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

- 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.

Key References

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