

# Surgical therapy for medication-related osteonecrosis of the jaw in osteoporotic patients treated with antiresorptive agents

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**Background.** Medication – related osteonecrosis of the jaw (MRONJ) is a rare but serious complication of antiresorptive and/or antiangiogenic therapy. It mainly affects oncological patients, however, it can occur in patients with metabolic bone diseases, although this is less frequent. These lesions not only significantly impair the quality of life but can also have impact on the treatment of any underlying disease. In some rare cases MRONJ can be life-threatening. There is still no ideal consensus for treatment, though surgical therapy has been mostly preferred in recent years.

**Materials and Methods.** A monocentric retrospective evaluation of surgical therapy of MRONJ in osteoporotic patients, treated in the time period 3/2014-3/2018 using the uniform department-specific protocol.

**Results.** 26 osteoporotic patients with 32 MRONJ lesions of stage 1 (9%), stage 2 (75%) and stage 3 (16%) were treated surgically. The maxilla: mandibula ratio was 1:2.2, in 19% of patients there was multiple jaw involvement. 69.2% of patients had received bisphosphonates, 15.4% denosumab and 15.4% had a history of both types of antiresorptive treatment. Complete healing was observed in all patients, in 9% of cases by secondary intention in the mean period of 6 weeks. The mean follow-up was 20.5 months.

**Conclusion.** The presented protocol for surgical therapy was effective in the management of all MRONJ stages in the osteoporotic patients described here. The surgery is indicated as an early treatment to prevent complications and the progression of the lesions. It leads to improvement in quality of life and option to resume antiresorptive therapy if interrupted.

**Key words:** osteonecrosis of the jaw, MRONJ, antiresorptive drugs, osteoporosis, fluorescence-guided surgery

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## INTRODUCTION

Osteoporosis is a metabolic bone disease highly prevalent in the developed countries (over 200 million people suffering from osteoporosis around the globe) (ref.<sup>1</sup>). It is defined as a progressive chronic disease of the skeleton characterized by excessive bone loss in its inorganic and organic component with microarchitectural disorders resulting in a decrease in bone mechanical resistance and increased risk of fractures<sup>2</sup>. Approximately 7% of the population of the Czech Republic suffer from osteoporosis, ie about 700,000 people with 50,000 registered osteoporotic fractures annually<sup>2</sup>. Primary osteoporosis is the most common form of the disease and includes postmenopausal osteoporosis and senile osteoporosis. Secondary osteoporosis has a clearly definable causal factor other than menopause and aging and it is caused by certain medical conditions or pharmacotherapy<sup>2</sup>. Currently, the mainstay forms of antiresorptive therapy for osteoporosis are bisphosphonates (mostly alendronate and ibandronate)

and denosumab. These drugs inhibit osteoclast mediated bone resorption and prevent fractures<sup>3</sup>.

A rare adverse effect of antiresorptive treatment in patients with osteoporosis but especially in patients with malignancies is Medication-Related Osteonecrosis of the Jaw (MRONJ). According to a position paper published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014, MRONJ may be considered in patients who fulfill all of the following characteristics. Exposed or probable bone through an intraoral/extraoral fistula(e) in the maxillofacial region without resolution for longer than 8 weeks in patients with history of antiresorptive and/or antiangiogenic therapy who have not received radiation therapy to the jaws and who are without obvious metastatic disease in this area<sup>4</sup>. In contrast, cancer patients, who use high doses of antiresorptive agents to prevent skeletal-related events, osteoporosis patients are considered to be significantly less at risk for the development of MRONJ (less than 10% of MRONJ cases) (ref.<sup>5</sup>). However, even in this group, MRONJ may have a severe

complicated course, significantly impairing the quality of life through pain, halitosis, teeth loss, affection of the trigeminal nerve branches with sensitivity disturbances, fistula formation with pus exudation, pathological fracture of mandible, oroantral or oronasal communication, deep neck space infection and chronic rhinosinusitis. In these patients, MRONJ may be perceived as worse than the underlying disease.

