRONJ. This low number could be due to the increased experience with MRONJ patients by clinicians in our institution and therefore might not reflect the true incidence of patients over-diagnosed with stage 0 disease. Furthermore, our study did not allow for the assessment of the incidence of under-diagnosis of stage 0 MRONJ, since all patients were referred to our institution with suspected disease. A prospective study focusing on patients on antiresorptive medication would be needed to address potential under-diagnosis. A final limitation is that the period from the development of the clinical symptomatology to the visit to our institution was not known.

In summary, we present a retrospective study exploring the radiographic profile of patients diagnosed with stage 0 MRONJ, based on clinical examination. The extent of radiographic changes was an important determinant in the differentiation between patients with dental disease vs. patients with MRONJ. Furthermore, sequestrum formation was an important radiographic predictor of patients with stage 0 MRONJ that subsequently developed clinical bone exposure. We conclude that all patients with a history of both antiresorptive/antiangiogenic medications and abnormal clinical symptoms or signs should receive a CBCT examination. Presence of sclerosis, cortical erosion, periosteal reaction, sequestration, or crater-like defect should alert the clinician of the presence of stage 0 MRONJ as opposed to common dental disease. Presence of sequestration, in particular, favors the diagnosis of stage 0 MRONJ with a higher risk for development of frank bone exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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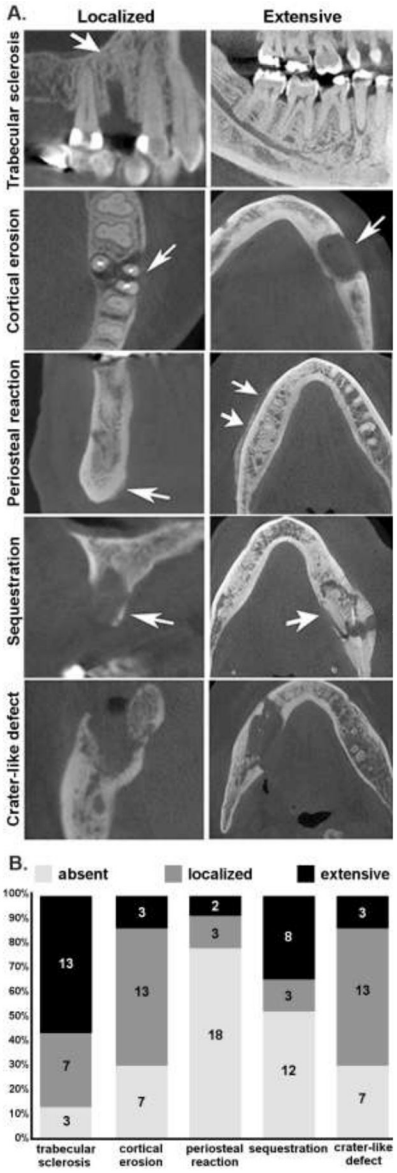

Figure 1:

Radiographic assessment. Representative examples of localized or extensive Trabecular Sclerosis, Cortical erosion, Periosteal reaction, Sequestration, Crater-like defect (A). Incidence and extent of these radiographic parameters in all patients (B)

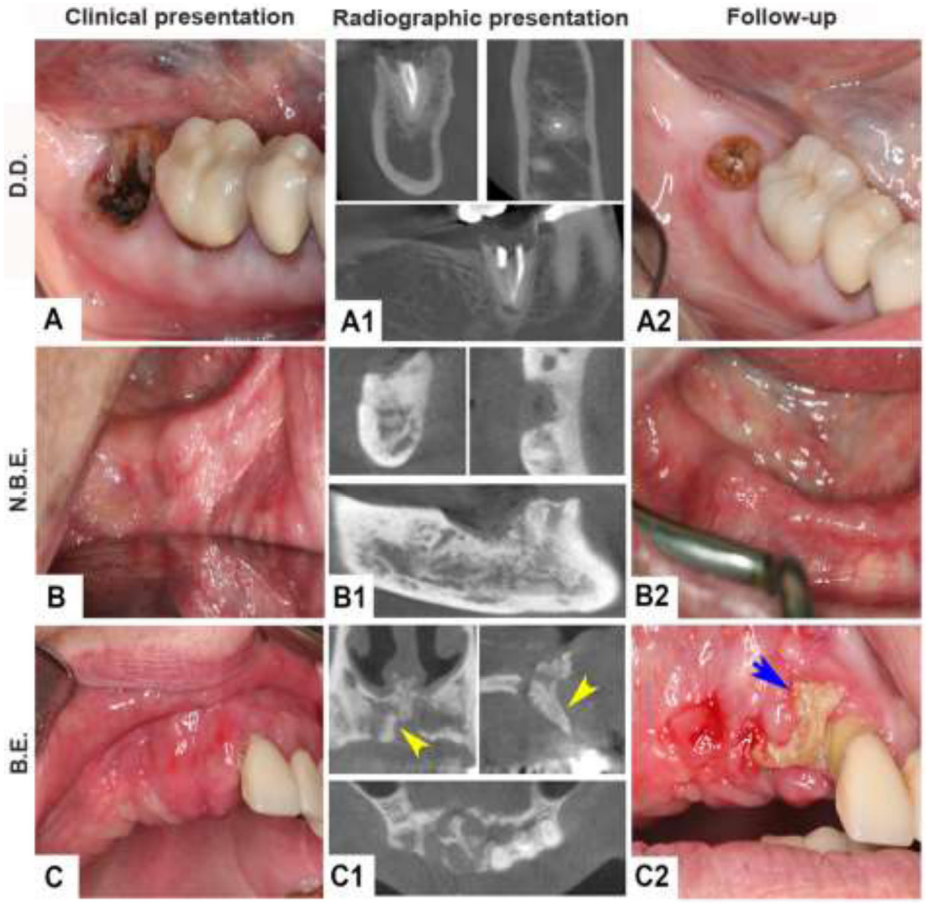

Figure 2:

