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Highlights

- MRONJ operative treatment was more efficient than non-operative treatment.
- Systematic non-operative treatment in the first place increased surgical success.
- Success was positively influenced by age and stage 0 and 1 MRONJ.
- A therapeutic window was managed to optimize MRONJ treatment.
- MRONJ prevention seems to be the best option since no gold standard is defined.

Title: Medication-Related Osteonecrosis of the Jaw: evaluation of a therapeutic strategy in oral surgery

Authors' names and affiliations:

- First author, corresponding author: Mathilde NATU^a (dr.mnatu@gmail.com)
- Second author: Vincent MEURIC^{ab}
- Third author: Paul ROGINSKI^c
- Fourth author: Romain GAMBY^d
- Last author: Sophie LEJEUNE^a (sophie.lejeune@univ-rennes.fr)

^aCentre de Soins Dentaires, CHU Pontchaillou, 2 rue Henri le Guilloux, 35000 Rennes, France

^bInserm, INRAE, Univ Rennes, Institut NUMECAN (Nutrition Métabolismes et Cancer) UMR-A 1341, UMR-S 1317, F-35000 Rennes, Inserm CIC1414, Rennes, France (ORCID: 0000-0001-5411-4001)

^cUniversité Paris-Saclay, CEA, CNRS, Institute for Integrative Biology of the Cell (I2BC), 91198 Gif-sur-Yvette, France (ORCID: 0000-0003-0297-723X)

^dClinique mutualiste La Sagesse, 4 place Saint Guérolé, 35000 Rennes, France

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Abbreviations:

- AAOMS: American Association of Oral and Maxillofacial Surgeons
- ART: AntiResorptive Therapies
- BPs: Bisphosphonates
- CBCT: Cone Beam Computed Tomography
- CI: Confidence Interval
- DMB: Denosumab
- FAMM: Facial Artery MusculoMucosal
- MRONJ: Medication-Related Osteonecrosis of the Jaw
- QoL: Quality of life
- SD: Standard deviation
- SRE: Skeletal-Related Events

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Colour should be used for *Figures 1 and 3* in print.

Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse illness linked to antiresorptive therapies (ART), for which there is no therapeutic gold standard. Many factors can influence MRONJ evolution such as cancer type, treatment, comorbidities, and accumulated dose of ART. The aim of this study was to determine the influencing factors of MRONJ treatments success.

Methods: This retrospective study focused on patients treated for MRONJ in a French tertiary centre. Non-operative therapy was always applied, ART were suspended if appropriate, and surgery (MRONJ removal and musculo-mucosal flap reconstruction) was performed in the absence of contraindication. The evaluation criteria were bone and mucosal healing 3 months after surgery.

Results: 81 MRONJ were included; medical treatment alone was administered to 26% while the remaining 74% received additional surgery. Therapeutic success reached 86.7% (52/60) for surgery compared to 42.9% (9/21) for medical treatment alone ($p < 0.001$). Age (OR=1.08, $p = 0.014$) and the

absence of infection (OR=5.32, $p=0.042$) were in favour of success, while medical treatment alone (OR=0.03, $p<0.001$) was highly unfavourable.

Conclusion: MRONJ healing is influenced by age, non-infectious stages, and surgery. Additional surgery in MRONJ treatment should be advised if the health of the patient permits.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse effect mainly linked to antiresorptive therapies (ART) such as bisphosphonates (BPs) and Denosumab (DMB). These medications are prescribed in osteoporosis, Paget's disease of bone, osteogenesis imperfecta, fibrous dysplasia, osseous metastases of solid tumours (mainly breast and prostate tumours), multiple myeloma, and hypercalcemia of malignancy. MRONJ was first described in 2003 [1], and its incidence is 0.001-0.15% in a rheumatologic context with low-dose antiresorptive agents, against 1-12% in a cancer context with high-dose antiresorptive agents [2-4]. MRONJ pathophysiology includes bone remodelling and angiogenesis inhibition, inflammation or infection, and immune dysfunction. BPs reduce bone resorption by inhibiting osteoclast activity; DMB is a fully humanised antibody against RANK ligand that inhibits osteoclast differentiation and function [5-8]. Disruption of homeostasis between osteoblastic apposition and osteoclastic resorption weakens bone remodelling. The association with the mucous toxicity of anti-tumoral drugs (as anti-angiogenic agents) results in local inflammation and altered healing in case of trauma or local pathologies [2-4,7,9]. MRONJ risk depends on the ART molecules, increases with the cumulated doses [5] and is worsened by local and general factors such as dento-alveolar surgery, poor oral hygiene, concurrent oral pathologies, smoking, diabetes, immune deficiency, and concomitant medications [2,3,5,7].