The life expectancy of osteoporosis patients is significantly longer than patients with an advanced stage of malignant disease, therefore, complete healing of these lesions with relief of all symptoms is the ultimate and highly desirable goal of the therapy. In the majority of patients, the symptoms of MRONJ, such as pain and those caused by infection, may be improved temporarily using conservative therapy (primarily antibacterial mouth rinses and systemic antibiotics), particularly at an early stage of disease<sup>5,6</sup>. However, complete mucosal coverage is rarely achieved. In addition, the healing is prolonged and difficult to predict<sup>7</sup>. A non-surgical approach is therefore rather more palliative and has greater importance in cancer patients<sup>5,6</sup>. Recently, a radical surgical therapy seems to have the most successful outcomes in terms of complete mucosal closure at any stage of disease<sup>7</sup>. The principle of this treatment is the complete removal of necrotic bone, smoothing of sharp bony edges and meticulous tension-free primary wound closure by adjacent soft tissues accompanied by perioperative antibiotics administration<sup>7</sup>. In some cases continuity resections including jaw reconstruction are required. Surgical techniques are still not standardized and they mostly depend on a surgeon's skills and experience<sup>5</sup>. Subsequent dental and prosthetic reconstruction enables restoration of the affected functions and such patients can continue with antiresorptive therapy if interrupted<sup>8</sup>.

## MATERIALS AND METHODS

This was a monocentric retrospective evaluation of the surgical therapy of MRONJ in osteoporotic patients, treated at the Department of Oral and Maxillofacial Surgery (University Hospital and Faculty of Medicine in Pilsen, Charles University in Prague, Czech Republic) from 3/2014-3/2018. The diagnostic criteria and staging of MRONJ was in the line with the AAOMS guidelines (2014) (ref.<sup>4</sup>)

Stage 0 No clinical evidence of necrotic bone, but non-specific symptoms and/or clinical and/or radiographic findings for more than 8 weeks, which could not be explained otherwise

Stage 1 Exposed and necrotic bone, or fistula(e) that probed to bone, in patients who were asymptomatic and had no evidence of infection

Stage 2 Exposed and necrotic bone, or fistula(e) that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage

Stage 3 as well as the 2<sup>nd</sup> stage and one or more of the following: exposed and necrotic bone extending beyond

the region of the alveolar bone, pathological fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

The uniform surgical protocol for the treatment of MRONJ was used. All surgical procedures were performed by the same specialized Oral and Maxillofacial Surgeons. Monitored parameters of this study were: gender, age, type of osteoporosis, concomitant risk factors, initiating factors, localization and stage of MRONJ, type and duration of antiresorptive therapy (till the time of MRONJ diagnosis) and outcomes of surgical therapy.

### The protocol of surgical therapy

All osteoporotic patients with MRONJ of 1st., 2nd and 3rd stage were indicated for surgical treatment. First, they were referred to their osteologist / rheumatologist in order to report the adverse effect of antiresorptive therapy to the State Institute for Drug Control. No drug holiday in cases of receiving bisphosphonates was required. In patients treated with denosumab, surgery was delayed for at least 3 months after the last dose, and further administration of denosumab was initiated 2-3 months after complete healing occurred. The changes in an antirheumatic therapy (glucocorticosteroids, cytostatics, targeted therapy, etc.) due to the planned surgery and anticipated healing disruptions were left to be resolved by the rheumatology specialist. All patients underwent cone beam computed tomography (CB CT) or CT as a part of preoperative planning.

The primary goal in MRONJ cases with symptoms caused by infection (2nd, 3rd stage) or accompanied by deep neck space infections was to treat these conditions before the treatment of osteonecrosis (antibiotics, incision, drainage). If the purulent discharge was a result of the separation of bone sequestrum, surgery was postponed till there was decrease in symptoms of infection and sequestrectomy was performed. Patients with MRONJ-induced maxillary or more extensive bacterial rhinosinusitis received nasal decongestant perioperatively (for one week) followed by nasal corticosteroids (long-term use). According to the extent of lesions, their localization, disease stage and compliance of patients, a surgery was planned including either local or general anesthesia, always during a short-term hospitalization. Patients underwent standard preoperative examinations. The fluorescence of tetracycline antibiotic bound in a bone tissue visualized intraoperatively during exposure of VELscope (Visually Enhanced Lesion Scope) light of 400-460 nm wavelength was used to distinguish between viable and necrotic bone. Patients received doxycycline 100 mg every 24 h perorally for 7 days prior to the surgery. The day before the operation, the doxycycline was discontinued and patients started to use antibiotic prophylaxis, namely co-amoxicillin intravenously or perorally in the usual dosage for 10-14 days (until healing occurred). In the case of allergy to penicillin, clindamycin was administered intravenously or perorally or doxycycline was continued.

