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CBCT evaluation of jawbone changes in patients receiving antiresorptive therapy: a clinical-radiographic approach to suspected stage 0 MRONJ

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Original Article

CBCT evaluation of jawbone changes in patients receiving antiresorptive therapy: a clinical-radiographic approach to suspected stage 0 MRONJ

Avaliação por TCFC de alterações ósseas dos maxilares em pacientes em uso de terapia antirreabsortiva: uma abordagem clínico-radiográfica para suspeita de OMAM em estágio 0

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Resumo

Objetivo: Avaliar se alterações ósseas detectáveis por tomografia computadorizada de feixe cônico (TCFC) estão presentes em regiões anatômicas clinicamente não afetadas de pacientes diagnosticados com osteonecrose dos maxilares associada à medicamentos (OMAM) e investigar associações entre esses achados de imagem e variáveis relacionadas ao paciente. **Material e método:** Este estudo retrospectivo e transversal analisou 94 sítios anatômicos provenientes de exames de TCFC de 27 pacientes com OMAM clinicamente confirmada. Foram avaliadas alterações ósseas, incluindo osteosclerose, aumento da densidade trabecular, espessamento cortical, osteólise,

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alterações do canal mandibular e alvéolos de extração persistentes, em sítios clinicamente afetados e não afetados. A regressão logística multivariada foi utilizada para investigar associações com idade, doença de base, tipo de medicação, via de administração, duração da terapia e uso de corticosteroides. **Resultado:** Todas as alterações observadas por TCFC nas lesões de OMAM também foram identificadas em sítios clinicamente não afetados. Osteosclerose e espessamento cortical mandibular foram associados à terapia antiangiogênica, enquanto alvéolos de extração persistentes foram mais frequentes em pacientes oncológicos. Não foram observadas diferenças estatisticamente significativas entre sítios clinicamente afetados e não afetados quanto à distribuição das alterações radiográficas. **Conclusão:** Alterações detectáveis por TCFC comumente associadas à OMAM também podem estar presentes em sítios anatômicos clinicamente não afetados. Esses achados sustentam a hipótese de manifestações imaginológicas precoces da doença e destacam o potencial valor da avaliação abrangente por TCFC em pacientes submetidos à terapia antirreabsortiva ou antiangiogênica. Estudos prospectivos e longitudinais são necessários para validar essas observações e determinar sua relevância clínica.

Descritores: MRONJ; CBCT; osteosclerose; terapia antirreabsortiva; estágio radiológico 0.

Abstract

Objective: To evaluate whether cone beam computed tomography (CBCT)-detectable bone alterations are present in clinically unaffected jaw regions of patients diagnosed with medication-related osteonecrosis of the jaw (MRONJ) and to investigate associations between these imaging findings and patient-related variables. **Material and method:** This retrospective cross-sectional study analyzed 94 anatomical sites from

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CBCT scans of 27 patients with clinically confirmed MRONJ. Bone alterations, including osteosclerosis, increased trabecular density, cortical thickening, osteolysis, mandibular canal changes, and persistent extraction sockets, were assessed in clinically affected and unaffected sites. Multivariate logistic regression was used to investigate associations with age, underlying disease, medication type, route of administration, duration of therapy, and corticosteroid use. **Result:** All CBCT alterations identified in MRONJ lesions were also observed in clinically unaffected sites. Osteosclerosis and mandibular cortical thickening were associated with antiangiogenic therapy, whereas persistent extraction sockets were more frequent in oncologic patients. No statistically significant differences were observed between clinically affected and unaffected sites regarding the distribution of radiographic alterations. **Conclusion:** CBCT alterations commonly associated with MRONJ may also be present in clinically unaffected anatomical sites. These findings support the hypothesis of early imaging manifestations of the disease and highlight the potential value of comprehensive CBCT assessment in patients receiving antiresorptive or antiangiogenic therapy. Prospective longitudinal studies are needed to validate these observations and determine their clinical significance.

Descriptors: MRONJ; CBCT; osteosclerosis; antiresorptive therapy; radiologic stage 0.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a known adverse effect associated with antiresorptive (AR) and antiangiogenic (AA) therapies, which are commonly prescribed for osteoporosis and malignant bone conditions[1,2]. AR drugs, such as bisphosphonates, impair osteoclast function by inducing apoptosis and suppressing bone resorption, thereby reducing bone turnover[3]. AA agents act on vascular endothelial

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growth factor (VEGF) pathways, inhibiting angiogenesis and limiting the vascular support required for normal bone remodeling[4]

The diagnosis and staging of MRONJ have traditionally relied on clinical criteria, including exposed necrotic bone, pain, and infection. Panoramic radiography (PR) is often the first imaging modality used by oral surgeons due to its accessibility and low cost[5,6]; however, PR lacks sensitivity for early or subtle alterations. Cone beam computed tomography (CBCT), in contrast, provides three-dimensional visualization of the maxillomandibular complex and enables the detection of changes not visible clinically or on PR[7-9]. Recent studies have highlighted the diagnostic value of CBCT, particularly its ability to identify alterations in patients without bone exposure or in regions appearing normal on 2D imaging[10-12].