MRONJ diagnosis is based on clinical and radiographical criteria, that show bone exposure in the oral cavity with a sclerotic aspect on X-ray. It can be symptomatic or not, of variable size, and it alters the quality of life of the patient (QoL). Indeed, patients with MRONJ undergo recurrent oral infections, pain, impaired speech, issues with swallowing and eating, additional treatments, and sometimes disfigurement [8,10]. MRONJ can be spontaneous or iatrogenic but is mostly caused by tooth extractions and compressive dentures. Almost all the recommendations on ART holiday relate to the prevention of MRONJ before an invasive procedure, and not to MRONJ treatment [3,5,7,8,11-15]. Its severity is graded from stage 0 to 3 according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) classification [7,16].

In the literature, therapeutic strategies follow this gradient and their objective is to limit the severity of the symptoms to improve QoL, but no gold standard has been defined yet [10]. Success rates are uneven while treatments are not standardised. Non-operative treatment relies on prevention, non-invasive local care, and systemic medication such as antibiotics and local antiseptic care. Additional surgery can be needed with different techniques, ranging from local sequestrectomy to marginal resection with free-flap reconstruction [3,4,6,7,9,13,16-20]. The goal of this retrospective study was to evaluate the success of non-operative treatment alone or associated with surgery, and to determine factors in favour of therapeutic success in a French tertiary centre.

Methods

1. Study design and patient population

This retrospective study was approved by the ethics committee of the Rennes University hospital (n°22.13) and follows the French DPA (French data protection authority; CNIL). Included patients were above 18 years old, presented with stage 0 to 3 MRONJ, and were exposed to ART. Non-included patients were those who had been treated with orofacial radiotherapy, who deceased before treatment, and patients with non-medication related necrosis. Exclusion criteria were loss at follow-up, unknown ART exposure and death before three months of treatment. Data was collected between 2012 to 2022 from two different hospitals in Rennes (France) from a cohort of patients with MRONJ. The main goal was to evaluate the therapeutic success rate while fulfilling all the following criteria: infection resolution, pain management, no MRONJ persistence or recurrence evaluated by Cone Beam Computed Tomography (CBCT) with mucosal stability, and no complication 3 months post procedure. The secondary objective was to identify influencing factors such as MRONJ characteristics (location, AAOMS stage and triggering factor) and ART molecules classified as rheumatologic indications (BPs – alendronate, ibandronate, pamidronate, risedronate, zoledronate once a year; and Rank-L inhibitor – DMB 60 mg once every 6 months) and oncologic indications (BPs – ibandronate, pamidronate, zoledronate once or twice a month and Rank-L inhibitor – DMB 120 mg once a month). Supplementary parameters from the patient were retrieved (sex, age, primary pathology, comorbidities, additional treatments, and specialised follow-up). Post treatment ART reintroduction and dental rehabilitation were also noted.

2. Patient care

Non-operative therapy

If the general state and prognosis of the patient allowed it, interruption of DMB therapy or oncologic BPs was jointly decided with the prescribing physician as soon as MRONJ was diagnosed according to the AAOMS recommendations. However, rheumatologic BPs were not suspended. Rigorous oral hygiene, elimination of denture, local antiseptic agents, and oral analgesics were prescribed. Antibiotics were used for 15 to 21 days in case of infection. MRONJ evolution was monitored by a monthly follow-up until complete DMB elimination (5 to 9 months) or until clinical resolution. A surgical procedure was proposed to the patient if the MRONJ did not resolve with medical therapy and after an appropriate wash-out period, or as soon as possible if ART were still administered.

Additional /complementary operative therapy

Each patient was provided with clear and comprehensive information about the surgical procedure under general anaesthesia and potential complications during the preoperative consultation. The main steps of the procedure were: elimination of the necrotic bone (inferior maxillectomy or marginal mandibulotomy), teeth extraction if necessary, bone and mucosa sampling, and reconstruction with musculo-mucosal flaps (buccal and palatal flap, labial and lingual flap, FAMM flap, Bozola flap - *Figure 1*). A nasogastric tube was used to feed the patient during early healing, and surgery was followed by a five-day hospitalisation. Mucosal healing was assessed 2, 5 and 10 weeks after surgery, and bone healing was assessed 3 months after surgery. ART reintroduction and dental rehabilitation were also decided at that time.

