

Predictors of Relapse in Surgical Treatment of Medication-Related Osteonecrosis of the Jaw - The Critical Role of Intraoperative Tooth Removal: a Retrospective Cohort Study

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ABSTRACT

Objectives: The purpose of this retrospective cohort study was to identify clinical and treatment-related predictors of relapse following surgical intervention in patients with medication-related osteonecrosis of the jaw.

Material and Methods: This retrospective single-centre cohort study conducted at Odense University Hospital, Denmark, included all consecutive patients diagnosed with medication-related osteonecrosis of the jaw (MRONJ) between 2009 and 2022. Patient demographics, medical indications, antiresorptive (AR) therapy, anatomical site, staging, and treatment modalities were recorded. Multi-model selection via exhaustive binary logistic regression was applied across 8,192 model combinations to identify key predictors of relapse, followed by multivariable logistic regression analysis.

Results: The study evaluated 124 patients (median age 70 years, interquartile range 62 to 77; 54% female). Indications for AR therapy were osteoporosis (36%), multiple myeloma (27%), adjuvant cancer therapy (27%), and bone metastases (10%). Surgical management was performed in 91 patients (73%), achieving complete mucosal healing in 71% (n = 65). Multivariable analysis identified four independent risk factors for MRONJ relapse: intraoperative tooth extraction in the MRONJ site (OR = 6.74), bilateral MRONJ presentation (OR = 6.56), smoking (OR = 3.88), and underlying disease diagnosis (osteoporosis vs. cancer; OR = 2.87 to 6.13). Concurrent tooth removal during MRONJ surgery significantly increased relapse rates compared to non-extraction procedures (48% vs. 17%; P = 0.002).

Conclusions: Surgical intervention provided acceptable mucosal healing rates. However, intraoperative tooth removal within the affected area, bilateral involvement, smoking, and underlying diagnosis significantly increase the risk of postsurgical relapse. Adequate resection margins around adjacent compromised teeth are essential to minimize postsurgical recurrence.

Keywords: bisphosphonate-associated osteonecrosis of the jaw; bone density conservation agents; multiple myeloma; osteonecrosis; osteoporosis.

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INTRODUCTION

Antiresorptive (AR) medications such as bisphosphonates (e.g., zoledronic acid, alendronate) and the RANK ligand (RANKL) inhibitor (denosumab) are widely used to manage metastatic bone disease, multiple myeloma, and osteoporosis. While AR therapy significantly reduces skeletal-related events in patients with cancer and strengthens bone density in patients with osteoporosis, they carry the risk of medication-related osteonecrosis of the jaw (MRONJ). The estimated risk of MRONJ varies with the indication, dose and treatment period of AR therapy: patients receiving high-dose intravenous bisphosphonates or denosumab for malignancy have reported MRONJ incidence of slightly less than 5% whereas those on low-dose oral bisphosphonates for osteoporosis have a much lower risk of less than 0.05% [1]. Despite the dose-related MRONJ occurrence rate, the reason for development of MRONJ is still unknown, but infection and microtrauma appear to play a role in both initiation and progression of MRONJ resulting in a pathologic inflammatory response [1-3]. The jaw bones are frequently exposed to infection risk due to the thin mucosal barrier (2 to 3 mm) separating bone from the oral microbial flora. Even minor mucosal injuries, periodontal disease, or tooth removal can introduce oral bacteria to the bone surface, potentially precipitating osteonecrosis [2-4].

Clinically, MRONJ most frequently manifests at sites of previous tooth removal or chronic mucosal trauma (e.g., beneath ill-fitting dentures). This supports the hypothesis that MRONJ pathogenesis is driven by a combination of local micro-trauma and underlying infection, and that it is this underlying pathological process that leads to MRONJ rather than the trauma from the tooth removal [1,2]. However, it is clear that MRONJ is a multifactorial pathophysiological disease, and no single factor can fully explain the development and progression of MRONJ [1].

Management of MRONJ remains challenging and controversial. Conservative approaches include antiseptic mouth rinses, antibiotics, and minimal intervention, aiming to manage symptoms and contain the disease [1]. However, conservative management often fails to achieve complete mucosal healing once bone is exposed [5,6]. Surgical intervention, ranging from local sequestrectomy to aggressive resection of the affected jaw segment, has shown higher success in achieving mucosal closure, especially for advanced cases [1,7].

