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Research Article

Surgical Management of Medication Related Osteonecrosis of the Jaws in Oncological Patients

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Abstract

Background: Current treatment of patients diagnosed with Medication-Related Osteonecrosis of the Jaw (MRONJ) varies from conservative approaches to surgical intervention. Although surgical treatment is widely accepted, the benefits of extensive surgical approach in treating MRONJ cases remain controversial.

Aim: The aim of this study was to evaluate the effect of standardized radical surgical therapy for medication-related osteonecrosis of the jaw stages II and III in cancer patients.

Methods: Sixteen patients, with 17 MRONJ sites stages II (n = 12) and III (n = 5) were included in this study. All patients were diagnosed with predisposing malignancies treated by intravenous application of bisphosphonate or antiresorptive (denosumab) therapies. Surgical intervention was planned with respect to the patient's general health status and life expectancy and consisted of complete resection of the necrotic bone with safe margin. The mean follow-up time was 23 months.

Results: 88% of osteonecrosis sites were treated successfully, with complete mucosal healing and lack of clinical and radiological symptoms.

Conclusions: The results of the present study support radical surgical therapy for MRONJ stages II or III. A detailed clinical decision-making protocol is also presented.

Keywords: *MRONJ; Cancer Patients; Bone Resection; Surgical Protocol*

Introduction

Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) refers to exposed bone in the maxillofacial region lasting for more than 8 weeks in patients receiving bisphosphonates (BPs) without exposure of the craniofacial region to radiation therapy [1,2]. BRONJ was first described by Marx in 2003 [1], yet in light of the increased incidence of maxillary and mandibular osteonecrosis related not only to BPs but also to other antiresorptive agents such as denosumab and antiangiogenic drugs, in 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended changing the nomenclature from "bisphosphonate-related osteonecrosis of the jaw (BRONJ)" to "medication-related osteonecrosis of the jaw (MRONJ)". MRONJ development depends on several factors including systemic and local factors of the individual, type of administrated agent, dosage, length of administration, and mainly administration route [3].

Despite a clear clinical classification of MRONJ staging [3] published in an attempt to standardize the appropriate therapeutic modality for each case, there is no standardized protocol for its treatment. Depending on the stage and severity of MRONJ, current management varies; the conservative approaches include mainly long-term antibiotics, mouth rinses, sequestrectomy, hyperbaric oxygen [4] and the use of leucocyte-and platelet-rich fibrin [5-7] while radical surgical techniques include jaw resection with or without microsurgical reconstruction [8,9].

Depending on symptoms of the patients and their overall performance status, surgical intervention for MRONJ stage III is an accepted approach; however, the extent of surgery and bone margins to be resected are still debatable. Moreover, the recommendations for surgical treatment of MRONJ stage II are still somewhat vague. Although several publications [10-14] have advocated extensive surgical intervention, the debate regarding surgical management of cancer patients with concomitant MRONJ becomes even more controversial in view of the underlying disease. When treating an oncologic patient with concomitant MRONJ lesions, the clinician must aim to improve quality of life by controlling pain, infection, and the progression of bony necrosis.

Aim of the Study

The current study therefore aimed to evaluate the results of a surgical approach consisting of bone resection with safe margins in combination with a standardized antimicrobial protocol, and to present exclusive surgical guidelines for treating cancer patients with MRONJ stages II and III.

Patients and Methods

This study was designed as a retrospective case study. For a standardized cohort population, the inclusion criteria included: (1) IV therapy for an underlying malignant disease with bisphosphonates or antiresorptive agents such as denosumab or antiangiogenic drugs for at least 1 year, (2) patient's life expectancy of at least 2 years from the time of MRONJ diagnosis and physical ability to withstand a surgical procedure, and (3) minimum follow-up of 6 months after surgical therapy.

16 cancer patients with 17 MRONJ sites stages II and III, treated in the Oral and Maxillofacial Surgery Department of Baruch Padeh Medical Center between 2014 and 2017, were included in this study.