Although current literature increasingly supports the use of CBCT for detecting early MRONJ—especially in so-called "stage 0" presentations, where radiologic abnormalities precede clinical symptoms[13]—most studies restrict their analyses to already affected areas. It remains unclear whether similar alterations are present in clinically unaffected regions, particularly in patients undergoing prolonged AR or AA therapy. While some investigations have evaluated imaging signs at extraction sites or proposed radiographic indices for severity assessment, few have explored diffuse skeletal changes across clinically normal quadrants[14-16].

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Early recognition of subclinical changes may be critical for preventing progression to symptomatic MRONJ. Detecting radiographic features such as osteosclerosis, cortical thickening, osteolytic areas, or delayed socket healing—even in the absence of clinical signs—could enhance treatment planning and risk assessment. This approach is especially relevant for high-risk individuals, including oncology patients and those receiving intravenous medications, where invasive dental procedures carry increased risk.

The objective of this study was to determine, using CBCT, whether bone alterations commonly associated with MRONJ are present in clinically normal regions of the jaws by evaluating multiple anatomical sites within each patient. Additionally, we assessed whether patient characteristics—including underlying disease, medication type and route, duration of therapy, and corticosteroid use—were associated with these CBCT findings. By addressing this gap, our study investigates the potential of CBCT to identify a radiologic "stage 0" pattern of MRONJ, supporting its application in early detection and preventive management of patients exposed to AR or AA therapy. Beyond characterizing CBCT-detectable alterations in clinically normal sites, this study aims to propose a structured clinical-radiographic framework for early-stage MRONJ detection—meeting the growing need for standardized imaging criteria emphasized in recent guidelines.

MATHERIAL AND METHOD

Study Design and Sample

This observational, cross-sectional, comparative prevalence study was conducted on a retrospective sample and approved by the Research Ethics Committee (CAAE: 36496320.9.0000.54[19]). Although 27 patients with clinically confirmed MRONJ were included, **the analytical unit was the anatomical site**, not the patient. Because each

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participant contributed multiple maxillomandibular regions, the sample size reported in the Results refers to **the total number of anatomical sites (n = 94)**. Because multiple anatomical sites were derived from the same patient, observations may not be fully independent. However, the analytical unit was intentionally defined as the anatomical site to allow the assessment of localized radiographic patterns across different jaw regions.

Because multiple anatomical sites were derived from the same patient, observations may not be fully independent. However, the analytical unit was intentionally defined as the anatomical site to allow the assessment of localized radiographic patterns across different jaw regions. This approach was chosen because MRONJ-related bone alterations may exhibit spatial heterogeneity within the same individual. Nevertheless, the potential influence of intra-patient correlation should be considered when interpreting the results.

The study followed STROBE guidelines for reporting observational studies[17].

Population

Imaging data were obtained from 27 CBCT scans of patients clinically diagnosed with MRONJ. Scans included complete or partial examinations of the maxilla and mandible. All exams were retrieved from the archive of the Stomatology and Oral Radiology Clinic, Bauru School of Dentistry, University of São Paulo.

The final analytical sample consisted of **94 anatomical sites**, distributed across the four quadrants of the jaws:

- **27 sites with clinically confirmed MRONJ**, and
- **67 clinically unaffected sites**, which served as **intrapatient controls**.

Clinically unaffected sites were defined as regions without bone exposure, fistulas, pain on palpation, or signs of infection according to AAOMS criteria.

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Data Collection

Clinical and demographic data were extracted retrospectively (2013–2021), including age, sex, underlying disease, medication type, route and duration of administration, and corticosteroid use. Confidentiality was preserved, and all patients had previously consented to research use of their data.

Inclusion Criteria

Participants were eligible if they had:

1. History of antiresorptive (AR) or antiangiogenic (AA) drug use;
2. Underlying disease (osteoporosis or malignancy, with/without metastasis);
3. High-quality CBCT scans;
4. No history of head and neck radiotherapy;
5. At least one clinically confirmed MRONJ site.

Examiner Calibration

All evaluated variables were dichotomously classified as present or absent. Calibration was performed under the supervision of an experienced oral and maxillofacial radiologist prior to formal data collection, which may have contributed to the high agreement observed. A calibration phase involving 20% of the sample produced perfect inter-examiner agreement (kappa = 1.0). Formal data collection was completed in four structured sessions with scheduled rest intervals.