The purpose of this single-center retrospective cohort

study was to identify clinical and treatment-related predictors of relapse following surgical intervention in patients with MRONJ. The study specifically aims to evaluate the impact of primary underlying diagnosis, AR drug type, and surgical variables on postsurgical relapse rates.

MATERIAL AND METHODS

Ethical approval

This retrospective cohort study design was performed at the Department of Oral and Maxillofacial Surgery, Odense University Hospital (Odense, Denmark). All consecutive patients diagnosed with MRONJ between January 1, 2009, and December 31, 2022, were identified through the hospital's electronic health records. The study was conducted in accordance with the Declaration of Helsinki ethical principles, and institutional review board (IRB) approval was obtained with a waiver of individual patient consent due to the retrospective design (Region of Southern Denmark, Protocol #21/9466, IRB S-20262000-160).

Selection criteria

The inclusion criterion was any patient diagnosed with MRONJ regardless of stage or treatment received. MRONJ diagnosis was established based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria [1]: a history of AR therapy and clinical evidence of infected or exposed jawbone persisting for at least 8 weeks.

Exclusion criteria were patients who had received radiation therapy to the head and neck, and patients with insufficient records or follow-up to validate the diagnosis of MRONJ.

Data collection

A retrospective chart review was conducted. Data were recorded on patient demographics (age and sex), relevant medical history (including cancer diagnoses, osteoporosis, diabetes, rheumatoid arthritis and other autoimmune disease), and lifestyle factors (tobacco and alcohol use). The underlying condition for AR therapy was recorded (metastatic tumour, adjuvant therapy in cancer, multiple myeloma, and osteoporosis). The specific AR drugs were recorded and if patients had exposure to more than one agent over time, the agent most recently administered was considered primary. Local oral factors contributing to development of MRONJ were also noted and included dental procedures such as tooth extraction or

dental implant insertion or removal, or the presence of removable dentures overlying the MRONJ area.

MRONJ staging and location

Each patient was classified by clinical stage according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) staging system [1]:

- Stage 0 - non-exposed bone with symptoms.
- Stage 1 - exposed necrotic bone without infection or symptoms.
- Stage 2 - exposed bone with infection and symptoms.
- Stage 3 - extensive disease with pathologic fracture, extraoral fistula, or osteolysis extending beyond the alveolar bone.

Staging was based on the time of MRONJ diagnosis at the area that was most affected. The anatomical location of MRONJ was categorized in the molar, premolar, or anterior regions. It was furthermore registered if the lesions were unilateral or bilateral and if the mandible, maxilla or both jaws were affected.

Treatment and surgical technique

Treatment modalities were recorded for each patient. It was noted whether initial management was conservative (antibacterial mouth rinses, antibiotics, and observation) or surgical. For those treated surgically, operative reports were reviewed to classify the type of surgery: sequestrectomy (removal of loose sequestrum and superficial debridement), osteoplasty (contouring of bone edges and removal of small necrotic foci), marginal resection of the alveolar process, or bloc resection of basal bone of the jaws. No patients in this series received patient specific implants for reconstruction. Reconstructions were performed with conventional stock titanium plates, individualized prior to surgery on a 3D printed model of the jaws. The choice of local anaesthesia or general anaesthesia for the procedure was also noted. All surgeries aimed for tension free primary mucosal closure, often with mucosal flaps. Perioperative antimicrobial prophylaxis was administered to all patients, consisting of systemic antibiotic therapy and chlorhexidine mouth rinses. Systemic antibiotics were initiated 2 days preoperatively and continued for 7 days postoperatively. The standard antibiotic regimen consisted of either phenoxymethylpenicillin (800 mg, 3 times per day, Primcillin - Viatris ApS; Allerød, Denmark) combined with metronidazole (500 mg, 3 times per day; Metronidazol Orifarm - Orifarm Healthcare A/S; Odense, Denmark),

or amoxicillin/clavulanic acid (500/125 mg, 3 times per day; Bioclavid - Sandoz A/S; Copenhagen, Denmark). Clindamycin (600 mg, 3 times per day; Dalacin, Pfizer Inc.; New York, NY, USA) was prescribed for patients with a penicillin allergy.