Upon patient admission, full medical history was revised and complete extraoral and intraoral examinations were performed, as well as panoramic radiographs and three-dimensional radiographic examination (CT scan) to determine the extent of bone involvement. Subsequently, the MRONJ stage was determined and surgical treatment was planned, including the extent of the required bone removal. A thorough consultation with the patient's oncologist regarding overall prognosis and life expectancy was undertaken, with emphasis on the extent of surgery and the planned anaesthesia. Patients with poor prognosis (< 2 years survival) were excluded from the study (as presented on flow chart protocol, figure 1). Drug holiday from the antiresorptive agents was not recommended unless the oncologist stated otherwise. Patients were treated under local or general anesthesia according to the extent of the required bone removal, reconstruction and general health. All patients were covered by a preoperative loading dose of Amoxicillin Clavulonate followed by a post-operative course of 4 weeks. Clindamycin was used in cases of Penicillin allergy.

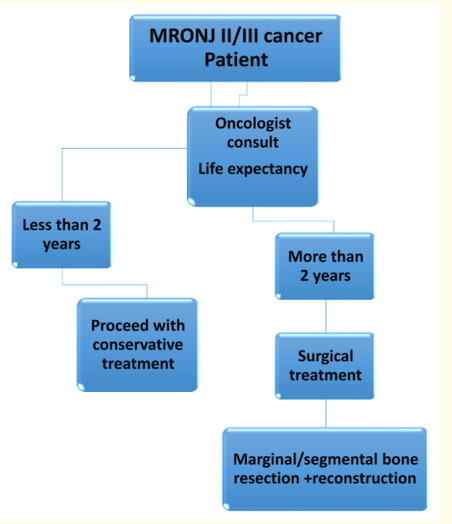

Figure 1: *Proposed treatment protocol for cancer patients suffering from MRONJ stages II and III in this study.*

Surgical procedure

Surgery consisted of the resection of all infected and necrotic bone, including a margin of normal surrounding bone. Resection margins were determined by the clinical appearance of bleeding bone and the extent of the necrotic bone as seen on computed tomography scans and on OPG panoramic radiographs. Teeth/implants in conjugation to the necrotic site were extracted/removed regardless of their prognosis (Figure 2 and 3). Three of our patients, who suffered from pathological fractures or extension of the necrosis to the inferior border of the mandible (Figure 2), were treated via segmental osteotomy with immediate reconstruction.

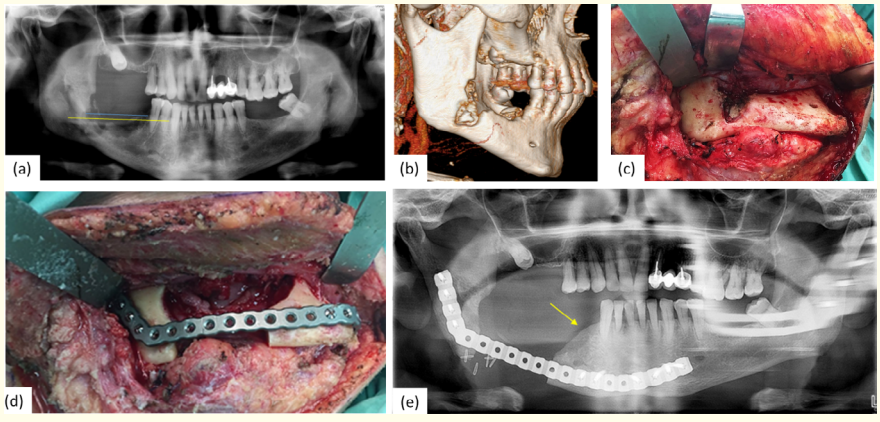

Figure 2: *Mandible continuity resection for treatment of MRONJ stage III. (a) Dental panoramic radiograph of the lesion. Note the borders of the osteolytic site marked by the blue line. The yellow line represents the "safe" surgical margin to be resected (teeth included). (b) Computed Tomographic 3-dimensional reconstruction demonstrating extensive destruction extending to the ascending ramus and inferior border of the mandible which mandates segmental mandibulectomy. (c) The lesion as seen intraoperatively, via cervical approach. (d) Intraoperative photograph following segmental mandibulectomy and reconstruction with a 2.4 titanium reconstruction plate. (e) Postoperative dental panoramic radiograph of the surgical site. Note smoothening of all sharp bony edges and of extraction sockets (yellow arrow) required to minimize the risk of perforation of the thin overlying mucosa.*