In the cases of extensive lesions without sequestration, radical removal of necrotic bone was performed by

resection with the borders in non-vital bone followed by removal of residual osteonecrosis by rotary burr into the viable bleeding bone margins and under VELscope control. In lesions with sequestration, the sequestrectomy was done and the remaining necrotic bone was then radically removed by rotary burr. The minimum amount of bone possible was removed to avoid unnecessary weakening of the jawbone and to create the best conditions for dental or prosthetic rehabilitation. The deperiostation of jawbone was as minimal as possible and neurovascular bundles were spared. Subsequent smoothing of sharp bony edges to at least 2 mm of margin width was performed. The teeth situated in a necrotic bone or resection margins and non-restorable teeth were extracted. Inflammatory granulation tissue within or neighbouring these lesions was also removed. The mucosa of the maxillary sinus with signs of infection was managed more conservatively. Samples of necrotic bone and adjacent soft tissues were sent for the histopathological examination to exclude primary jaw tumor, metastasis or other diseases. In some cases (e.g. maxillary sinus empyema) pus was sent for microbiological examination and determination of antibiotic sensitivity. After radical removal of the necrotic bone, wound antisepsis was performed using 3% hydrogen peroxide and iodine solution. The wounds were closed with local soft tissues, in the distal parts of jaws in two layers using the mylohyoid flap in the mandible and the buccal fat pad flap in the maxilla (even in the absence of oroantral communication). In the frontal parts of both jaws, where the closure in two layers is problematic, deep suspension suture was used. The load-bearing fixation of mandibular pathological fractures or in patients with continuity resections was performed using reconstruction plates prebended on jaw models created by 3 D printer using patient's CT data. This approach shortened duration of the surgery.

Postoperatively, patients had oral intake of liquid/semi-liquid diet (no nasogastric tube) and other symptomatic therapy and supportive care. Mostly, resorbable suture was used. Otherwise the suture was removed in 14 days. In patients with secondary healing, watchful waiting approach was chosen and in non-healing lesions and secondary surgery was considered individually. The healed lesions had follow-up in time intervals of 1 month / 1 month / 6 months / 6 months and then once a year or the patient was further referred to his dental practitioner. A control radiological examination was indicated on an individual basis, usually only in cases of clinical symptoms arising. The procedure success was assessed as a maintenance of complete mucosal coverage without pain and signs of infection during regular follow-up. A restoration of remaining teeth and prosthetic rehabilitation with an emphasis on chronic trauma avoidance was performed by dental practitioners.

## RESULTS

32 MRONJ lesions in 26 osteoporotic patients were treated surgically.

### Demographic data

The majority of patients were female (n=25; 96.2%), only one man was included in the study (3.8%). The mean age at the time of diagnosis of MRONJ patients was 73.4 years (standard deviation 10.1 years, range 53–92 years).

### Underlying disease

In the majority of cases antiresorptive agents (bisphosphonates, denosumab) were administered because of postmenopausal osteoporosis (PMO) (n=20; 76.9%). In the remaining 6 patients (23.1%) a glucocorticosteroids-induced osteoporosis (GIOP) was identified as the underlying disease. The secondary osteoporosis developed as an adverse side effect of corticosteroids during the treatment of rheumatoid arthritis (n=4; 15.4%) and multiple sclerosis (n=2; 7.7%).

### Antiresorptive treatment data

69.2% of patients (n=18) received bisphosphonates (alendronate, risendronate or ibandronate perorally/ intravenously). The duration of receiving bisphosphonates were identified only in 17 patients. Bisphosphonates administration was typically long term with a mean duration of medicament intake to the emergence of MRONJ being 73.1 months (standard deviation 38.0 months, range 18–144 months). 7 patients (38.9%) were treated with more than one type of bisphosphonate during whole osteoporosis therapy. 15.4% of patients (n=4) were treated with denosumab. On average, the MRONJ arised after receiving 6 doses of this drug. 15.4% of patients (n=4) had history of both type of antiresorptive treatment, i.e. bisphosphonates (alendronate or ibandronate perorally) and then denosumab.