Outcome measures

The primary outcome was postoperative relapse, defined as the recurrence of infection and/or exposed bone (visible or with fistula). This meant any case where, after surgery, the patient developed either re-exposure of bone or purulent infection in the same site during follow-up, requiring additional intervention. Conversely, surgical success was defined as complete mucosal healing of the treated site with no signs of infection at the latest follow-up. The time to relapse (interval between surgery and documented relapse) was also registered when available. Secondary outcomes included any postsurgical complications (such as wound dehiscence or need for revision surgery). Patients were typically followed with clinical exams at 1 to 2 weeks following surgery and continued at regular intervals until complete mucosal coverage was confirmed. Patients who achieved uneventful, complete soft tissue healing without signs of infection were typically discharged from active follow-up, whereas patients with delayed healing or persistent symptoms were monitored longer intervals. Each patient's outcome was categorized as "no relapse" or "relapse" based on the entirety of his or her follow-up course.

Statistical analysis

All data were entered into a secure spreadsheet of Microsoft Excel version 2608 (Microsoft Corporation; Washington, USA) and analysed using R Software version 4.5.3, (The R Foundation for Statistical Computing, Vienna, Austria).

Categorical variables were presented as absolute frequencies and percentages. Continuous variables (age) were non-normally distributed and presented as medians with interquartile ranges (IQR). Baseline differences across diagnostic groups were compared using Pearson's chi-square (χ^2) test or Fisher's exact test for categorical parameters. For sparse contingency tables (e.g., antiresorptive agent distribution), P-values were calculated using Fisher's exact test with Monte Carlo simulations based on 2,000 replicates. Continuous group differences across the four cohorts were evaluated using the Kruskal-Wallis rank sum test. Statistical significance level was defined at $P = 0.05$.

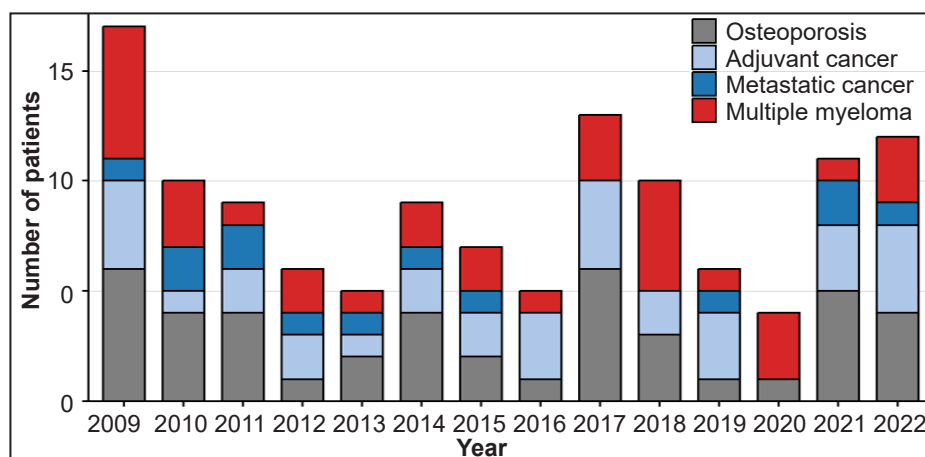


Figure 1. Annual distribution of medication-related osteonecrosis of the jaw by antiresorptive treatment diagnosis.

To evaluate potential risk factors for MRONJ relapse following surgical intervention, a brute-force exhaustive multimodel selection analysis was performed. This exhaustive approach screened every possible combination of independent variables to eliminate manual selection bias by analysing all possible non-interactive binary logistic regression model combinations. Model performance was evaluated using the corrected Akaike Information Criterion (AIC) for small sample sizes. Relative variable importance was computed by summing the statistical weights of all models in which a given variable appeared, yielding a score between 0.0 and 1.0. Variables with an importance score exceeding 0.50 were identified as key drivers of disease relapse.

These key predictors of relapse were further evaluated using a single binary logistic regression analysis, and results were reported as odds ratios (OR), standard error (SE) and 95% confidence intervals.

RESULTS

The cohort included 124 patients diagnosed with MRONJ from 2009 to 2022 (Figure 1). Indications for AR treatment were osteoporosis (36%), multiple myeloma (27%), adjuvant cancer therapy (27%) and metastases from breast, prostate or lung cancers (10%) (Table 1). The median age summarized across all indications was 70 years (IQR = 62 to 77 years),

Table 1. Cohort diagnosed with medication-related osteonecrosis of the jaw (n = 124) and surgically treated (n = 91) according to diagnosis