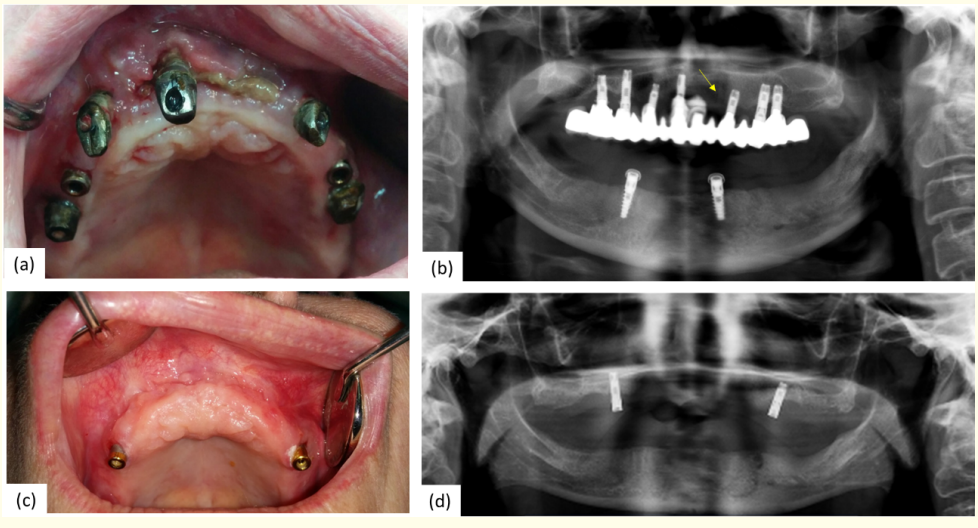

Figure 3: *Clinical example of peripheral bone resection for the management of MRONJ stage II. (a) Clinical photograph on initial diagnosis of maxillary MRONJ with exposed necrotic bone surrounding dental implants. (b) Radiographic findings corresponding to the clinical photograph (yellow arrow depicts osteolytic lesion). (c) Postoperative intraoral picture, taken 15 months postoperatively with no signs of MRONJ. (d) Panoramic radiograph 15 months postoperative showing bone defect and removal of conjugated dental implants.*

Extraction sockets were reduced in height, and sharp bony edges smoothed to reduce the depth of the bony defect and facilitate soft tissue coverage over the surgical site, as described by Markose., *et al* [10]. All mucoperiosteal flaps were designed with a large basis from the vestibulum in order to ensure a passive, tension-free wound closure. Local soft tissue flaps were utilized as buccal fat flaps (Cases No. 7 and 10, table 1) (Figure 4) in appropriate cases.