### Initiating and risk factors, localization, staging of MRONJ

The most common initiating factor of MRONJ in the study population was tooth extraction (n=26; 81.3%) with subsequent failure of wound healing. Other cases (n=6) had no patent trigger event (oral surgery, dental implant placement, etc.) except for potential possibility of chronic traumatization by removable oral prosthesis (pressure sores). Most cases of osteonecrosis occurred in the mandible (n=22; 68.8%) with the maxilla: mandibula ratio being 1:2.2. In 19.2% of patients multiple jaw involvement arised. The majority of cases (n=24; 75.0%) were categorized as stage 2 followed by stage 3 (n=5; 15.6%) and stage 1 (n=3, 9.4%). Deep neck space infection (abscess of lateral pharyngeal, infratemporal and submental space) as a complication caused by MRONJ was detected in two patients. The maxillary osteonecrosis of third stages were accompanied by maxillary rhinosinusitis and in some patients also by ethmoiditis. In one case, this infection of paranasal sinuses was complicated by orbital cellulitis with proptosis, ophthalmoplegia and diplopia (Fig. 1 and 2.) One patient suffered from mandibular pathological fracture as a result of MRONJ. Two lesions of MRONJ were adjacent to residual cysts of mandible. Concomitant risk factors were identified in 10 patients (38.5%), 5 patients with co-morbidity such as diabetes mellitus (type 1 or 2) and 5 patients with immunosuppressive co-med-



**Fig. 1.** MRONJ emerged after 6 years exposure to oral ibandronate in 53-year-old women.



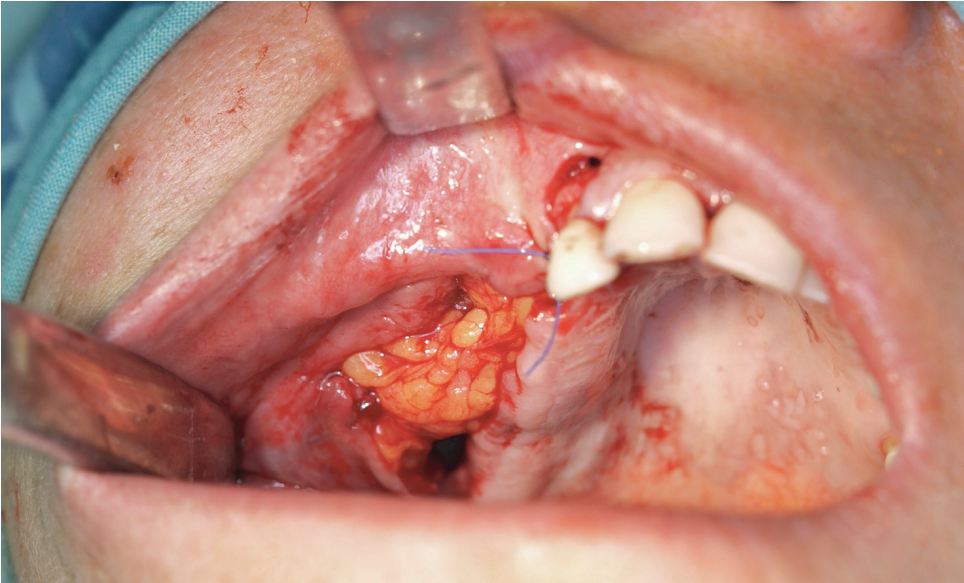
**Fig. 2.** Orbital cellulitis as the complication of MRONJ-induced maxillary rhinosinusitis and ethmoiditis in the patient from Fig. 1.

ication (corticosteroids, leflunomide, methotrexate, azathioprine, etanercept).

#### **Outcomes of the MRONJ surgical therapy**

Deep neck space infections (2 patients) were successfully managed with extraoral incisions, pus drainage and antibiotic therapy. The cases of rhinosinusitis were resolved with the removal of necrotic bone as an inducing factor and conservative therapy (nasal decongestants and corticosteroids). Only in one patient with orbital cellulitis a functional endoscopic sinus surgery with middle meatal antrostomy and ethmoidectomy was necessary. The

orbital infection was managed without necessity of other surgical approaches into the orbit and complete healing with no functional morbidity was achieved only by antibiotic therapy. Two residual cysts adjacent to MRONJ lesions were removed (extirpated) concomitantly with a MRONJ surgery. Surgical treatment of 28 MRONJ lesions (87.5%) was performed under local anesthesia and in remaining 4 cases (12.5%) under general anesthesia. A mylohyoid flap and a buccal fat pad flap were used in 9 and 4 cases respectively (in 3 cases to cover the oroantral communication) (Fig. 3). The pathological mandibular fracture was managed with a necrotic bone removal and



**Fig. 3.** Two-layers wound closure with buccal fat pad flap to cover oroantral communication in the patient from Fig. 1.