		Osteoporosis	Adjuvant cancer	Metastases	Multiple myeloma	P-value
		N = 44	N = 33	N = 13	N = 34	
Female (n [%])		35 (80%)	17 (52%)	7 (54%)	8 (24%)	< 0.001**
Age (median [IQR] years)		71 (66; 79)	71 (63; 78)	62 (61; 73)	70 (60; 73)	0.08 ^a
Smoking (n [%])		20 (45%)	6 (18%)	4 (31%)	7 (21%)	0.04**
Alcohol (n [%])	< 14 units/week	13 (30%)	10 (30%)	3 (23%)	13 (38%)	0.7 ^a
	≥ 14 units/week	3 (7%)	1 (3%)	2 (15%)	1 (3%)	
Comorbidities (n [%])	Diabetes (type II)	7 (16%)	4 (12%)	3 (23%)	3 (9%)	0.6 ^a
	Autoimmune disease	6 (14%)	1 (3%)	-	-	0.3 ^a
	COPD	2 (22%)	-	-	1 (17%)	0.4 ^a
	Steroid treatment	2 (22%)	-	1 (33%)	3 (43%)	0.11 ^a
Antiresorptive therapy (n [%])	Alendronate	27 (61%)	-	-	1 (3%)	< 0.001 ^{b*}
	Ibandronate	-	5 (15%)	2 (15%)	-	
	Pamidronate	-	-	-	3 (9%)	
	Zoledronic acid	7 (16%)	14 (42%)	6 (46%)	27 (79%)	
	Denosumab	10 (23%)	14 (42%)	5 (38%)	3 (8.8%)	

^aKruskal-Wallis rank sum test (age) and Fisher's exact test, ^bFisher's exact test with simulated P-value (based on 2000 replicates).

*Statistically significant at level P < 0.05.

N = number of patients; IQR, inter-quartile range; COPD = chronic obstructive pulmonary disease.

Table 2. Dental treatment prior to medication-related osteonecrosis of the jaw (MRONJ) development (n = 124)

		Osteoporosis	Adjuvant cancer	Metastases	Multiple myeloma	P-value ^a
		N = 44	N = 33	N = 13	N = 34	
Prosthesis in MRONJ area		21 (47%)	6 (18%)	4 (31%)	10 (30%)	0.12
Exostosis (mandibular)		-	3 (9%)	1 (8%)	4 (14%)	0.12
Dental treatment prior to MRONJ	Extraction of teeth	22 (50%)	20 (61%)	7 (54%)	10 (29%)	0.20
	Endodontic and extraction	3 (7%)	2 (6%)	-	2 (6%)	
	Dentoalveolar surgery	1 (2%)	-	-	-	

^aFisher's exact test for count data with simulated P-value (based on 2000 replicates). *Statistically significant at level P < 0.05. N = number of patients.

and 54% of all participants were female. Female proportion was significantly higher in osteoporosis patients (80%) than in the three oncological groups (24 to 54%, combined 40%) (P < 0.001, Fisher's exact test). Smoking was reported in 37 patients (30%), with a significant higher prevalence in osteoporosis patients (45%) compared with patients in the three oncological subgroups (18 to 21%) (P = 0.03, Fisher's exact test). Alcohol consumption was noted in 46 patients (37%) where 7 patients (6%) consumed more than 14 units per week. Zoledronic acid was the primary AR medicine, followed by denosumab and alendronate.

Across all groups, dental treatment prior to MRONJ diagnosis consisted primarily of extractions (Table 2), including seven patients treated with root canal treatment prior to extraction (presented in three osteoporosis patients, two patients in adjuvant cancer therapy and 2 multiple myeloma patients), as the root canal treatment was unable to establish infection control or pain relief. Less common conditions were dentoalveolar surgery with implant placement (1 patient), mandibular exostosis or tori (8 patients: three patients in adjuvant cancer therapy, one patient with metastases and four multiple myeloma patients) and prosthesis in direct contact with the MRONJ area (41 patients: 21 osteoporosis patients, six patients in adjuvant cancer therapy, four patients with metastases and ten multiple myeloma patients).