3. Statistics

Statistical analysis was performed using the RStudio environment. Characteristics of the population and treatments were presented as the number (n) and proportion (%) and the mean \pm standard deviation (SD) for numerical variables, as appropriately. All the analyses were based on the number of MRONJ and not on the number of patients, since it was decided to consider each MRONJ as an isolated event. Univariate analyses were performed to measure the association of each variable with therapeutic success. Therapeutic success needed to meet all the following criteria: infection

resolution, pain management, no MRONJ persistence or recurrence evaluated by CBCT with mucosal stability and no complication 3 months post procedure. Failure was defined when one or more criteria were not fulfilled. MRONJ stages were analysed separately and merged as follows: stages 0 and 1 as “not infected”, and stages 2 and 3 as “infected”. Primary pathologies were split as “breast cancer” and “other pathologies”. The Wilcoxon rank sum test was used to compare two independent samples. Chi-squared and Fisher’s tests were used to compare differences between groups for categorical variables as appropriately. Statistical significance was set at $p < 0.05$. For the multivariable analysis, logistic regression was performed to explain therapeutic success according to confounding factors (sex, age, primary pathology, concomitant treatments, comorbidities, ART cumulated dose, MRONJ stage).

Results

1. MRONJ characteristics

Seventy-five patients were treated for MRONJ between 2012 and 2022. Twelve subjects were excluded for lost at follow-up, unknown ART exposure and death before treatment or quickly after surgery, resulting in 63 patients with 81 MRONJ as shown in *Figure 2*.

Most of MRONJ were found in women ($n=48$; 76.2%) with a mean age of 67.2 ± 11.7 years (range 31-87 years). Malignant solid tumours were mostly breast tumours ($n=42$; 67.7%) but prostate cancer, kidney cancer, lung cancer, thyroid cancer and nasopharyngeal cancer were also identified. Medical comorbidity was present in 23.5% of the cases ($n=19$) such as diabetes, low body mass index, cardiovascular disease, immunodeficiency, or smoking. Other therapies (as hormone therapy or kinase inhibitors) were identified in 77.8% of the MRONJ ($n=63$). 58.2% of the BPs were used for rheumatologic treatments and 41.8% for cancer treatments while most of the DMB treatments were used for cancer patients (69.1%). MRONJ location followed a 2:1 mandible/maxilla ratio, with the most frequent location being the posterior mandible. MRONJ stages were: stage 0 - 12.4% ($n=10$); stage 1 - 37% ($n=30$); stage 2 - 37% ($n=30$) and stage 3 - 13.6% ($n=11$). Most MRONJ ($n=65$; 80.3%) were not regularly monitored in a specialised consultation. Almost 62% ($n=50$) of the MRONJ were caused by invasive procedures including tooth removal ($n=47$; 58%). Characteristics of the population and MRONJ are described in *Table 1* separated by success or failure of the treatment.

2. Efficiency of treatments

Only one MRONJ responded rapidly to simple medical treatment. For all the other MRONJ, additional surgery was proposed to improve oral health, prevent MRONJ worsening and increase the QoL of the patient. However, 20 MRONJ went continuously through medical care as the patient or the physician refused surgery (altered general state, fear of surgery and complications) (*Figure 2*).

All treatments combined, 75.3% of the MRONJ (61/81) were recuperated. Additional surgical treatment was used in the majority ($n=60$; 74.1%) and non-operative therapy was more frequent in the oncological group ($n=19/68$; 27.9%) than in the rheumatological group ($n=2/13$; 15.4%). Non-operative therapy success rates were up to 42.9% (9/21), but additional surgery was significantly more effective with 86.7% (52/60) of success (Chi-2, $p < 0.001$).

In the univariate analysis, trends in favour of success were observed for older age ($p=0.2$), absence of concomitant chemotherapy ($p=0.039$), absence of MRONJ infection at the time of diagnosis or surgery ($p=0.14$ and $p=0.2$ respectively) and in an oncological context, a lower number of injections of BPs ($p=0.12$), or a higher number of DMB injections ($p=0.11$). Distributions of success/failure in MRONJ treatment were significantly different in primary disease ($p=0.032$) with an over-representation of breast cancer for failure and osteoporosis for success.

After analysis through logistic regressions (*Table 2*), three factors remained statistically significant in the final regression model of success of treatment. Age (OR=1.08, $p=0.014$) and the absence of infection (OR=5.32, $p=0.042$) were in favour of therapeutic success, while non operative therapy alone (OR=0.03, $p < 0.001$) was highly unfavourable.

Follow-up duration was 19±12 months (13±12 months for non-operative therapy and 21±12 months for operative therapy, including 14±12 months post-operatively) allowing ART reintroduction in 8 (38.1%) MRONJ cases with non-operative therapy and 40 MRONJ (66.7%) with additional surgery. Dental rehabilitation was allowed in 8 cases (38.1%) with non-operative therapy and in 50 cases (83.4%) with additional surgery (*Table 3*).