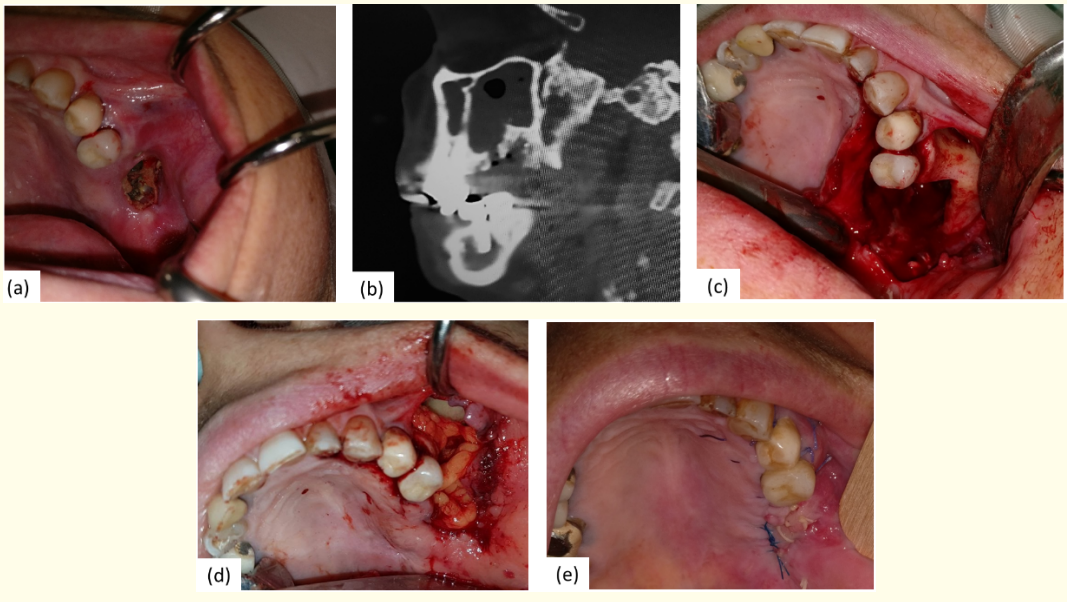

Figure 4: *MRONJ stage III of the left maxilla: (a) Clinical appearance at initial diagnosis of MRONJ with exposed necrotic bone in the left maxilla. (b) Sagittal computed tomography with extensive osteolysis extending to the maxillary sinus. (c) Intraoperative picture after resection. (d) Closure of the surgical site utilizing the buccal fat pad. (e) Healing of the surgical site two weeks postoperatively shows excellent site closure.*

Surgical sites were sutured with either long-term resorbable sutures (Ethicon Coated Vicryl) or non-resorbable sutures (ETHILON Nylon Suture). All patients were prescribed 0.2% Chlorhexidine Gluconate mouthwash (UK, Nottingham) postoperatively for a month.

Bone specimens of each site were sent for histopathological analysis in order to rule out metastatic disease to the jaws.

Gastric feeding tubes for 5 days were placed for patients undergoing mandibular/maxillary resection with Reconstruction Plate or obturator (Cases No. 4, 6, 12, 13, 14, table 1).

Patients were examined at 1 week, 2 weeks and on a monthly basis for 3 months postoperatively. Patients were then followed on 3 monthly intervals and asked to contact the clinic in-between visits if they felt any discomfort. Success of the surgical procedure was based on clinical signs (lack of pain, swelling, non-healing mucosa with exposed necrotic bone, and/or fistulas with connection to the bone), radiographic examination of OPG panoramic radiographs conducted routinely post operatively, and on patient experience.

Patients were instructed to avoid wearing their dentures for at least 2 months postoperatively, after which dentures were either re-lined or replaced. Patients and treating dentists were advised of the importance of routinely examining the dental prosthetic appliances and make adjustments accordingly.

Results were evaluated as a modification of Bodem., *et al.* [13] (1) successful treatment/absolute healing (complete mucosal healing and lack of clinical and radiological signs - no exposed necrotic bone, no residual mucosal defect and no fistulas) or (2) unsuccessful treatment resulting in no healing (regression to MRONJ stage III/no change in stage/recurrence of clinical signs of MRONJ).