CBCT Evaluation

All CBCT examinations were acquired using a 3D Accuitomo 170 unit (J. Morita Corp., Kyoto, Japan). Images were obtained with a voxel size of 0.2 mm and field of view (FOV) protocols of 10 × 10 cm or 14 × 10 cm, depending on the anatomical extension required for each examination, particularly in cases involving both

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dental arches. All scans were acquired following standardized institutional imaging protocols and were evaluated under identical viewing conditions.

A pilot evaluation of 20% of the sample identified relevant radiographic features. The following CBCT alterations were assessed in **all 94 anatomical sites**:

1. Osteosclerosis;
2. Generalized increase in trabecular density;
3. Osteolytic areas;
4. Mandibular cortical thickening;
5. Thickening of the mandibular canal cortex;
6. Persistent extraction socket (delayed healing beyond normal expectations)[18].

Examples are illustrated in Figure 1.

All CBCTs were evaluated in sagittal, axial, and coronal planes. Each feature was classified as **PRESENT** or **ABSENT**, and both examiners achieved 100% agreement in final readings.

Statistical Analysis

All analyses considered **anatomical sites** as the analytical unit. Statistical procedures were performed in JAMOVI (versions 1.6 and 2.0.0.0)[19], using multivariate logistic regression (MLR).

For each CBCT feature (osteosclerosis, trabecular density increase, osteolytic areas, cortical thickening, mandibular canal changes, and persistent extraction sockets), separate multivariate logistic regression models were constructed using the presence or absence of the feature as the dependent variable.

Stage 1 — Diffuse Pattern Analysis

Sites with clinically diagnosed MRONJ were compared to clinically unaffected intrapatient control sites. A hierarchical MLR model tested whether CBCT features

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typically associated with MRONJ also appeared in clinically normal regions. Variables with $p \leq 0.2$ were included in the preliminary model; only significant predictors remained in the final model.

Stage 2 — Association With Patient Variables

MLR was used to evaluate whether the following variables predicted CBCT alterations:

1. Age;
2. Sex;
3. Underlying disease (oncologic vs. osteoporotic);
4. Affected arch (maxilla vs. mandible);
5. Medication type (bisphosphonate vs. AA);
6. Administration route (intravenous vs. oral);
7. Duration of drug use (months);
8. Corticosteroid use.

Odds ratios (OR) with 95% confidence intervals were calculated. A p-value ≤ 0.05 was considered statistically significant.

This analytical strategy directly supports the study's central objective: to investigate whether MRONJ-related CBCT alterations may be present in clinically unaffected regions, supporting the hypothesis of early radiographic manifestations associated with MRONJ.

RESULT

All analyses were conducted at the anatomical site level (n = 94), with each site treated as an independent observational unit for radiographic assessment, regardless of patient clustering.

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Population Characteristics

The study included 27 patients, 62% of whom were female (n = 17) and 37% male (n = 10). Among the affected sites, 59.3% were located in the mandible (n = 16) and 40.7% in the maxilla (n = 11). Regarding systemic conditions, 70% of patients (n = 19) had oncologic diseases and 30% (n = 8) had osteoporosis. In terms of medication, 25 patients (92%) had received bisphosphonates (BP), while 2 patients (8%) received antiangiogenic agents (AA). No patient had used monoclonal antibodies.

The route of administration was intravenous in 60% (n = 16) of patients and oral in 40% (n = 11). Concomitant corticosteroid use was reported in 22% (n = 6) of patients. The mean duration of medication use was 88 months. These demographic and clinical data are summarized in Table 1.

Table 1. CBCT Findings in MRONJ vs. Clinically Normal Sites

Characteristic	**Value**
Female (%)	17 (63%)
Oncologic indication (%)	19 (70%)
Antiangiogenic therapy	2 (7%)
Oral bisphosphonates	10 (37%)
Endovenous administration	17 (63%)
Mandibular cases	16 (59%)
Corticosteroid users	5 (18%)
Mean drug duration (months)	XX (± SD)

Note: n refers to number of anatomical sites, not number of patients

The initial analysis compared CBCT-detected alterations in MRONJ-affected sites to those in clinically normal sites. Multivariate logistic regression (MLR) using a hierarchical model revealed no statistically significant differences between the two groups, even when a liberal threshold ($p \leq 0.2$) was applied in the preliminary model.

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This indicates that the CBCT findings commonly associated with MRONJ—such as osteosclerosis, trabecular density increase, osteolytic lesions, cortical thickening, and delayed socket healing—also occurred in sites without clinical evidence of disease.