**Fig. 4.** Reconstruction plate prebended on the patient-specific model of the mandible.

a load-bearing osteosynthesis from an intraoral and sub-mandibular approach. A mandibular reconstruction plate as an osteosynthesis device was used. It was prebended on the individual jaw model created by 3 D printer using patient's CT data (Fig. 4). A complete healing (the achievement of complete mucosal closure) was observed in all patients (100%), in 9.4% of cases (n=3) by secondary intention in the mean period of 6 weeks. No second surgery to achieve complete healing was necessary. The rest of the lesions (n=29; 90.6%) healed by primary intention in two weeks. Further course was uneventful. The mean follow-up was 20.5 months.

## DISCUSSION

Patients receiving antiresorptive medication (bisphosphonates, denosumab), anti-angiogenic drugs (e.g. bevacizumab, aflibercept) and tyrosine kinase inhibitors (e.g. sunitinib, imatinib) are at the risk of development of MRONJ (ref.<sup>4</sup>). The concurrent use of these agents with or without additional immunosuppressants may increase the odds for emergence of these lesions, shorten the latency period and also contribute to more serious clinical course of this disease<sup>3,4,9</sup>.

The risk of MRONJ emergence is mostly dependent on the type of antiresorptive drugs, route of administration, dosage and duration of treatment<sup>10</sup>. When compared to cancer patients receiving high-dose regimens of antiresorptive therapy, the risk of MRONJ for patients with osteoporosis exposed to medications of low doses is about 100 times smaller<sup>4</sup>. The prevalence of MRONJ in osteoporotic patients treated with oral bisphosphonates was reported up to 0.1% with an increasing tendency for more than 4 years of drug exposure<sup>11</sup>. Patients who are under treatment with corticosteroids and/or immunosuppressants may have a higher risk for developing MRONJ even if the bisphosphonates duration is less than 4 years<sup>3</sup>. The prevalence associated with zoledronate or denosumab treatment in osteoporotic patients was reported 0.017% and 0.3% respectively<sup>12,13</sup>. Although MRONJ is a rare disease in osteoporotic patients, the real number of affected patients appears to be higher than the published incidence, which is best explained by large population of osteoporotic patients exposed to antiresorptive agents. Furthermore, the number of osteoporosis patients is steadily enlarging.

The pathogenesis of MRONJ is probably multifactorial and it has not yet been fully clarified. None of the known etiopathogenetic factors itself is able to explain the emergence of these lesions. The main pathogenetic mechanism is a drug-induced disturbance of bone homeostasis caused by afflicting cells of a monocyte-macrophage lineage<sup>9</sup>. It results in decrease of bone re-modeling (an impairment of physiological repair of the jaw bone) and inhibition of local bone defence mechanisms against infection. Trauma to the bone or soft tissue (oral surgery, dental implants, ill-fitting dentures) and infection caused by oral microorganisms (e.g. marginal and apical periodontitis) are considered as the major risk factors of MRONJ (ref.<sup>5</sup>). The oral mucosal cytotoxicity, infection-related pH-changes increasing cytotoxicity of bisphosphonates and their release from the bone and anti-angiogenic effect of some of drugs may also contribute to MRONJ pathogenesis<sup>4,14</sup>. Various concomitant risk factors have been published to date with varying degree of significance indicating that this issue is not yet well understood<sup>15</sup>. Only an immunodeficient state of patient was monitored as the main concomitant risk factor in this study (e.g. immunosuppressive medication, diabetes mellitus etc.).

According to the largest systematic review of 680 MRONJ cases in osteoporotic patients, these lesions mainly affected women (93.5%, male to female ratio 1:14.4) and the mean age of patients was  $69.7 \pm 5.2$  years<sup>3</sup>. Bisphosphonates were administered mainly orally in 86.7% of cases and the most often received drug was alendronate (72.6%). A combination of more than one type of antiresorptive agent was reported only in 4% of cases. Corticosteroids or immunosuppressants were the most common concomitant medications in MRONJ. The bisphosphonates treatment was typically long term with the average duration of intake  $51.9 \pm 18$  months. The most common initiating event was tooth extraction (48.5%). Lesions occurred most frequently in the mandible (70.6%),

followed by maxilla (27.2%) and both jaws (2.2%) and were most often classified as stage 2 (50.5%) (ref.<sup>3</sup>).

In the present study, there was a slightly higher age of affected patients and a significantly higher proportion of patients were treated with more than one type of antiresorptive agent (42.3% versus 4%). A smaller proportion of patients received bisphosphonates orally (65.4% versus 86.7%) and a longer latency period was identified ( $73.1 \pm 38.0$  months versus  $51.9 \pm 18$  months). Other characteristics were consistent with the referred study.