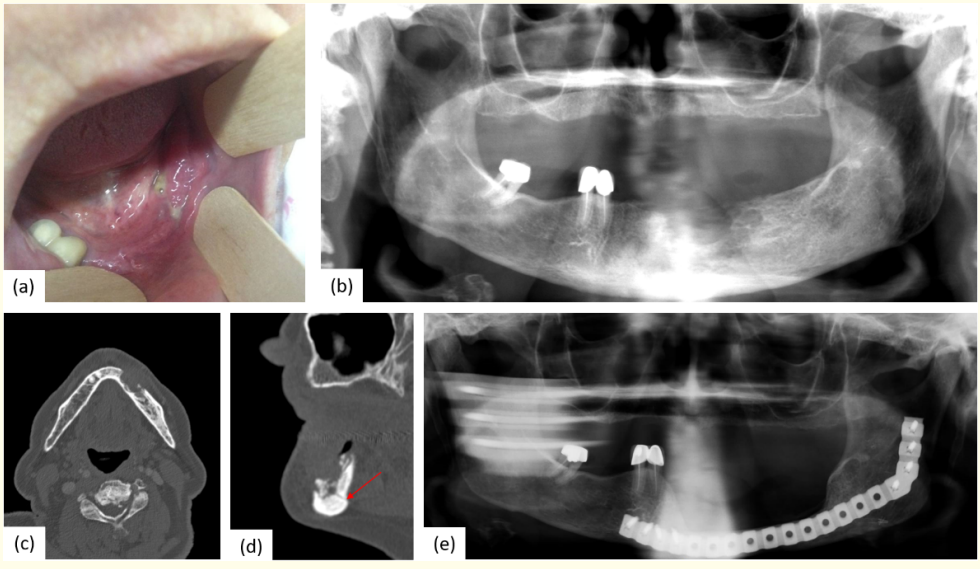

Figure 5: *Marginal mandibulectomy for treatment of MRONJ stage III. (a) intraoral photograph showing infection with active pus discharge. (b) an example how plain film (panoramic X-ray) can mislead in diagnosis of MRONJ- the X-ray does not exhibit pathologic fracture and the true extent of the lesion which is shown in the CT –(c)+(d). (e) Note marginal mandibulectomy and reconstruction with a 2.4 titanium reconstruction plate.*

Results

18 patients were included in the preliminary cohort. Two patients were excluded from the study and treated conservatively due to poor prognosis of their underlying malignant disease.

16 cancer patients with 17 MRONJ sites, stages II and III were surgically treated in this study. The mean age was 66.5 ± 9 years, including 8 males with a mean age of 69.1 years and 8 females with a mean age of 64 years (Table 1).

Twelve sites were classified as stage II, and 5 as stage III according to the AAOMS system. 53% (n = 9) of patients were female and 47% (n = 7) male. As expected, 29% (n = 5) of MRONJ sites were located in the maxilla and 71% (n = 12) in the mandible. 70% of MRONJ lesions developed spontaneously with no preceding surgical procedure. Mean follow up time was 23 ± 12 months.

15 (88%) of the 17 MRONJ sites were treated successfully, with complete healing. 14 (82%) of our 16 patients stated a significant improvement in their quality of life due to resolution of pain, halitosis and disturbance while eating following the first postoperative period.

Treatment was unsuccessful in 2 mandibular MRONJ sites (12%) – both initially staged as MRONJ stage II (Table 1).

In all cases, histopathological analysis of the bone specimens demonstrated no metastatic disease to the jaws.

Discussion

In this study, we have assessed the outcome of extensive surgical treatment of MRONJ in cancer patients. With adherence to our protocol, we successfully treated 88% of the MRONJ sites. Moreover, 82% of our patients stated a significant improvement in their quality of life due to resolution of pain, halitosis and discomfort while eating.

There is still a great debate concerning conservative approaches versus surgical treatment for the management of MRONJ lesions. Marx [1] indicated that there is no known resolution for the drug-induced avascular necrosis of bone. Marx has moreover expressed his concern