The mandible was predominately affected by MRONJ (84 patients) compared with the maxilla (30 patients), and the cohort included 10 bimaxillary and 17 bilateral MRONJ presentations. Each involved location of MRONJ and MRONJ stage of each location showed that the molar area was primarily affected followed by the premolar area (Table 3, note multiple locations and stages may be present in each patient). The posterior molar region was the most frequently affected location. Using the AAOMS staging system, stages were registered at each area at the first examination. Three patients with Stage 0 at first examination (no exposed bone, but radiographic

Table 3. Medication-related osteonecrosis of the jaw (MRONJ) location and stage (n = 124 patients)

		Maxilla (n)	Mandible (n)	P-value ^a
Location	Ramus	-	4 (3%)	0.12
	Molar	23 (48%)	85 (63%)	
	Premolar	17 (35%)	29 (21%)	
	Frontal	8 (17%)	17 (13%)	
MRONJ stage	Stage 0	1 (2%)	5 (4%)	0.8
	Stage 1	28 (59%)	73 (54%)	
	Stage 2	15 (31%)	49 (36%)	
	Stage 3	4 (8%)	8 (6%)	

^aFisher's exact test. *Statistically significant at level P < 0.05. N = number of patients.

Note: Location was counted as positive for each affected area, thus MRONJ involving both molar and premolar region was counted once for each area. Stage was assessed for each MRONJ site.

changes and symptoms) all progressed to Stage 1 or 2 with bone exposure prior to surgical treatment. Most Stage 3 cases occurred in oncology patients receiving high-dose AR therapy.

Surgical treatment

Surgical treatment was performed in 91 patients (73%) (Figure 2). The remaining 33 patients received conservative management as they either had medical contraindications to surgical treatment or opted against surgery. The conservative regimen included daily chlorhexidine mouth rinses combined with systemic antibiotic therapy as clinically indicated in signs of local infection. Complete mucosal resolution under nonoperative management occurred in only 7 patients, all of whom presented with Stage 1 MRONJ and superficial sequestrum.

The time to surgery showed a mean of 22 days (IQR = 7 to 65) (Table 4). Marginal resection of the alveolar process was performed in 56 patients, predominantly presenting with Stage 1 or 2 MRONJ. Bloc resection of basal bone was required in 14 patients with Stage

2 or 3 disease. Among the mandibular bloc resections, segmental resection resulting in a continuity defect was performed in three patients during the initial operation and in one patient during secondary surgery following relapse. Reconstruction strategies within the bloc resection group included immediate rigid reconstruction plate fixation in 5 patients, indicated by either a continuity defect or a high risk of pathological fracture. Two of these patients subsequently underwent delayed microvascular free fibula flap reconstruction following uneventful mucosal healing. In terms of anaesthesia, 63 patients (69% of surgical treatments) had their primary surgical procedure performed under local anaesthesia. These were generally the sequestrectomy and minor marginal resections for Stage 1 or 2 disease. The remaining 28 patients (31%) underwent surgery under general anaesthesia in the operating theatre, which included all 14 bloc resections, 10 large marginal resections and a hemi-maxillectomy, as well as a few patients

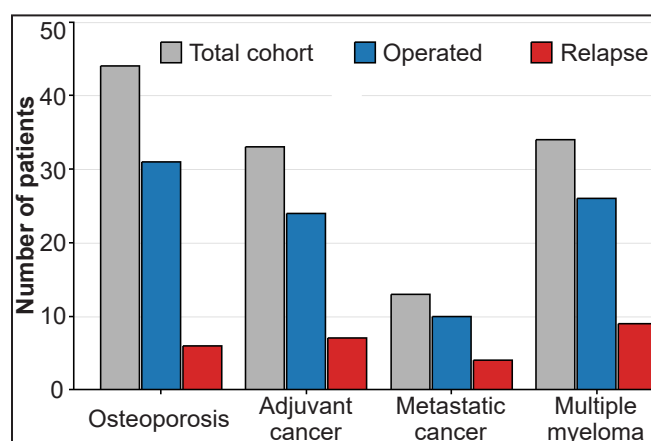


Figure 2. Surgical treatment and relapse rates by diagnostic group.

who could not endure surgery in local anaesthesia. The patients treated under general anaesthesia tended to have more severe MRONJ presentations (all Stage 3 and some profound Stage 2 patients) which required more invasive surgery.