Discussion

Within this cohort, surgical management was performed in 74.1% of the MRONJ, with an 86.7% success rate. It is in the high range of published success rates for operative therapy, which vary from 60% to 90%. Furthermore, it is significantly higher than the 42.9% success rate for non-operative therapy, which varies from 15% to 65% in the literature [8,12,15,21]. Additional factors in favour of healing were the preliminary successful treatment of infection before surgery (stage 2-3 MRONJ reducing to 0-1) and, surprisingly, the age of the patient. No other factors were identified as significantly influencing the healing process, but this result should be taken with caution. Even though it is larger than many studies [4,5,8,20,21], the size of the cohort may hide factors of interest.

The characteristics of the cohort are similar in the literature (women, age, location of MRONJ and ART treatment duration). MRONJ triggering factors and frequencies are also similar [2–5,7,9,13,22]. Even though the correlation between patient sex and MRONJ has not been established, the proportion of women could reflect the primary pathologies requiring ART administration (*i.e.*: breast cancer) [5,7]. MRONJ risk depends on treatment. For osteoporosis, non-nitrogenous BPs were not considered (tiludronate, etidronate and clodronate: no risk of MRONJ) whereas 3 years of nitrogenous BPs (alendronate, ibandronate, pamidronate, risedronate, zoledronate) is usually considered a threshold [6,16]. BPs in cancer are more concentrated and the repetitive injections drastically increase the risk of MRONJ [8]. The number of DMB injections was registered, reflecting the exposure time on a 6-month basis for Prolia® (rheumatological context) and on a monthly-basis for Xgeva® (cancer context). DMB is the main cause of MRONJ, followed by Zoledronate [7,13,16,22,23] which are the main therapies prescribed in this cohort. However, the surgical success was not affected by DMB nor BPs in terms of injections or times of usage. Co-medications (even when analysed as a sum of medications) as well as co-morbidities (tobacco, diabetes, autoimmune disorders) did not influence success rates, even though they are usually recognised as risk factors for treatment failure.

Criteria of success is a matter of concern between studies. The agreement in the management of MRONJ has yet to be established [8,15]. Sometimes, the stability of the lesion is considered as a success, especially in the case of medical treatment where controlling pain and infection preserves the QoL [5,10]. However, complete alleviation of symptoms and the absence of recurrence should be sought with clinical mucosal coverage and radiographic bone healing [5,6,11,13,15]. Long term evaluation should be considered, but patient health is at stake with a high mortality rate due to cancer. Therefore, evaluating therapeutic success at 90 days could be enough considering the physiology of bone remodelling [3,6,16,19]. In this study, surgery is performed as soon as possible (after an adequate wash-out period if necessary) as opposed to previously published reports where surgery is usually carried out at a later stage [5,15]. Thus, we have differentiated the evaluation of medical treatment versus additional surgery based on a strict criterion of success evaluated by bone healing on CBCT, mucosal stability and no complication 3 months post procedure.

Preventing MRONJ is essential [7,8,11], unfortunately 80% of this cohort did not have regular dental check-ups and dentists are not sufficiently aware of the risk of MRONJ (*e.g.* in case of dental extraction, periodontal surgery, or the unbalanced use of dentures). Concerning the drug holiday before dental extractions, literature disagrees [5–7,12,24–26]. However, when MRONJ is diagnosed, ART cessation should systematically be discussed with the treating physician, for as short a time as possible, taking into consideration the primary disease and the severity of MRONJ [5–7,13]. Supportive care (antibiotics, analgesics, local antiseptics) should be established if the drug holiday seems

unreasonable. Even though it is still controversial because it increases the risk of skeletal-related events (SRE) [6,11], drug holiday is favourable especially for DMB, as it shows higher success rates and more predictable results [3,5,13–15]. While BPs have a 10-year remanence, a 28-day half-life for DMB means a single dose is almost eliminated after 4 to 6 months [8,9,14]. However, accumulated doses increase more rapidly in patients with cancer than with rheumatologic diseases. Within our cohort, BPs were not suspended in rheumatologic diseases; however, they were interrupted in cancer patients to limit the accumulated dose and MRONJ aggravation. DMB was discontinued as often as possible for 5 to 9 months for wash-out.