Clinical and radiographic evaluation at initial presentation and clinical follow-up. Initial clinical and radiographic presentation and clinical follow-up of a patient who was classified as a dental disease (D.D.) case (A, A1, A2), a patient with stage 0 MRONJ and no progression to bone exposure (N.B.E., B, B1, B2) and a patient with progression to bone exposure (B.E., C, C1, C2). Yellow arrowheads point to areas of sequestration. Blue arrow points to bone exposure

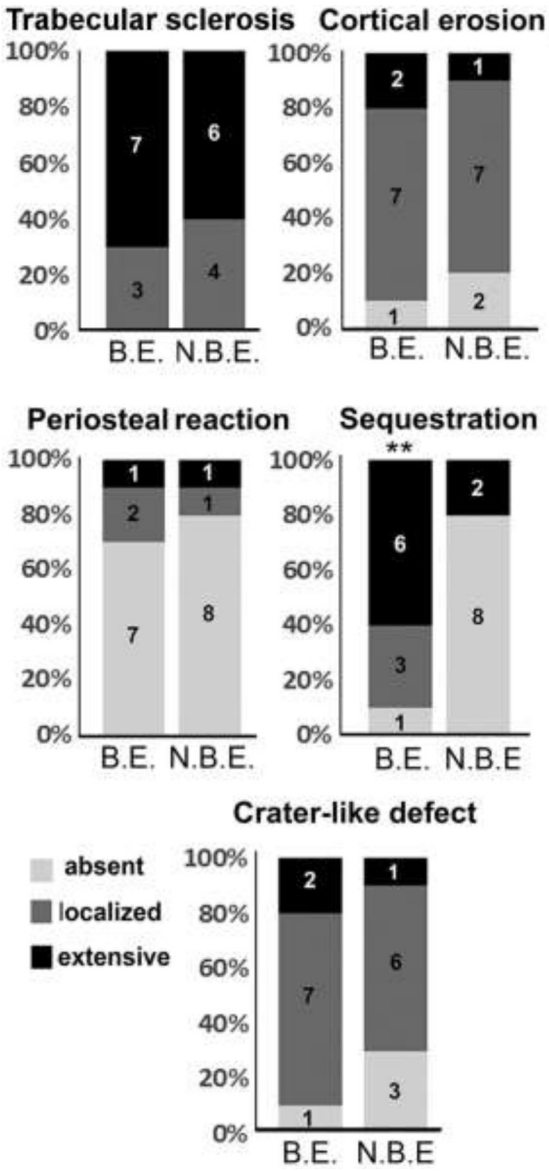

Figure 3:

Incidence and extent of Trabecular Sclerosis, Cortical erosion, Periosteal reaction, Sequestration and Crater-like defect in patients who progressed to bone exposure (B.E.) or showed no bone exposure (N.B.E.). **: statistically significant with $p<0.01$

Table 1:

Patient demographics and antiresorptive treatment information.

Disease	No. of patients	Sex	Mean Age (+/− SD)	AR treatment	AR duration
Osteoporosis	11	F (11)	78 (+/− 5)	BP (10) Dmab (1)	6y (+/− 7.5y)
Multiple myeloma	3	F (3)	69 (+/− 2)	BP (3) BP	22 mo (+/− 3 mo)
Breast cancer	3	F (3)	59(+/− 14)	BP+Dmab (3)	38mo (+/− 8 mo)
Prostate cancer	2	M (2)	80 (+/− 3)	BP(1) BP+Dmab (1)	60 mo (16 mo)
Lung cancer	1	M (1)	58	Dmab	36 mo
Chondrosarcoma	1	M (1)	74	Dmab	36 mo
Sacrum sarcoma	1	M (1)	30	BP+Dmab	24 mo
Giant cell tumor	1	F (1)	63	Dmab	6 mo
Total	**23**	**F(18) M(5)**	**70**	**BP(15) Dmab(4) BP+Dmab(4)**	**52 mo (+/−64mo)**

AR= antiresorptive, y=years, mo=months, BP=bisphosphonates, Dmab=denosumab, SD= standard deviation

Table 2:

Follow-up data and composite radiographic index (CRI) of dental disease patients (D.D.), patients who did not progress to bone exposure (N.B.E.) and patients who progressed to bone exposure (B.E).

Patient categories	No. of Patients	Mean Composite Radiographic Index (+/− SD)
Dental disease (D.D.)	3	0.33 +/− 0.57[#,&]
No bone exposure (N.B.E.)	10	4+/−0.51[+]
Bone exposure (B.E.)	10	5.8 +/−1.68
Total	23	

[#]: statistically significant to N.B.E. $p<0.05$,

[&]: statistically significant to B.E. $p<0.001$,

[+]: statistically significant to B.E. $p<0.05$, SD= standard deviation