Table 4. Surgical treatment (n = 91)

		Osteoporosis	Adjuvant cancer	Metastases	Multiple myeloma	P-value ^a
		N = 31	N = 24	N = 10	N = 26	
Time to surgery (median [IQR] days)		15 (3; 64)	25 (12; 47)	33 (3; 69)	26 (14; 92)	0.5
Follow-up (median [IQR] days)		36 (18; 118)	42 (28; 94)	55 (34; 216)	89 (55; 175)	0.09
Type of anaesthesia	Local anaesthesia	22 (71%)	18 (75%)	4 (40%)	19 (73%)	0.2
	General anaesthesia	9 (29%)	6 (25%)	6 (60%)	7 (27%)	
Type of treatment	Sequestrectomy	7 (23%)	2 (8.3%)	1 (10%)	10 (38%)	0.08
	Alveolar process resection	21 (68%)	17 (71%)	5 (50%)	13 (50%)	
	Bloc resection	3 (9%)	4 (17%)	4 (40%)	3 (12%)	
	Hemi-maxillectomy	-	1 (4.2%)	-	-	
Additional treatment	Closure with buccal fat pad	17 (53%)	16 (67%)	5 (50%)	11 (42%)	0.4
	Reconstruction with vascular graft (fibula)	1 (3.1%)	-	1 (10%)	-	
Relapse of MRONJ		6 (19%)	7 (29%)	4 (40%)	9 (35%)	0.4
Number of surgeries	1	24 (77%)	19 (79%)	6 (60%)	18 (69%)	0.4
	2	6 (19%)	4 (17%)	1 (10%)	6 (23%)	
	3	1 (3%)	1 (4%)	2 (20%)	1 (4%)	
	4	-	-	-	1 (4%)	
	5	-	-	1 (10%)	-	
Number of teeth removed	0	22 (72%)	12 (50%)	7 (70%)	17 (65%)	0.9
	1	5 (16%)	8 (33%)	3 (30%)	4 (15%)	
	2	2 (6%)	1 (4%)	-	3 (12%)	
	3	1 (3%)	2 (8%)	-	1 (4%)	
	4	1 (3%)	1 (4%)	-	1 (4%)	

^aKruskal-Wallis rank sum test (time to surgery and follow-up) and Fisher's exact test for count data with simulated P-value (based on 2000 replicates).

*Statistically significant at level $P < 0.05$.

N = number of patients; IQR, inter-quartile range.

Relapse

At the follow-up period (combined for all patient groups median of 54 days [IQR = 29 to 120]), 65 of the 91 surgically treated patients (71%) had achieved surgical success with complete mucosal coverage of the affected area with no signs of infection following the first surgical treatment. Success rates were higher among patients with osteoporosis (81%) than among those with malignant conditions (overall success rate of 67%: bone metastases 60%, multiple myeloma 65%, and adjuvant cancer therapy 71%) (Table 4).

To determine the relevance of potential risk factors for MRONJ relapse, the importance of each of the 13 variables were evaluated across all 8,132 model combinations. The pre-specified cutoff threshold of 0.50 identified four variables as primary predictors of relapse: tooth removal, bilateral MRONJ, smoking, and underlying disease type (osteoporosis

compared with the three oncological groups) (Figure 3). A multivariable logistic regression analysis incorporating the four key variables influence on MRONJ relapse (Table 5). The odds of relapse were increased by an odds ratio of 6.74 in patients with intraoperative tooth removal in the MRONJ area and by an odds ratio of 6.56 if MRONJ involved bilateral regions. Additionally, smoking showed an odds ratio of 3.88 indicting a significant increase in risk of relapse.

Tooth removal in combination with MRONJ surgery showed a significant correlation with MRONJ relapse and was further examined post-hoc. The 33 patients with tooth removal in relation to the MRONJ showed relapse in 16 patients (48 %) while 58 patients without tooth removal showed relapse in only 10 patients (17 %) ($P = 0.002$, Pearson's χ^2). Of the 16 patients with tooth removal and relapse of MRONJ, seven patients had adjacent teeth removed in the following surgery.