regarding surgical treatment, as extensive operations might lead to further necrotic bone exposure. Despite Marx's concerns, several publications [10-14] have advocated surgical intervention for the management of MRONJ. In a retrospective study conducted by Coropciuc., *et al.* [7], conservative treatment and minimally invasive surgery were found to be effective up to MRONJ stage II in oncological patients. Finally, a recently published meta-analysis [15] concluded that contrary to recommendations for the prevention of MRONJ, surgical intervention does not result in high rates of recurrence and, in fact, may result in better treatment outcomes compared with nonsurgical interventions. In light of the literature there was a need to establish a clear clinical protocol involving radical surgical management of cancer patients with MRONJ stages II and III. We therefore suggest the following protocol: After diagnosing a cancer patient with MRONJ stages II or III, and following a thorough consultation with the treating oncologist, life expectancy is to be determined. Next, adequate surgical planning is essential. Since the clinical manifestations do not usually correlate with the actual extent and severity of MRONJ, the extent of bone to be resected is determined based on three-dimensional imaging of the site. We argue that at the time of MRONJ diagnosis, the site of necrotic bone is already progressing and thus has to be managed properly to prevent deterioration [16]. Therefore, early surgical intervention by experienced surgeons should be encouraged, while debridement is not sufficient as a sole treatment. In order to insure successful surgical outcomes, the following key parameters should be addressed:

1. The extent of bone to be resected is to be determined on OPGs and CT scans, and include safe margins from the necrotic site. Teeth or implants in conjugation with the necrotic site are to be extracted (Figure 2 and 3).
2. No sharp bone margins are to be left; smoothing all sharp bony edges (Figure 2), including extraction sites, is of major importance in minimizing the risk of perforation of the thin mucosa.
3. Maximal tension-free, soft tissue coverage is mandatory. Inspection of the soft tissue and design of the flap for suitable bone access and for appropriate coverage is essential prior to the surgical procedure. If deficiency of soft tissue is to be expected, local soft tissue flaps should be applied, mainly buccal fat pads (Figure 4), buccal advancement flaps, or nasolabial flaps.
4. Placement of Reconstruction Plates should be considered even when marginal mandibulectomy in non-atrophic mandibles is performed, for 2 reasons: first, to assist with load sharing and second, to enable fast resection if required, in case of MRONJ recurrence or aggravation.
5. Microvascular flaps should be considered whenever segmental mandibulectomy is planned, as was presented by Sacco., *et al.* [8] and later on by Spinelli., *et al* [9].

In line with previously published data [17] reporting MRONJ to be more prevalent in the mandible (73%) than the maxilla (22.5%), 71% of our MRONJ cases were located in the mandible and 29% in the maxilla. Two mandibular lesions were treated initially unsuccessfully. Although it was postulated [15] that mandibular MRONJ is more common due to the mandibular bone's relatively low vascularity along with a diminished ability to heal, we believe that in our cohort, the sites did not heal properly due to nonsufficient resection of bone. Indeed, repeating the surgical procedure with extended margins resulted in no recurrence of MRONJ during the follow-up period.

According to the AAOMS position paper (2014) [3] although a small percentage of patients treated by antiresorptive agents develop osteonecrosis of the jaw spontaneously, the majority of MRONJ cases occur as a complication following dentoalveolar surgery. Interestingly, most patients in this study (70%) developed MRONJ lesions spontaneously. This emphasizes the importance of regular dental follow-ups for cancer patients receiving antiresorptive agents.

Although MRONJ cannot be fully prevented, the AAOMS position paper [3] states that dental screening before initiating antiresorptive therapy reduces the risk of jaw osteonecrosis. Effective prevention requires a multidisciplinary approach with an intensive cooperation among general practitioners, oncologists, craniomaxillofacial surgeons and dentists.

The main limitation of this paper is its retrospective nature. Of course, further prospective randomized clinical trials are needed to determine in a higher level of reliability that surgery is the main therapeutic protocol to manage oncological patients suffering from MRONJ stages II and III.

MRONJ compromises quality of life due to pain, intraoral and extraoral fistulas, halitosis, discomfort while eating and frequent consultations with the maxillofacial surgeon. Complete healing of 88% of the MRONJ sites was achieved in our cohort. Thus, successful healing

following appropriate surgical procedure implies an improved life quality for our patients. Moreover, successful surgical procedure leads to shortened periods of analgesics and antibiotics consumption, resulting in less medication-associated side effects (including less bacterial resistance) and a further improvement of life quality.

Conclusions

The results of the present study support radical surgical management with adequate soft tissue coverage for MRONJ stages II and III in cancer patients.

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