Association Between CBCT Findings and Patient Characteristics

The second stage of analysis explored the relationship between CBCT-detected alterations and patient-related variables, using MLR with a significance level of $p \leq 0.05$ and a 95% confidence interval. Key associations observed:

- Osteosclerosis was significantly more frequent in sites from patients receiving AA therapy ($p = 0.022$, OR = 52.78) and in older individuals ($p = 0.019$, OR = 1.127 per year);
- Thickening of the mandibular cortex was also associated with AA use ($p = 0.047$, OR = 26.22);
- Persistent extraction sockets were significantly associated with oncologic patients ($p = 0.044$, OR = 0.0375);

Other CBCT findings—such as increased trabecular density, mandibular canal thickening, and osteolytic areas—did not show statistically significant associations with any of the independent variables. A full breakdown of the MLR results is provided in Table 2 – discriminated in 2A and 2B.

Table 2A. Tomografic Findings – Part 1

Osteosclerosis ($R^2 = 0.308$)

Variable	p-value	Odds Ratio
Underlying disease	0.992	1.79
Route of administration	0.164	5.33
Corticosteroids	0.896	1.19

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Generalized increase in trabecular bone density ($R^2 = 0.0886$)

Variable	p-value	Odds Ratio
Underlying disease	0.526	0.58
Route of administration	0.664	1.36
Corticosteroids	0.132	0.40

Osteolytic areas ($R^2 = 0.0961$)

Variable	p-value	Odds Ratio
Underlying disease	0.296	4.27
Route of administration	0.177	5.40
Corticosteroids	0.855	0.79

Table 2B. Tomografic Findings – Part 2

Thickening of the mandibular cortex ($R^2 = 0.249$)

Variable	p-value	Odds Ratio
Underlying disease	0.064	16.00
Route of administration	0.054	7.61
Corticosteroids	0.353	7.61

Thickening of the mandibular canal cortex ($R^2 = 0.193$)

Variable	p-value	Odds Ratio
Underlying disease	0.210	5.45
Medication	0.335	3.87
Route of administration	0.233	2.99
Corticosteroids	0.948	0.94

Presence of persistent extraction socket ($R^2 = 0.245$)

Variable	p-value	Odds Ratio

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Underlying disease	0.044*	0.04
Route of administration	0.099	0.12
Corticosteroids	0.973	1.02

Multivariate Logistic Regression (MLR); Reference groups: Bisphosphonate, Osteoporosis, Oral administration, No corticosteroids.

Significant p-values ($p < 0.05$) are marked with an asterisk (*).

All CBCT-detected alterations observed in MRONJ sites were also present in clinically normal sites, supporting the hypothesis that bone changes related to AR and AA medication use are not restricted to symptomatic regions. These results suggest a diffuse skeletal response, which may represent a radiologic "stage 0" of MRONJ.

DISCUSSION

Medication-related osteonecrosis of the jaw (MRONJ) is a multifactorial condition that poses significant diagnostic and therapeutic challenges in oncology and dental practice. Although the clinical criteria for MRONJ—especially those involving exposed necrotic bone—are well established[20,21], the possibility of early or subclinical manifestations remains insufficiently documented. In this study, we evaluated CBCT findings in patients with confirmed MRONJ and demonstrated that radiographic alterations classically associated with the disease were also present in clinically unaffected sites. These findings suggest that AR and AA therapies may exert a diffuse skeletal effect throughout the jaws. The presence of CBCT alterations in clinically unaffected regions supports the hypothesis that radiographic changes may occur before

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overt clinical manifestations, contributing to the ongoing discussion regarding possible early imaging presentations of MRONJ.

A key methodological aspect of this study is the use of the anatomical site as the unit of analysis. Although multiple sites were obtained from the same patient, MRONJ-related radiographic findings are known to exhibit spatial heterogeneity, with different regions of the jaws showing distinct patterns of bone alteration. Therefore, analyzing data at the site level allowed a more precise assessment of localized bone changes, which would not be captured by patient-level analysis alone.

Localized radiographic features—such as osteosclerosis, sequestration, osteolysis, and mandibular canal involvement—have long been described in MRONJ[5,6,11,15]. In the present study, however, these alterations were not limited to clinically affected regions; they also appeared in areas without clinical signs of disease. This finding is consistent with emerging descriptions of "stage 0" MRONJ[7,8,22], in which radiologic abnormalities may be identified in the absence of overt clinical manifestations. However, because of the cross-sectional nature of the present study, no temporal relationship can be established between these imaging findings and the subsequent development of clinically evident disease. Importantly, most published studies do not extend imaging analyses to clinically unaffected quadrants within the same patient, limiting the understanding of diffuse skeletal involvement and the true distribution of radiographic changes.