Treatment options for MRONJ are still under debate. There is a lack of well-designed, prospective, randomized clinical trials and no evidence-based guidelines are available<sup>16</sup>. When evaluating the outcomes of MRONJ treatment, conservative therapy leads to complete healing in only a small percentage of cases (18-23%) (ref.<sup>17,18</sup>). A very low likelihood of resolving of these lesions is especially in advanced disease (stage 3) (ref.<sup>5</sup>). The outcome of a predominantly long-lasting healing process is difficult to predict. With increasing experience over the last ten years, more evidence has emerged to support the surgical approach as the most effective management of MRONJ in terms of complete healing. The success rate 59-100% was reported, with mostly more than 90% in recent years<sup>19-27</sup>.

Some authors still recommend surgical treatment only for the higher symptomatic stages of the disease or in cases of conservative therapy failure<sup>8</sup>. But surgery seems to be effective for the treatment of MRONJ at any disease stage. It also offers the best condition for healing regardless of the type of a drug that induced osteonecrosis of the jaws<sup>28-30</sup>. Based on these findings and considering life expectancy of osteoporotic patients, surgical therapy should be the first choice for all MRONJ stages with the aim of complete healing. In addition, better outcomes are achieved compared to cancer patients<sup>31,32</sup>. Some authors reported relatively good effect of the conservative therapy of MRONJ in osteoporotic patients, but particularly early stages were included<sup>33</sup>. In contrast, the surgical therapy usually achieves shorter healing period, better predictability and success rate even in advanced disease. Surgery should be indicated as an early treatment to prevent complications and progression of lesions<sup>34</sup>. A bacterial embolism in the internal jugular vein after a MRONJ-induced submandibular abscess resulting in bacterial sepsis, multi-organ failure syndrome and death in an osteoporotic patient receiving alendronate was published in the literature<sup>35</sup>. It should be noted that this is a rare complication.

The surgery should preserve viable bone and soft tissues as much as possible. In our opinion and according to some other authors, no preventive extension with safety margins is necessary<sup>5</sup>. Distinguishing between viable and necrotic bone is challenging and intraoperative visualization of fluorescent patterns of viable and nonviable bone (fluorescence-guided surgery) may improve surgical outcomes<sup>27</sup>. It requires an experienced surgeon familiar with this technique. Viable bone shows bright greenish fluorescence during this examination, while necrotic bone has none or only pale fluorescence. A reddish fluorescence is associated with a bacterial colonization or infection of

nonvital bone and is not conditioned by a doxycycline exposure<sup>27</sup>. Various protocols of doxycycline administration have been published including a single intravenous drug administration<sup>24</sup>. In addition, auto-fluorescence-guided bone surgery probably shows comparable success rates to tetracycline fluorescence-guided surgery<sup>36</sup>.

A wound closure in two layers, which is very feasible only in the distal areas of both jaws, is beneficial. The mylohyoid flap and buccal fat pad flap are reported as the procedures of choice in this indication<sup>37,41</sup>. In our experience, the buccal fat pad flap is preferred in all large lesions of osteonecrosis in the premolar and molar maxillary area, not only to cover oroantral communication. This low-risk and high-yield approach promote the healing process by a rich vascularization of the flap and an abundant source of adipose-derived adult stem cells<sup>37,40</sup>. The two-layers wound closure provides low failure rates of mucosal coverage and also mechanic protection of the affected area for possible rehabilitation by removable prosthesis. Another advantage is minimal donor site morbidity.

There is no evidence that a drug holiday facilitates healing in surgical sites and safety of this approach as well as optimal timing have not been verified<sup>5</sup>. Even though some physicians recommend an interruption of antiresorptive treatment. According to pharmacokinetic properties of denosumab, which has a reversible effect on bone remodeling, drug holiday could have some respond in terms of better healing<sup>4,5,42</sup>. Considering the dosing of denosumab (60 mg every 6 months) in osteoporotic patients, the surgical therapy of MRONJ is possible without disturbing the drug administration cycle (i.e., in the middle of the cycle).

## CONCLUSION

The presented protocol for surgical therapy is effective in the management of all MRONJ stages in osteoporotic patients. The surgery is indicated as an early treatment to prevent complications and the progression of lesions. It leads to an improvement in the quality of life and it offers the option of resuming antiresorptive treatment if interrupted.

**Author contributions:** LH, JJ: manuscript writing; LH, MCH, SR, PP: data collection, data analysis; LH, JJ: study design; LH, DH, VV: final approval.

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