Medical and surgical treatment are both accepted for all stages in the literature and must be adapted to each patient [7,20], following the decision tree proposed in *Figure 3*. Conservative treatment is generally preferred in the early stages, with success rates above 80% [11,13,16] that outperform our results (42.9%). This discrepancy might be due to the different criteria of success. However, medical treatment should be started as soon as possible as it led to a stage down-shift as shown in 19 cases (23.5%), and therefore improved the success of additional surgery. Surgical management is indicated if the MRONJ is not responding to medical treatment [7,11,15]. In addition, surgery implemented during severe stages (2 and 3) results with higher success rates, shorter remission times and lower recurrence rates than medical treatment [4,5,9,13,16,18,27]. The impact of MRONJ location is not detailed in the literature and it did not influence success in the cohort. A specific surgical technique cannot be recommended since MRONJ presentations are very diverse [18,27] and we could not determine which one had the best result.

Resuming ART treatment is one of the objectives of MRONJ treatment [9], but it was not the main success criterion in this study. ART were not systematically resumed, probably because either the patient or the physician fear MRONJ recurrence. In the same way, dental rehabilitation was not always carried out. Both criteria were more frequent with operative therapy than with non-operative therapy. The average medical treatment time is 12 months and may be lengthened by comorbidities and comedications, so ART may be suspended for longer [2,8,9]. In this cohort, the mean follow-up duration post-surgery was 14 ± 12 months, which is higher than most of the studies (recommendation of ~ 12 months) [5,8,21].

Risk of bias: The criteria of success was discussed between studies; as we were seeking mucosal and bone stability, no QoL study was realised, which was missing to show the superiority of additional surgery. The better QoL was only assessed by medical opinion from individual medical interviews but was not monitored. Medical treatment is also a confounding factor as this is influenced by the refusal by the patient or physician due to a poorer general condition and reduced healing capacity, and therefore an altered medical success. Finally, all surgeries were performed by the same two operators, limiting the risk of bias with the different techniques that are presented in *Figure 1*.

Both strategies, non-surgical and surgical, are complementary. However, the results presented here suggest that when surgery is possible it should be performed, following *Figure 3*. Undoubtedly, each decision must be considered carefully with the patient and the multidisciplinary team, as the QoL and the survival of the patient are implicated. The main role of the dentist is to diagnose the MRONJ and carry out the initial treatment to reduce infectious symptoms, after interrupting ART if relevant, and in agreement with the physician. Stage down-shift is being sought by non-operative therapy to obtain a non-infected MRONJ, which reduces surgical iatrogenicity and increases predictability. The best possible strategy is proposed, and non-operative therapy is chosen for patients who are unwilling to undergo surgery or whose general conditions does not allow it. Additional surgery is performed as soon as possible when the drug has been washed out since it is more efficient than non-operative therapy alone. Age should not be an issue since older patients presented good success rates. Finally, ART reintroduction and dental rehabilitation must be considered once mucosal stability and bone healing are acquired.