Prior literature—including studies by Moreno-Rabié et al.[24], Simpione et al.[11], and Wongratwanich et al.[17]—has examined CBCT findings in MRONJ, but each differs from the present investigation in scope and methodological depth. Moreno-Rabié et al.[24] focused on extraction sites in osteoporotic patients, reporting lamina dura thickening and delayed mucosal healing, but did not evaluate clinically unaffected bone or investigate diffuse skeletal patterns. Simpione et al. compared affected and unaffected quadrants but

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did not test whether radiographic alterations reflect systemic rather than localized processes. Wongratwanich et al.[17] underscored CBCT's diagnostic potential in Stage 0 MRONJ while emphasizing the absence of standardized radiologic criteria. In contrast, the present study systematically examined multiple anatomical sites per patient—including regions with no clinical involvement—and demonstrated that MRONJ-like alterations detected by CBCT are widespread rather than restricted to areas with exposed bone or infection.

The absence of significant differences between clinically affected and clinically normal sites reinforces the hypothesis that AR and AA drugs may alter bone physiology diffusely across the jaws, not only in regions exposed to trauma or infection. This diffuse radiologic pattern aligns with previous findings by Bagan et al.[16], who reported increased sclerosis contralateral to MRONJ lesions, as well as studies employing radiographic software for quantitative assessment[14,25,26]. Our results extend these observations by demonstrating that multiple CBCT features associated with MRONJ—not solely sclerosis—appear in regions free of clinical disease, reinforcing the concept of a systemic skeletal vulnerability detectable before clinical onset.

Significant associations between imaging features and clinical characteristics were observed. Osteosclerosis and mandibular cortical thickening were more frequent in sites derived from patients receiving antiangiogenic therapy, consistent with the documented effects of angiogenesis inhibition on bone vascularization and remodeling[18,20]. However, these findings should be interpreted with caution due to the small number of AA-exposed patients included in the sample. Consequently, the high odds ratios observed may reflect statistical instability and should be considered exploratory rather than definitive evidence of a causal relationship. Persistent extraction sockets were more common among oncologic patients, which may reflect impaired

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healing associated with the underlying disease or its treatment. These findings suggest that CBCT alterations may have potential utility as imaging markers associated with increased MRONJ susceptibility, although prospective studies are required to determine their predictive value.

Clinically, these results emphasize the necessity of comprehensive CBCT evaluation in patients exposed to AR or AA therapies—even when asymptomatic. Surgical decisions, including tooth extractions and implant placement, should incorporate radiologic findings rather than relying solely on clinical inspection. Early detection of subtle CBCT changes may facilitate conservative interventions and reduce the likelihood of progression to clinically overt necrosis.

Based on these findings and the available literature, we propose a preliminary clinical–radiographic guide intended to support the identification and monitoring of patients with suspected early MRONJ-related imaging alterations. This exploratory framework integrates CBCT findings with recognized clinical risk factors and should be regarded as hypothesis-generating until validated in prospective studies. The full guide is provided in Supplementary Material 1 and is supported by studies from Simpione et al.[11], Wongratwanich et al.[17], Moreno-Rabié et al.[24, 25], along with the findings of the present CBCT-based analysis. A complementary Clinical Decision Pathway for suspected Stage 0 MRONJ appears in Supplementary Material 2.

This site-based approach aligns with the concept that MRONJ may represent a diffuse but regionally variable skeletal response to antiresorptive and antiangiogenic therapies. This study has limitations, including the absence of baseline imaging to confirm that observed alterations developed after initiation of medication therapy, as well as the limited number of AA-treated patients, which restricts subgroup interpretation. However, current evidence demonstrates that AA agents can induce skeletal changes comparable to

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those caused by AR drugs. The Italian Consensus Update[27] states that both classes produce similar clinical and radiologic presentations. Furthermore, a systematic review by Soundia et al.[22] identified 35 MRONJ cases induced exclusively by AA medications, confirming their ability to cause jaw osteonecrosis and corresponding imaging abnormalities. These findings justify the inclusion of AA-treated patients in MRONJ surveillance frameworks[28].

The study by Yfanti et al. [29], which validated the modified Composite Radiographic Index (CRIm), contributes valuable information for quantifying radiographic severity in established MRONJ. However, their analysis exclusively encompassed AAOMS stages 1–3 and did not include stage 0 or clinically normal sites. While CRIm correlates with clinical severity, our findings indicate that several radiologic features—such as osteosclerosis, increased trabecular density, and cortical thickening—may already be present in asymptomatic regions. Additionally, our application of multivariate logistic regression identified associations between imaging alterations and patient variables such as age, medication class, and oncologic status, expanding the interpretive potential of CBCT beyond severity grading toward early detection and risk prediction.