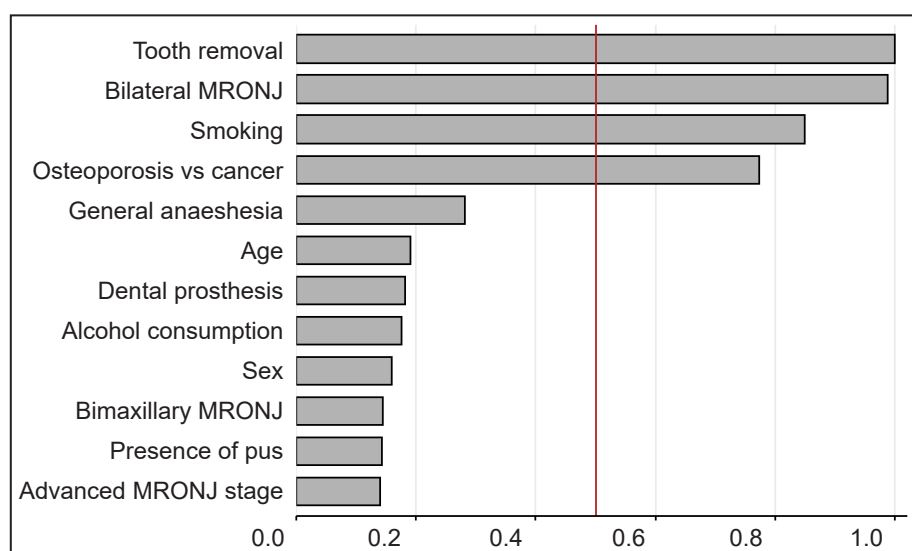


Figure 3. Relative variable importance for medication-related osteonecrosis of the jaw (MRONJ) relapse.

Risk factors evaluated across all possible combined models (8132 models) to determine their overall relevance (brute force analysis), where a value close to 1.0 indicates a consistent key predictor of relapse across all models. The red vertical line (0.50) marks the threshold for variables with high predictive value. Advanced MRONJ stage, compares Stage 0 to 1 with Stage 2 to 3 to minimize distortion caused by low numbers in Stage 0 and Stage 3.

Table 5. Multivariate logistic regression of the four factors contributing to relapse (n = 91)

		Relapse (n)	Odds ratio	P-value	95% confidence interval	
					Lower limit	Upper limit
Tooth removal during surgery		16	6.74	0.001*	2.23	23.3
Bilateral MRONJ		7	6.56	0.01*	1.58	30.9
Smoker		11	3.88	0.04*	1.14	14.7
Antiresorptive diagnose (baseline osteoporosis)	Adjuvant cancer	7	2.87	0.2	0.59	15.6
	Metastases	4	6.13	0.05*	0.99	41.8
	Multiple myeloma	9	4.23	0.06	1.00	21.0

Pseudo $R^2 = 0.346$. *Statistically significant at level $P < 0.05$.

Note: number of relapse events for each positive variable out of the 26 total relapse events.

DISCUSSION

This 13-year retrospective study summarizes surgical outcomes of MRONJ and underscores the challenges of managing this complex condition. Successful restoring of mucosal integrity and complete infection resolution was achieved in 71% of surgically treated patients. However, infection-related relapse occurred in more than one out of four patients, emphasizing that MRONJ present a recurrent and persistent problem in a subset of patients. Furthermore, this study supports previous literature showing that surgical debridement or marginal resection is more effective than conservative therapy in achieving complete soft tissue healing. The relapse rate in this cohort was lower than most studies, but still within the reported range of relapse rates, suggesting that infection-related factors rather than drug type or surgical extent may drive recurrence [8-10].

The use of AR medications continues to increase globally as the population's age and survival improves in patients with malignancies and metabolic bone disease [1]. The increased use of AR therapy in patients with osteoporosis and malignancies improves the quality of life in general but may increase the risk of MRONJ [11]. We detected no increase in MRONJ in the 13-year period, despite this general trend in increased use of AR medications in the population (Figure 1). The indications for AR treatment in this study were evenly distributed between osteoporosis, adjuvant cancer treatment, and multiple myeloma, differing from several comparative studies where either osteoporosis or malignant diagnoses are the dominant indication for AR therapy [12-15].

In this study, the most influential reason for relapse was tooth extraction in conjunction to MRONJ treatment. Tooth extraction is known as an initiating event for MRONJ but has not previously been reported as a significant contributing factor to postsurgical relapse [1]. While this study cannot establish causation, several pathophysiological explanations are supported by the literature. Numerous studies have shown that tooth extraction is the precipitating event in up to 70% of MRONJ cases, yet emerging evidence suggests that the extraction trauma itself is not the primary cause [12,16]. New evidence suggests that the pre-existing infection and inflammatory condition, necessitating the extraction, may be the initiator of MRONJ [1,2,7]. Soutome et al. demonstrated over a two-year period, that patients with symptomatic teeth had a higher incidence of MRONJ when the infected tooth was left in situ compared to extraction, highlighting that infection

control, not extraction trauma, is the key factor [4,17]. Similarly, Ristow et al. found that biopsies from alveolar bone surrounding symptomatic teeth showed areas with MRONJ in more than 50 % of the patients [18]. This suggests that the alveolar process may have areas with MRONJ outside what is readily identified in the 3D radiographic analysis and thus not sufficiently resected during the MRONJ and extraction therapy. In support of this, 7 out of 16 patients had removal of adjacent teeth during the following surgery in this study, indicating that residual MRONJ may be located in the alveolar bone around adjacent teeth that were not removed during the initial surgery. Upon review of the medical records, the majority of patients preferred tooth preservation in the primary operation, these wishes may have influenced the surgeon's intraoperative decision against removal of the adjacent teeth at the expense of a higher risk of recurrence of MRONJ. However, it is not known if these patients' quality of life is affected negatively from the tooth sparing approach resulting in an additional surgical procedure.

In contrast, recurrence did not appear to be significantly influenced by traditional factors such as surgical extent, MRONJ stage, or the use of local versus general anaesthesia as a surrogate marker for surgical extent. Most of MRONJ cases were identified in Stage 1 or 2, and therefore treated with marginal alveolar process resections, resulting in a relatively homogeneous cohort. Consequently, the analysis may have lacked the statistical power to detect differences between the traditional influencing factors. Nevertheless, the general trend in the literature supports that more extensive resection is associated with higher initial surgical success rates [12]. Several systematic reviews, including recent meta-analyses, have consistently shown that radical resection with tension-free closure achieves healing rates above 80%, whereas conservative or minimally invasive surgery is associated with healing rates of 50 to 60% [5,19,20].

Surgical treatment aims to remove all necrotic and infected bone while preserving as much vital bone as possible. While overly conservative treatment risks leaving necrotic and infected bone behind resulting in local MRONJ progression, overly aggressive resection of small lesions can cause unnecessary morbidity [21,22]. In this context, virtual surgical planning (VSP) represents a promising adjunct to optimize the balance between surgical radicality and preservation [23]. Although not applied in this study, VSP can help define clear resection margins, guide intraoperative precision, and reduce operative time. Thereby both reducing the likelihood of residual disease and risk

of relapse. Future studies should explore whether digitally planned resections can reduce relapse rates by ensuring complete removal of necrotic bone while avoiding excessive sacrifice of healthy tissue.

Likewise, a correlation was observed between relapse, smoking and the underlying reason for AR therapy. Although smoking is well known to delay healing and to be associated with poorer outcomes following MRONJ treatment [1], this study only showed a negative influence of smoking on healing in the logistic regression analysis, however this was not evident from summarized data. This discrepancy may be explained by confounding factors: patients treated for osteoporosis had a markedly higher proportion of smokers compared with cancer patients. This indicates that smoking may have been precipitating in the development of MRONJ but did not show a significant influence on healing following surgical treatment.

Limitations

This study has several limitations. First, its retrospective design restricts conclusions to associations rather than direct causation; these observed trends must be validated in prospective, controlled trials. Second, cumulative AR drug dosage and treatment duration were not systematically available and could not be included as confounding variables in the multivariable analysis. Although the primary indication for AR therapy served as a reasonable proxy for high- vs. low-dose regimens, treatment duration remained unadjusted for. Third, radiographical examination was also not conducted, but categorization of MRONJ (evaluating sequestration, osteolysis, osteosclerosis and periosteal reaction) may also significantly influence the risk of relapse [13,24,25]. Periosteal reactions represent an area of interest for future prospective studies as this seems to be correlated with higher risk of relapse [24,25]. Fourth, relatively small sample size within subgroup analyses limited statistical power potentially obscuring clinical associations. However, the use of brute-force exhaustive model selection approach helped identify consistent predictive variables despite cohort size constraints. Finally, as a single-centre

study, these findings reflect the specific surgical protocols and patient demographics of our institution, which may differ from other regions.

CONCLUSIONS

In conclusion, surgical intervention achieves complete mucosal healing in the majority of patients with medication-related osteonecrosis of the jaw, offering reassurance that disease resolution is achievable. However, relapse remains a relevant risk, particularly when tooth removals are performed concurrently within the medication-related osteonecrosis of the jaw site probably due to subclinical bone involvement around adjacent teeth. For clinicians, recognizing these local predictors of recurrence highlights the need for careful preoperative assessment and adequate resection margins around compromised teeth. Ultimately, improving surgical protocols to ensure complete micro-environmental debridement is essential to minimize the need for secondary procedures.

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Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors utilized Gemini to enhance the fluency and readability of the text. After employing this AI-based writing assistance tool, the authors thoroughly reviewed and edited the content to ensure accuracy and appropriateness. The authors take full responsibility for the content of this publication.

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