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Figures and Tables

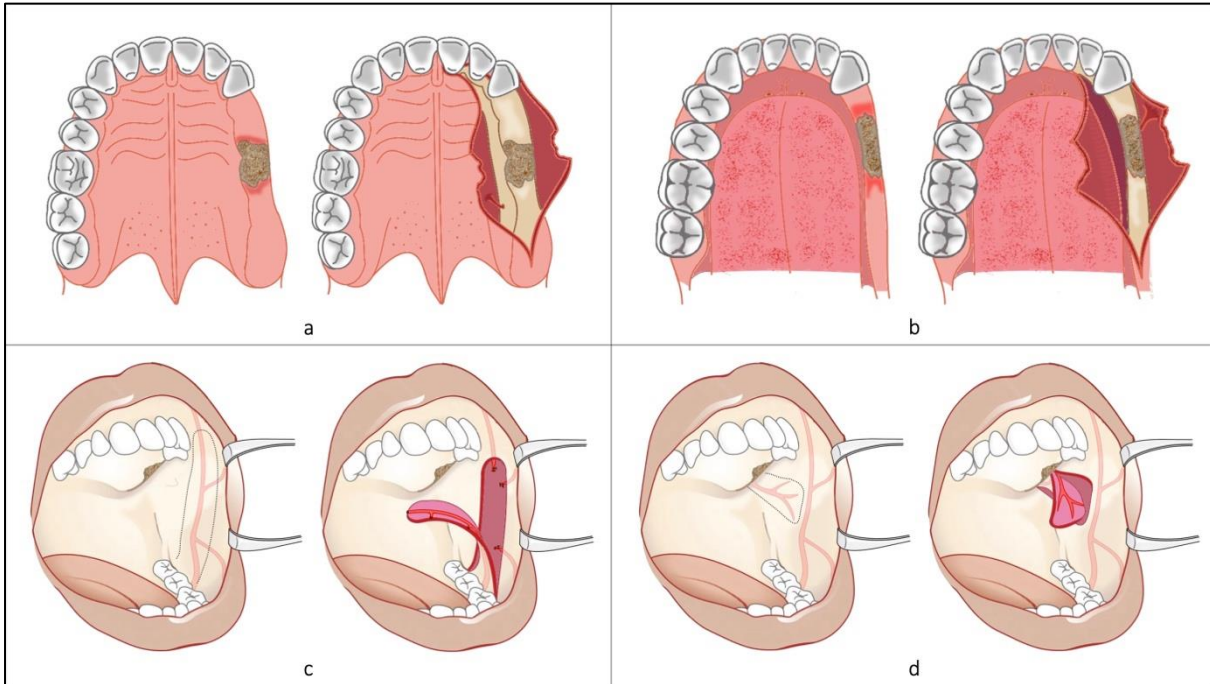


Figure 1: a. Buccal and palatal flap; b. Labial and lingual flap; c. FAMM flap; d. Bozola flap.

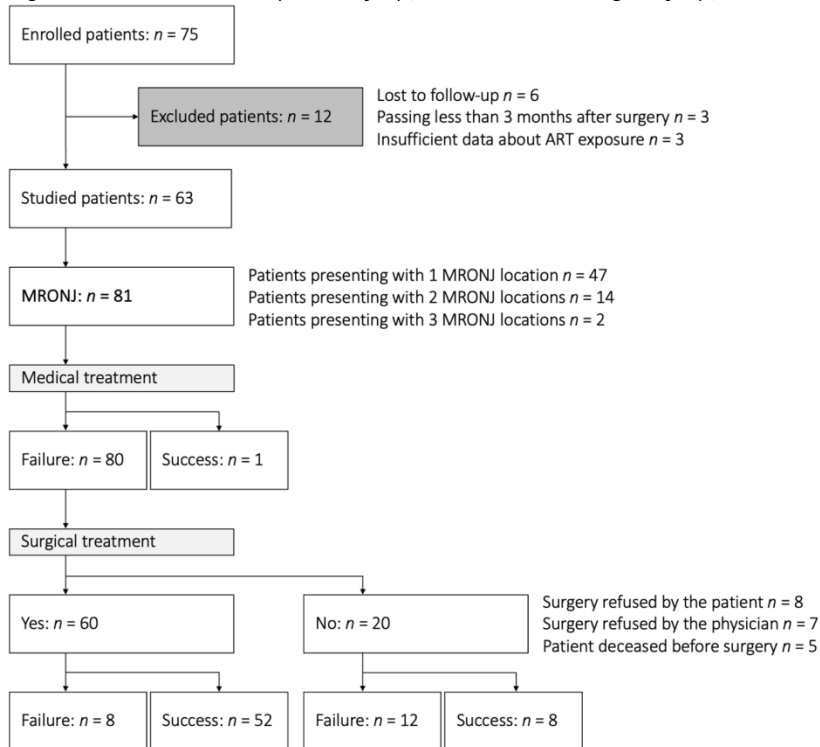


Figure 2: Flow chart.