Additional limitations include the retrospective design, the relatively small sample size, the imbalance between medication groups, and the potential influence of intra-patient correlation resulting from the inclusion of multiple anatomical sites from the same patient.

In summary, the present findings indicate that radiographic alterations commonly associated with MRONJ may also be observed in clinically unaffected regions. Although these observations support the hypothesis of early imaging manifestations of the disease, the cross-sectional design precludes temporal or causal inferences. Nevertheless, the

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results highlight the potential value of comprehensive CBCT assessment and support further investigation into imaging-based approaches for MRONJ risk assessment and early detection. Tools such as the Radiologic Suspicion Levels Based on CBCT Findings table (Supplementary Material 3) may support risk stratification in asymptomatic patients and enable earlier, individualized interventions.

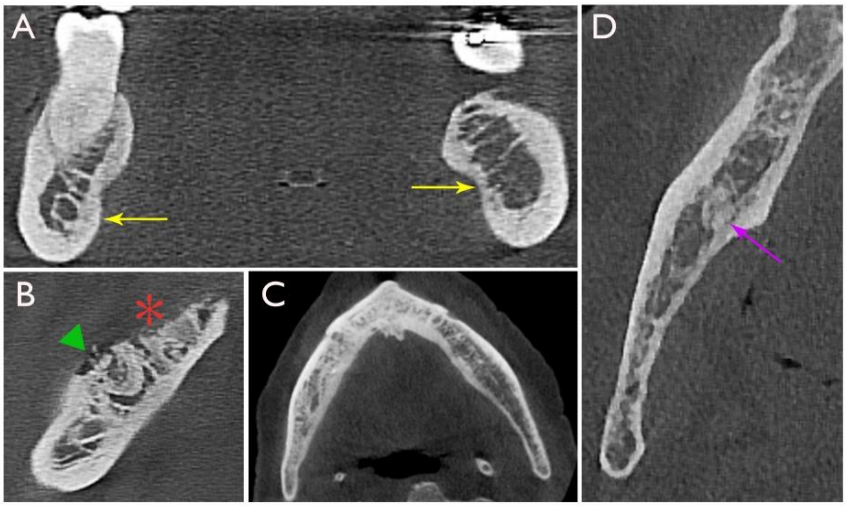
CONCLUSION

This study showed that CBCT alterations commonly associated with MRONJ may also be observed in clinically unaffected anatomical sites within the same patient. These findings support the hypothesis of early imaging manifestations of MRONJ and suggest that radiographic changes may extend beyond clinically evident lesions. The proposed clinical–radiographic guide should be considered a preliminary exploratory framework, and prospective longitudinal studies are needed to validate these observations and establish standardized imaging criteria for the early detection and monitoring of MRONJ.

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Figures

Figure 1. Bone alterations



A- Yellow arrows – thickening of mandibular canal cortical *versus* normal mandibular canal cortical in the contralateral side. Also is possible to observe the thickening of mandibular cortical in both sides. B- Green arrow – osteolytic area; Red asterisk – persistent extraction socket. C – generalized increase in in trabecular bone density. D – Purple arrow – osteosclerosis

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AUTHORS' CONTRIBUTIONS

- Mariel Ruivo Biancardi: data analysis, research, validation of data, design of data presentation, writing the original manuscript.
- Mariana Quirino Silveira Soares: conceptualization, data analysis, methodology, proofreading and editing.
- Rogerio Jardins Caldas: data curation, data analysis, research
- Heitor Marques Honório: methodology, validation of data
- Paulo Sergio Silva Santos: conceptualization, data curation, proofdreading and editing.
- Izabel Regina Fischer Rubira Bullen: conceptualization, methodology, Project management, supervision, proofreading and editing.

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CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

DATA AVAILABILITY

The contents underlying the research text are included in the manuscript.

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Supplementary Material 1

Clinical-Radiographic Guide for Suspected Stage 0 MRONJ (CBCT-Based)

Operational Definition (Ruggiero et al., 2022; Shibahara et al., 2019, present study)
Patients undergoing or with a history of antiresorptive (AR) or antiangiogenic (AA) therapy, with no clinical bone exposure, but presenting radiographic alterations compatible with patterns observed in MRONJ.

1. Clinical Inclusion Criteria (Ruggiero et al., 2022; Aghaloo & Tetradis, 2014, present study)
- Current or past use of AR or AA drugs (e.g., bisphosphonates, denosumab, bevacizumab)
- No visible signs of bone exposure
- Presence of unexplained pain, paresthesia, sensitivity, or incidental findings on CBCT

2. CBCT Findings Suggestive of Stage 0 MRONJ (Soundia et al., 2018; Moreno-Rabié et al., 2022; Kajihara et al., 2024; Wongratwanich et al., 2021, present study)
For each site evaluated (posterior or anterior region of the mandible/maxilla), assess the presence of the following features:

CBCT Finding	Description
Osteosclerosis	Focal or diffuse areas of densely mineralized bone
Increased trabecular bone density	Thickening of the trabecular pattern, especially if bilateral or crossing midline
Mandibular cortical thickening	Thickening of the inferior or posterior mandibular cortex
Mandibular canal wall thickening	Loss of definition, sclerosis or thickening of the canal wall
Mixed osteolytic areas	Regions with heterogeneous density (hypo- and hyperdense)
Delayed socket healing	Extraction site showing incomplete bone remodeling after the expected healing period (>8 weeks)

📌 Suggestive criterion: The presence of at least two alterations in a clinically asymptomatic region may indicate risk for Stage 0 MRONJ.

3. Associated Clinical Risk Factors (Ruggiero et al., 2022; Ko et al., 2024; Moreno-Rabié et al., 2022, present study)
- Intravenous administration of AR or AA medications
- Cancer diagnosis (especially with intensive AA use)
- Long-term drug use (>24 months)
- Concomitant corticosteroid therapy
- Recent extractions or oral surgical procedures

4. Suggested Clinical Management (Ko et al., 2024; Shimamoto et al., 2018; Aghaloo & Tetradis, 2014, present study)
- Avoid invasive surgical procedures in areas with suggestive radiographic findings
- Monitor with CBCT within 3–6 months

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- Refer for multidisciplinary evaluation (oral surgery, oncology, radiology)
- Consider temporary discontinuation or adjustment of medication (if clinically appropriate)

5. Radiologic Classification (Proposed) (Soundia et al., 2018; Moreno-Rabié et al., 2022; Bedogni et al., 2012, present study)

Classification	Proposed Criteria
Radiologic Stage 0-A	One radiographic finding in an asymptomatic region
Radiologic Stage 0-B	Two or more findings in a single quadrant
Radiologic Stage 0-C	Findings in two or more quadrants, or bilateral involvement without symptoms

Rationale contribution of the present study

The present study contributed to all five steps outlined in the proposed clinical-radiographic guide for early MRONJ detection. It reinforced the **operational definition** of a radiologic Stage 0 by demonstrating CBCT-detectable bone alterations—such as osteosclerosis and trabecular changes—in clinically unaffected sites, supporting the existence of a subclinical phase even in the absence of exposed bone.

Regarding **Step 2 (CBCT Findings Suggestive of Stage 0 MRONJ)**, the study identified imaging features consistent with those listed in the guide, including cortical thickening, trabecular densification, delayed socket healing, and alterations in the mandibular canal, thereby validating these as relevant early indicators.

For **Step 3 (Associated Clinical Risk Factors)**, multivariate logistic regression revealed significant associations between imaging findings and clinical variables such as medication type (AR vs. AA), oncologic diagnosis, intravenous administration, and patient age, empirically supporting the risk factors emphasized in the guide.

Although not focused on clinical interventions, the findings indirectly support **Step 4 (Management Considerations)** by suggesting that early radiographic detection may guide conservative monitoring and inform individualized surgical decisions, particularly in asymptomatic patients.

Finally, in **Step 5 (Radiologic Classification)**, the study proposed a stratification of radiologic severity based on the number and type of CBCT findings, contributing directly to the guide's goal of developing a structured, imaging-based classification system for Stage 0 MRONJ.

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Supplementary Material 2

Clinical Decision Pathway for Suspected Stage 0 MRONJ (Based on CBCT Findings)

Step 1: Begin by identifying patients currently or previously treated with antiresorptive (AR) or antiangiogenic (AA) medications who do not present with clinical signs of bone exposure. These patients are at potential risk of developing MRONJ and warrant radiographic screening. **References:** Ruggiero et al., 2022; Shibahara et al., 2019; Moreno-Rabié et al., 2023; Shin et al., 2024.

Step 2: Conduct a CBCT scan of the entire maxillomandibular complex to assess bony structures in both jaws comprehensively. Full-arch imaging is essential to detect subclinical or early-stage MRONJ features. References: Ko et al., 2024; Wongratwanich et al., 2021; Zhou et al., 2021; Shimamoto et al., 2018; Ristow et al., 2023, present study)

Step 3: Evaluate each quadrant for CBCT findings suggestive of early MRONJ, including:

- Focal or diffuse osteosclerosis
- Increased trabecular bone density (especially crossing the midline)
- Cortical thickening (mandibular inferior border or ramus)
- Thickening or irregularity of the mandibular canal cortex
- Mixed radiolucent-radiopaque osteolytic areas
- Persistent extraction sockets (with delayed bone remodeling beyond 8 weeks) These features have been reported as early or subclinical radiographic markers of MRONJ in both symptomatic and asymptomatic regions. **References:** Soundia et al., 2018; Moreno-Rabié et al., 2022, 2023, 2024; Kajihara et al., 2024; Simpione et al., 2020; Zhou et al., 2021; Shin et al., 2024, presente study

Step 4: Count the number of radiographic alterations per site or quadrant. A greater number of findings in a given area may indicate increased risk of disease progression, even in the absence of clinical signs. **References:** Soundia et al., 2018; Badabaan et al., 2023, presente study

Step 5: Determine the appropriate clinical management based on the number and distribution of findings:

- If 0–1 alteration is present, routine follow-up and annual CBCT are recommended.
- If 2 or more alterations are found in a single region, avoid invasive procedures and schedule CBCT re-evaluation in 3–6 months.
- If 2 or more alterations are found in multiple quadrants or bilaterally, the patient should be classified as high risk. Referral to a specialist and close CBCT monitoring (every 3–6 months) is advised. **References:** Shimamoto et al., 2018;

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Aghaloo & Tetradis, 2014; Simpione et al., 2020; Pimolbutr et al., 2018; Moreno-Rabié et al., 2024; Campisi et al., 2020, present study

Rationale to include presente study in the steps above

Step 2 – CBCT Imaging

Rationale:
The present study employed **full-arch CBCT imaging** in patients at risk of MRONJ and demonstrated that **radiographic alterations (osteosclerosis, trabecular coarsening, cortical thickening, etc.) were present even in clinically unaffected areas**. This directly supports the use of CBCT as an early detection tool for Stage 0 MRONJ, in alignment with Step 2's rationale. It provides empirical validation for using CBCT beyond symptomatic regions, contributing to early identification in asymptomatic patients.

Step 3 – CBCT Radiographic Findings

Rationale:
The study identified **all major radiographic features** outlined in Step 3—osteosclerosis, thickened lamina dura, mandibular canal alterations, delayed socket healing, and increased trabecular density—in asymptomatic sites. These findings confirm the diagnostic value of such features even outside clinically evident lesions. Thus, the present study supports the inclusion of these findings as Stage 0 indicators.

Step 4 – Number of Alterations & Risk Stratification

Rationale:
Through **multivariate logistic regression**, the study showed that the **presence of multiple radiographic features** was significantly associated with clinical risk factors (e.g., antiangiogenic therapy, oncologic diagnosis). This supports the concept that **cumulative imaging findings correlate with higher MRONJ risk**, validating the risk stratification logic described in Step 4.

Step 5 – Management Guidance Based on Imaging Severity

Rationale:
Although not an interventional study, the present work proposes that **early identification of imaging changes in asymptomatic patients** should influence management strategies. It supports **conservative monitoring or altered surgical**

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planning based on CBCT findings, reinforcing the need for **severity-based clinical decision-making**, as proposed in Step 5.

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Supplementary Material 3

Radiologic Suspicion Levels Based on CBCT Findings

Suspicion Level	CBCT Criteria	Recommended Action
Low (Soundia et al., 2018)	1 isolated finding in a single quadrant	Routine follow-up in 12 months Soundia et al., 2018
Moderate (Moreno-Rabié et al., 2022; Kajihara et al., 2024, Simpione etal 2020)	≥2 findings in one region/quadrant	Avoid surgery; monitor CBCT in 6 months Kajihara et al., 2024 Moreno-Rabié et al., 2022 Wongratwanich et al., 2021 Simpione et al., 2020 present study
High (Pimolbutr et al., 2018; Ruggiero et al., 2022)	Findings in ≥2 quadrants or bilateral involvement	Refer to specialist; CBCT every 3–6 months Ristow et al., 2023 Ko et al., 2024 Pimolbutr et al., 2018 Ruggiero et al., 2022 Present study

Rationale for Inclusion of the Present Study:

The present study demonstrated multiquadrant involvement of CBCT features commonly associated with MRONJ—including osteosclerosis, cortical thickening, and trabecular coarsening—even in clinically unaffected regions of the jaws. Furthermore, significant associations were observed between these radiographic alterations and clinical risk factors such as oncologic diagnosis and intravenous antiresorptive or antiangiogenic therapy. These findings support the hypothesis of a systemic skeletal effect and reinforce the value of CBCT in identifying subclinical disease. Taken together, this evidence aligns with the moderate-to-high suspicion criteria for radiologic stratification, particularly in asymptomatic patients at elevated risk, and substantiates the proposed framework for early imaging-based risk classification.

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versão 29 de junho de 2020

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