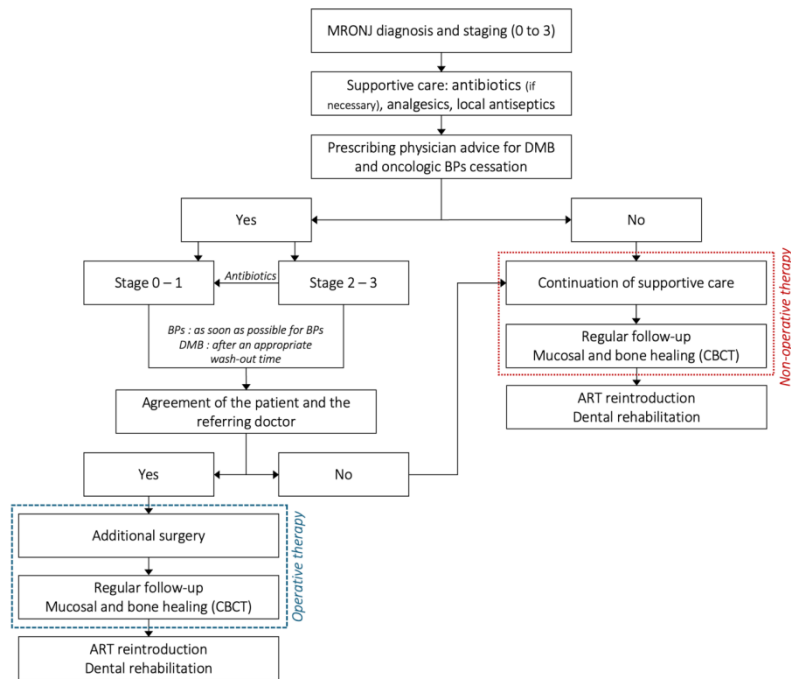


Figure 3: Decisional tree for MRONJ treatment

Sex	MRONJ n (%)	ART	Injections ± SD	Duration ± SD	MRONJ n (%)
Male	19 (23.5%)	- BPs			
Female	62 (76.5%)	Rheumatologic disease	* 29.5 ± 25.7	82% > 3 years	17 (20.9%)
		Malignant disease		2.5 ± 2.1 years	16 (19.6%)
Age (mean ± SD)	67.2 (± 11.7)	- DMB			
Primary disease		Rheumatologic disease	7.4 ± 3.9	3.7 ± 2 years	7 (8.6%)
Malignant solid tumours	62 (76.5%)	Malignant disease	20.4 ± 10.2	1.7 ± 0.9 years	56 (69.1%)
- Breast cancer	- 42 (51.9%)	MRONJ trigger events			
- Prostate cancer	- 7 (8.6%)	Dental extraction			47 (58.0%)
- Kidney cancer	- 5 (6.2%)	- With a therapeutic window			- 6 (7.4%)
- Lung cancer	- 4 (4.9%)	- Without any protocol			- 41 (50.6%)
- Thyroid cancer	- 3 (3.7%)	Spontaneous MRONJ			16 (19.6%)
- Nasopharyngeal cancer	- 1 (1.2%)	Removable prosthesis			15 (18.5%)
Multiple myeloma	6 (7.4%)	Other invasive procedures			3 (3.7%)
Osteoporosis	13 (16.0%)	Specialised follow-up before diagnosis			
Concomitant therapies	67 (82.7%)	None		65 (80%)	
Hormonotherapy	43 (53.1%)	MRONJ location	Maxilla n = 28 (34.6%)	Mandible n = 53 (65.4%)	
Kinase inhibitors	35 (43.2%)	Anterior	6 (7.4%)	13 (16.0%)	
Chemotherapy	22 (27.2%)	Posterior	22 (27.2%)	40 (49.4%)	
Steroids	17 (20.9%)	MRONJ stage n (%)	Maxilla n = 28 (34.6%)	Mandible n = 53 (65.4%)	
Monoclonal antibodies	8 (12.3%)	Stage 0 - 10 (12.3%)	5 (6.2%)	5 (6.2%)	
Antiangiogenic agents	4 (4.9%)	Stage 1 - 30 (37.0%)	13 (16.0%)	17 (20.9%)	
Proteasome inhibitors	2 (2.4%)	Stage 2 - 30 (37.0%)	6 (7.4%)	24 (29.6%)	
Medical comorbidities		Stage 3 - 11 (13.6%)	4 (4.9%)	7 (8.6%)	
None	62 (76.5%)				
One or more	19 (23.5%)				

*Non relevant as only underdosed BP Zoledronate (Aclasta®) is injected for rheumatologic disease

Table 1

Table 1: Characteristics of the population and MRONJ

Characteristics	Success (n, %)	Failure (n, %)	p-value	Success (n, %)	Failure (n, %)	p-value
Sex			0.5			0.6
DMB Injections In						

				rheumatologic diseases		
Female	48 (79%)	14 (70%)		0	55 (90%)	19 (95%)
Male	13 (21%)	6 (30%)		2	1 (1.6%)	0(0%)
				4	1 (1.6%)	1 (5.0%)
Age			0.2	≥10	4 (6.5%)	0(0%)
Mean± SD	68 ± 10	62 ± 15				
Minimum; Maximum	49;87	31; 84		MRONJ location		0.7
				Anterior maxilla	6 (9.8%)	0(0%)
Primary pathologies			0.032	Posterior maxilla	14 (22.9%)	8 (40.0%)
Malignant diseases:				Anterior mandible	10 (16%)	3 (15%)
- Breast cancer	28(46%)	14 (70%)		Posterior mandible	31 (51%)	9 (45%)
- Prostate cancer	6 (9.8%)	1 (5.0%)				
- Multiple myeloma	3 (4.9%)	3 (15%)		MRONJ aetiology		0.7
- Kidney cancer	5 (8.2%)	0(0%)		Dental extractions	37 (61%)	10 (50%)
- Lung cancer	3 (4.9%)	1 (5.0%)		Compressive dentures	10 (16%)	5 (25%)
- Thyroid cancer	3 (4.9%)	0(0%)		Spontaneous	12 (20%)	4(20%)
- Nasopharyngeal cancer	0(0%)	1 (5.0%)		Invasive procedures (other than dental extractions)	2 (3.3%)	1 (5.0%)
Osteoporosis	13 (21%)	0(0%)				
				MRONJ stage at diagnosis		0.5
Comorbidity	15 (25%)	4(20%)	0.8	0	9 (15%)	1 (5.0%)
				1	24 (39%)	6 (30%)
Concomitant				2	20	10

therapies					(33%)	(50%)	
Hormonotherapy	29 (48%)	9 (45%)	0.6	3	8 (13%)	3 (15%)	
Corticosteroids therapy	12 (20%)	5 (25%)	0.8				
Antiangiogenic agents	3 (4.9%)	1 (5.0%)	>0.9	MRONJ Infection at diagnosis			0.14
Chemotherapy	13 (21%)	9 (45%)	0.039	Not infected (stages 0 and 1)	33 (54%)	7 (35%)	
Monoclonal antibodies	7 (11.5%)	1 (5.0%)	0.8	Infected (stages 2 and 3)	28 (46%)	13 (65%)	
Kinase inhibitors	27 (44%)	8 (40%)	0.7				
Proteasome inhibitors	2 (3.3%)	0(0%)	>0.9	MRONJ stage before surgery			0.5
				0	1 (19%)	3 (15%)	
Number of concomitant therapies			0.5	1	36(61%)	10 (50%)	
0	12 (20%)	2 (10%)		2	6 (10%)	5 (25%)	
1	14 (23%)	7 (35%)		3	6 (10%)	2 (10%)	
2	19 (31%)	6 (30%)					
3	11 (18%)	5 (25%)		MRONJ Infection before surgery			0.2
4	5 (8.2%)	0(0%)		Not infected (stages 0 and 1)	47 (80%)	13 (65%)	
				Infected (stages 2 and 3)	12 (20%)	7 (35%)	
BPs Injections in malignant diseases			0.12				
Mean± SD	6 ± 19	8 ± 12		MRONJ treatment			<0.001
Minimum; Maximum	0;94	0;36		Operative therapy	52 (85.2%)	8 (44.4%)	

OMB Injections In malignant diseases			0.11	Non operative therapy	9 (14.8%)	12 (60.0%)
Mean± SD	15 ± 13	10 ± 9		Type of surgery		0.11
Minimum; Maximum	0;56	0;32		Buccal and palatal flap (maxilla)	9 (17%)	0(0%)
BPs duration In rheumatologic diseases			>0.9	FAMM flap (maxilla)	4 (7.7%)	3 (38%)
< 3 years	3 (19%)	0(0%)		Bozola flap (maxilla)	5 (9.6%)	0(0%)
3 years	13 (81%)	1 (100%)		Labial and lingual flap (mandible)	30 (58%)	4(50%)
None	45	19		FAMM flap (mandible)	4 (7.7%)	1 (12%)

Or: Table 1: Characteristics of the cohort according to therapeutic success or failure
 *Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test

Characteristic	N	Event N	OR*	95% CI*	p-value
Age	79	59	1.08	1.02, 1.15	0.014
Primary pathology					
- Other pathologies	37	31	—	—	
- Breast cancer	42	28	0.35	0.07, 1.48	0.2
MRONJ stage before surgery					
- Infectious	19	12	—	—	
- Non infectious	60	47	5.32	1.11, 30.5	0.042
MRONJ treatment					
- Additional surgery	60	52	—	—	
- Medical	19	7	0.03	0.00, 0.12	<0.001

*OR = Odds Ratio, CI = Confidence Interval

Table 2

Table 2: Logistic regression for prediction MRONJ treatment success. Final variables entered are age, MRONJ stage as infectious or non-infectious, MRONJ treatment.

	ART reintroduction		Dental rehabilitation	
	Non-operative therapy (<i>n</i> = 21)*	Additional surgery (<i>n</i> = 60)	Non-operative therapy (<i>n</i> = 21)*	Additional surgery (<i>n</i> = 60)
Effective	<i>n</i> = 0 (0%)	<i>n</i> = 11 (18.3%)	<i>n</i> = 1 (4.8%)	<i>n</i> = 22 (36.7%)
Possible but not effective	<i>n</i> = 8 (38.1%)	<i>n</i> = 40 (66.7%)	<i>n</i> = 7 (33.3%)	<i>n</i> = 28 (46.7%)
No	<i>n</i> = 13 (61.9%)	<i>n</i> = 9 (15%)	<i>n</i> = 13 (61.9%)	<i>n</i> = 10 (16.7%)

*Results only in 16 patients as 5 deceased shortly after MRONJ diagnosis.

Table 3

Table 3: ART reintroduction and dental rehabilitation after MRONJ treatment.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for the Journal of Stomatology oral and Maxillofacial Surgery and was not involved in the editorial review or the decision to publish this article.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: