Medication Related Osteonecrosis Of The Jaws

Experience of a surgical treatment center

A dissertation presented

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Because the main aim of all of us is to learn from the better practice and positive experience and to improve ourselves and there is no better tool for doing so than research

Introduction

This thesis aims to illustrate the research activity carried out during the PhD course.

This effort is the ending product of a series of different projects activity and research studies conducted over the past three years at the Oral Surgery Unit of the Department of Dentistry of the University of Messina.

Our research group is studying the Medication-Related Osteonecrosis of the Jaws (MRONJ) with a focus on the surgical treatment of the disease and aim to develop new therapeutic strategies to overcome failures and recurrence and improve patient care.

Never forgetting that a considerable part of our work is concentrated on the patient's quality of life.

Our objective is also to examine the potential culprits in the pathophysiology of MRONJ using epidemiological data contributing to the growing knowledge in the field of MRONJ prevention and treatment.

The two pathways work in tandem to explore the etiological underpinnings of MRONJ and move towards transforming those findings into MRONJ treatments.

Therefore we will examine the different performed studies, mainly observationals, both on prevention and treatment of MRONJ because personalized care can only come from a thought understanding of individual risk factors.

Early predictors of outcome reflect long-term prognosis and support clinical decision-making.

While there is a risk of MRONJ with bone-modifying agents, this should be considered in relation to the benefits of treatment on the patient's quality of life.

Bearing in mind that the best therapeutic approach is identified through the integration of patient, primary physician and oral surgeon assessments and the application of a combined paradigm that allows to tailor prevention and treatment strategies for each of our MRONJ patients.

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Background and definition

In 2003, Marx reported the first case of osteonecrosis of the jaw in 36 cases related to zoledronic acid or pamidronate. Painful bone exposure in the mandible or maxilla unresponsive to medical or surgical management was observed [1].

This causal association was cautiously denied in a letter by Tarassof and Csermak representing Novartis, given the fact that no such reports had occurred in multiple, well-controlled clinical trials of more than 3000 cancer patients that had been conducted as far back as the early 1990s [2].

During 2004, Novartis, manufacturer of pamidronate (Aredia) and zoledronic acid (Zometa)—two IV BPs—labeled this product as at risk for osteonecrosis of the jaws (ONJ) [3].

Consequently, the subsequent year a warning followed for all BP drug class to be at risk for ONJ, which was renamed as bisphosphonate-related ONJ (BRONJ) [4].

In the 2009 a Special Committee appointed by the Board of the American Association of Oral and Maxillofacial Surgeons (AAOMS), published a Position Paper and defined this pathological condition as BRONJ (Bisphosphonate-Related Osteonecrosis of the Jaws) a condition of exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks in patients who have received or

are receiving treatment with bisphosphonates and have no history of radiation therapy of the jaws [5].

In 2014, the AAOMS updated the Position Paper by changing the definition on the basis of the gained knowledge in this field and revising the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ) acknowledging that this pathological condition could be related to an increasing number of other drugs [6].

However, the nomenclature concerning this pathology has been subject of further debate following the recognition of the non-exposed clinical variant [7,8].

The current definition recommended according to the Italian Association of Maxillofacial Surgery,(SICMF), and Italian Association of Oral Medicine and Pathology (SIPMO), working group is the following: “adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment”[9].

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Chapter 1: Medication related osteonecrosis of the jaws

Epidemiological notes

MRONJ incidence in patients who are prescribed oral bisphosphonates for the treatment of osteoporosis is low ranging from 0.01% to 0.07% [1].

It is worth mentioning in this regard the patients assuming denosumab 60 mg (Prolia®) for the prevention and treatment of the cancer induced bone loss for which there are no consolidated data about MRONJ incidence [2].

In cancer patients the incidence of MRONJ range from 1.2 % to 9.9 % in patients exposed to the antiresorptive medications Zometa® and Xgeva® prescribed to prevent skeletal-related events associated with solid tumors-related bone metastases and with lytic lesions associated to multiple myeloma and reach the 15-20% in some case series[3-6]; since they are probably contemporaneously exposed to a high number of MRONJ risk factors [7-9].

ONJ incidence in this particular setting may be influenced by the malignancy type/severity, immunodeficiency as well as by the assumption of other drugs that may impact bone health, such as glucocorticoids therefore the oncologic setting appears to be very peculiar compared to other clinical conditions involving the skeleton.

MRONJ incidence increases with increasing duration of exposure to antiresorptive agents, confirming the known dose-dependent fashion [10,11].

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Chapter 1: Medication related osteonecrosis of the jaws

Diagnosis and patient identification

MRONJ is a pathological condition that can remain asymptomatic for weeks or months and then cause symptoms of itself as a result of secondary infections or in the case of trauma to neighboring soft tissues or caused by the irregular surface of the bone exposure.

Typical clinical manifestations are:

- Appearance of exposed bone in the oral cavity. The size of the exposed bone in MRONJ can range from a few millimeters to several centimeters.
- Intra and / or extra-oral fistula from which it is possible to probe until the underlying necrotic bone is reached.
- Absence of bone exposure or fistula formation. These cases are identified only through instrumental diagnostics.

The vast majority of patients present with localized bone disease, which is often painful and infected [1].

The anatomical site can be unilateral or bilateral with 63-68% affecting only the mandible, 24-28% of cases affecting only the maxilla and 4.2% of both maxillaries [2].

Commonly recorded signs are: halitosis, odontalgia sine causa, odontogenic abscess, purulent discharge, mandibular asymmetry, lack of post-extraction alveolar mucosa repair, rapid onset dental mobility, impaired mobility of the jaw with or without preserved occlusion, intra-oral mucosal fistula, extra-oral fistula, paraesthesia / dysesthesia

of the lips, leakage of fluids from the nose, spontaneous seizure of bone fragments, trismus and soft tissue swelling [2,3].

A lot of patients appear to show clinical manifestations of a more severe advanced form of MRONJ which includes: extension of necrosis and infection to the lower margin of the mandible and / or branch of the mandible, extension of necrosis to the maxillary sinuses or zygomatic bones; this involves severe facial pain, sinusitis, pathological fractures and oro-antral and / or oro-nasal communication [1].

Patients with MRONJ are evaluated radiologically, both with 1st level radiographic examinations (orthopantomography), and with 2nd level radiographic examinations (CT).

Radiographic alterations, on orthopantomography and intraoral radiographic examinations, in the early stages are not always evident until there is significant bone involvement [3].

Late radiographic changes can simulate classic periapical inflammatory lesions or osteomyelitis [2].

Other radiographic findings include enlargement of the periodontal ligament space or osteosclerotic lamina dura [3].

In cases of extensive bone involvement, necrosis can be highlighted as an area of spotted bone similar to that of diffuse osteomyelitis. In cancer patients some of these changes may raise the suspicion of myeloma or metastatic bone lesions [3].

The currently adopted staging system recommended by the Italian Society of Maxillofacial Surgery (SICMF) and the Italian Society of

Pathology and Oral Medicine (SIPMO) is both clinical and radiological [4].

The stage is determined on the radiological extent of the disease while the symptoms, pain and inflammation / infection, are used to distinguish between symptomatic and asymptomatic forms of MRONJ within the same stage; thus avoiding the continuous passage of stage of patients with MRONJ in which we witness, as a consequence of the cyclical exacerbations of the infectious process and the pain associated with it; furthermore, this distinction helps to better define the therapeutic needs of patients.

Stage 1

Focal MRONJ: In the presence of at least one minor clinical sign and with bone thickening on CT limited to the dentoalveolar process of the jaws only, with or without other early radiological signs.

1a Asymptomatic

1b Symptomatic (presence of pain and / or suppuration)

Minor clinical signs and symptoms: halitosis, odontogenic abscess, mandibular asymmetry, odontogenic and bone pain, bone exposure, mucosal fistula, failure to repair the post-extractive alveolar mucosa, rapid onset dental mobility, paraesthesia / dysesthesia of the lips, purulent discharge, seizure spontaneous bone fragments, trismus, soft tissue swelling.

CT signs: trabecular thickening, focal medullary osteosclerosis, with or without thickening of the alveolar ridge and lamina dura, persistence

of the post-extraction alveolus, widening of the periodontal ligament space [4,5].

Stage 2

Diffuse MRONJ: In the presence of at least one minor clinical sign and with bone thickening on CT scan also extended to the basal process of the mandible or maxilla, with or without late radiological signs.

2a Asymptomatic

2b Symptomatic (presence of pain and / or suppuration)

Minor clinical signs and symptoms: halitosis, odontogenic abscess, mandibular asymmetry, oral pain, bone exposure, mucosal fistula, unhealed post-extractive socked, rapid onset of tooth mobility, paraesthesia / dysesthesia, purulent discharge, spontaneous expulsion of bone fragments, trismus, soft tissue swelling.

CT signs: diffuse osteosclerosis, with or without oro-antral and oro-nasal fistula, thickening of the alveolar canal, periosteal reaction, sinusitis [4,5].

Stage 3

Complicated MRONJ: In the presence of one or more of the following minor clinical signs and with bone thickening on CT also extended to the basal process of the mandible or maxilla, with or without late radiological signs.

3a Asymptomatic

3b Symptomatic (presence of pain and / or suppuration)

Minor clinical signs and symptoms: extraoral fistula, fluid leakage from the nose, preternatural mobility of the jaw with or without preserved occlusion.

CT signs: cutaneous fistula, pathological fracture, extensive osteolysis of the maxillary sinus, osteosclerosis of the jawbone and / or hard palate [4,5].

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Chapter 2: Quality of Life of MRONJ patients

Preparatory and initial phase was identification of the cohort of MRONJ patients and / or patients at risk of developing MRONJ to be examined and recruited for further investigation.

This objective was addressed through a retrospective analysis of the data available at the Department of Oral Surgery of the University of messina which since 2007 is a referral center for prevention and treatment of MRONJ.

This chapter reviews a critically important aspect that a researcher and a clinician has to evaluate that is the extent to which the disease impacts a patient's quality of life and whether investigating the condition has any point and the reason why it is important for us all to consider it.

Chapter 2: Quality of Life of MRONJ patients

Treatment of Medication-Related Osteonecrosis of the Jaw and its Impact on a Patient's Quality of Life: A Single-Center, 10-Year Experience from Southern Italy

Introduction

Medication-related osteonecrosis of the jaw (MR-ONJ) is a serious side effect initially described for intravenous and oral use of bisphosphonates (BPs) for the treatment of bone-resorptive oncologic

pathologies (e.g. multiple myeloma and bone metastases) and long-term treatment of dysmetabolic bone diseases (e.g. osteoporosis), respectively [1].

MR-ONJ has also been described as a complication of different monoclonal antibodies, such as denosumab, an antiresorptive agent used as alternative treatment to BP, and bevacizumab, a novel antiangiogenic cancer therapy [2].

Recently, the American Association of Oral and Max- illofacial Surgeons (AAOMS) provided an updated defi- nition of MR-ONJ as an area of exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks, occurring with current or previous treatment with antiresorptive or antiangiogenic agents and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws [3].

To date, no official guidelines are available for the management of patients with MR-ONJ; the existing clinical management is the result of position papers and the experience of clinical centers [3–9].

Since MR-ONJ affects both general health and patients' quality of life (QoL), epidemiological data regarding dental health and morbidity are of primary importance for a proper clinical evaluation. In addition, QoL significantly decreases with worsening MR-ONJ. Although this impairment may influence clinicians' decisions regarding treatment, to date only a few published studies have eval- uated QoL in relation to MR-ONJ [10, 11].

In general, the administration of QoL measurement instruments at first examination and at follow-up allows the identification of key clinical components necessary to assess the comparative value of therapeutic interventions, putting the patient's needs at the center of the clinical process [12].

With respect to the treatment of MR-ONJ, one of the debated questions is whether surgery can offer an addi- tional benefit in the treatment of MR-ONJ compared with pharmacological treatment alone. MR-ONJ-related QoL is a valuable parameter to assess whether potential negative complications of surgery could outweigh the potential benefit of surgical treatment for MR-ONJ [4–9].

This study aimed to evaluate the changes in patients' MR-ONJ-related QoL after pharmacological treatment, with (or without) conservative osseous resective surgical treatment of a large cohort of patients with MR-ONJ from a single specialist center from southern Italy.

Methods

Routine Clinical Care

Patients are referred to the dental specialists at the Osteonecrosis of the Jaw Treatment Center, School of Dentistry, University of Messina, by their general practitioner. On arriving at the center, patients are diagnosed with MR-ONJ based on (a) clinical findings of MR-ONJ (e.g. exposition or probing of the necrotic bone); (b) drug history of current or previous treatment with antiresorptive and/or antiangiogenic

agents; and (c) dental X-ray exami- nations plus lower/upper jaw computed tomography (CT) scan suggestive of MR-ONJ (Fig. 1). Routine procedures include identification of anatomic location, and the number of exposed maxillary necrotic bone areas are described and evaluated. Possible etiology and the presence of potential oral/ dental triggers, such as periodontal surgery, dental extraction or implant placement, as well as sores related to denture use, are identified. The dental findings are then classified according to the Decayed, Missing, Filled Teeth (DMFT) Index [13]. Comprehensive periodontal evaluation (presence of inflammation, probing depths, and attachment loss) are assessed using the Community Periodontal Index of Treatment Needs (CPITN). To assign the score for the CPITN, the highest score for each sextant is recorded (code 0, 1, 2, 3, 4) and is assigned to one of four treatment need categories (score 0, I, II, III) [14]. All patients receive an orthopantomography and a CT scan to confirm the diag- nosis and to determine the extent of the MR-ONJ lesions [15]. MR-ONJ staging is categorized according to the updated AAOMS classification [3]. Patients are also clas- sified according to the Italian Society of Oral Medicine and Pathology (SIPMO) approach, based on the clinical find- ings and CT scan to assess the extent of bone disease, i.e. whether it is focal or diffuse [16].

In addition to thorough clinical evaluation, routine clinical practice within the center also involves a QoL assessment when the diagnosis of MR-ONJ is confirmed (T0) [5, 6, 17]. Patients are initially started on pharmaco- logical treatment, including treatment with topical

antibacterials, systemic antibiotics, and/or analgesics. QoL questionnaires are again administered 8–10 weeks after the initiation of pharmacological treatment (T1) to compare observed changes [18]. The clinical course of MR-ONJ after pharmacological treatment is divided into four categories: progressive, unchanged, partially resolved, and resolved [19]. The result of pharmacological treatment is defined as suc- cessful (partially resolved and resolved categories) if an improvement of the clinical manifestation, symptoms, and QoL in the explored fields is observed at follow-up. These patients are considered to have stable necrotic bone dis- ease and are included in a routine follow-up program [20]. Vice versa, patients were included in the unchanged and progressive categories if their clinical condition did not experience any benefit from pharmacological treatment or even worsened. In such patients, the indication for sur- gical treatment is evaluated, and surgery is performed in patients who (a) do not show any significant improvement after pharmacological treatment; and (b) are considered eligible for conservative surgery because of focal osteonecrosis. The appropriateness of surgery is discussed with a multidisciplinary team, including the chief oncol- ogist and/or primary care physician who advise the dental specialists if patients have a sufficient life expectancy to be eligible for surgery. If patients are eligible for surgery, they undergo conservative osseous resective surgery with primary wound closure [9]. Surgery consists of resection of all infected and necrotic bone using a piezoelectric device. and is combined with standardized perioperative adjuvant treatment [21]. In

the follow-up period, all patients undergo oral examinations every 4 weeks. Twelve weeks after the surgery (T2), a panoramic examination is carried out to evaluate bone healing, and the QoL questionnaire is administered again, allowing the evaluation of potential clinical improvements. The out- come is again classified as progressive, unchanged, partially resolved, and resolved. When an improvement of symptoms and QoL is recorded (i.e. partially resolved and resolved categories) [19], patients are included in a rou- tine 6-month follow-up program. If the clinical manifes- tation of MR-ONJ worsens (i.e. progressive or unchanged categories) [19], a tailored treatment with a close and personalized schedule is defined on a patient basis.

Data Source

Two datasets were used for this study: the electronic health records (EHRs) of the Osteonecrosis of the Jaws Treatment Center, School of Dentistry, University of Messina, and a QoL instruments dataset. Both datasets contain fully anonymized data from patients treated for MR-ONJ between January 2005 and December 2015, and who had regular follow-up visits within 10 weeks after MR-ONJ diagnosis. The EHRs contain data on patient demographic characteristics, medical history, and clinical details of MR-ONJ, which are routinely col- lected in clinical practice by dental specialists at the treatment center, as described above. This dataset also contains information on comorbidities, lifestyle (alcohol and tobacco use, either previous and/

or concomitant and moderate or intense) and, for cancer patients, previous or concomitant use of drugs other than BPs related to MR-ONJ. With regard to drug history, data were available on the type of BP, cumulative dose, and the indication of use for BP (i.e. osteoporosis or cancer).

The QoL instruments dataset used in this study con- tains information derived from two validated and self- reported, health-related QoL questionnaires that are routinely administered to patients at T0, T1, and T2. These two assessment instruments consisted of the European Organisation for Research and Treatment of Cancer (EORTC) QOL Module for Head and Neck Cancer (EORTC-H&N 35), used in conjunction with the QLQ-C30 core questionnaire [5, 6], and a visual analog scale (VAS) [17]. Both EORTC QLQ-C30 core and EORTC-H&N 35 questionnaires were administered to patients, but this study only uses data from the latter since it is strictly related to oral health. Given the evi- dence on its validity and reliability concerning the impact of oral health on personal well-being [10, 11], EORTC-H&N 35 version 3.0 was adopted, including 35 questions, divided into seven multi-item scales and 11 single items. The EORTC-H&N 35 focuses on specific aspects, such as pain, swallowing, senses (taste and smell), speech, social eating, sexuality and social con- tact. In detail, the item ‘trouble with social contact’ specifically refers to patient’s emotional discomfort, and impact of the disease on the patient’s social life and interpersonal relationships. Patients were asked to answer the

questions as follows: not at all, a little, quite a bit, and very much. For all considered items, high scores indicate more problems [22].

To complement the EORTC-H&N 35, the VAS was used, which consists of a psychometric response scale, widely used in epidemiological surveys concerning oral health. In the context of this study, it was adopted to better identify the changes, perceived by patients, regarding pain and QoL, using numerical values ranging from 0 (worst state of health) to 100 (best state of health) [23]. The QoL results were used to decide whether pharmacological treatment was successful (partially resolved and resolved categories), along with improvement in clinical manifes- tation and symptoms.

Data Analysis

Frequency analyses of the characteristics of MR-ONJ cases, stratified by indication of use, were initially per- formed. At T0 (date of MR-ONJ diagnosis), data were stratified on the basis of primary indications of BP drug use (osteoporosis or cancer) and were described in relation to demographic and clinical status, as well as patient's life- style habits (alcohol and tobacco use, either previous and/ or concomitant and moderate or intense), comorbidities, and, for cancer patients, previous or concomitant use of drugs, other than BPs, related to MR-ONJ.

For each patient, scores from the EORTC-H&N 35 survey were calculated based on the official scoring pro- cedure [24], where a score is calculated for each scale or item that can take any value between 0

and 100. For all items and scales, high scores indicate more health prob- lems. Thereafter, mean values were calculated for all items and scales, together with standard deviations (SDs), strat- ified by indication of use, at T0, T1, and T2.

A global oral health status (GOHS) score was calcu- lated as the mean of the inverse score of all scales and items, except for the 'sexual dysfunction' scale, due to the high frequency of missing answers. The GOHS provided a score that reflected the overall perceived oral health status (a high score represents a high QoL). Similarly, the VAS score was determined for each patient and the cor- responding mean values were calculated, together with SD, stratified by indication of drug use, at T0, T1, and T2. Finally, a total score was assessed, taking into account equally both the GOHS and the VAS score. Results ranged from 0 (worst state of health) to 100 (best state of health) and were stratified by indication of use, at T0, T1, and T2.

All statistical analyses were performed using SAS^{Ò} for Windows version 9.3 (SAS Institute, Cary, NC, USA), while artworks were created using Microsoft Office 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

Characterization of the Medication-Related Osteonecrosis of the Jaw (MR-ONJ) Cohort

The characteristics of patients enrolled in the MR-ONJ cohort, including detailed demographic data, primary dis- eases, type of administered BP and corresponding cumu- lative dose, dental history, (potential trigger events), anatomic location of MR-ONJ, and classification, are reported in Table 1.

A total of 100 patients were enrolled in the MR-ONJ cohort: 36 received BPs for the treatment of dysmetabolic bone disease (OSTEO group), and 64 were onco-hemato- logic patients (ONC group).

Overall, the mean age of MR-ONJ patients was 69.5 ± 10.0 years, with patients treated for osteoporosis being older than cancer patients (72.8 ± 10.1 vs. 67.7 ± 9.6 years). A higher proportion of women was observed in both groups (n = 32 [88.8%] among the OSTEO group, and n = 45 [70.3%] among the ONC group). Patients in the ONC group were more likely to be current or former smokers (n = 35; 54.7%) than patients in the OSTEO group (n = 10; 27.8%). Similarly, alcohol use was more frequent in the ONC group than in the OSTEO group (18.8% and 2.8%, respectively). Among patients enrolled in the MR-ONJ cohort, the most frequent comorbidity was heart disease (52.0%), followed by anxiety/depression (16.0%), diabetes (15.0%), and lipid disorders (15.0%).

The most commonly administered BP was zoledronic acid in the ONC group (n = 63; 98.4%) and alendronate in the OSTEO group (n = 26; 72.2%), followed by clodronate and ibandronate, which were both administered to 16.7% of patients in the OSTEO group. Among drugs previously or currently administered to patients enrolled in the cohort

and potentially related to MR-ONJ, the most common were corticosteroids (35.0%). In both groups, the mean cumula- tive dose from the start of treatment to MR-ONJ onset was significantly lower with zoledronic acid (114.2 ± 123.1 mg) than with alendronate (22,537 ± 13,096 mg).

The most common location of MR-ONJ was the mandible in both the OSTEO and ONC groups (n = 29 [80.6%] and n = 45 [70.3%], respectively), followed by the upper max- illa. On the other hand, a higher number of cases involving both jaws (12.5%) were observed in the ONC group than in the OSTEO group (2.8%). The presence of a potential oral trigger was recorded in 34 (53.1%) patients in the ONC group and 24 (66.7%) patients in the OSTEO group, with the most common being dental extraction.

In the ONC group, the overall health oral condition was worse than in the OSTEO group in terms of untreated caries and missing or filled teeth. Periodontal disease was

observed in one (2.8%) patient in the OSTEO group and one (1.6%) patient in the ONC group. The mean CPITN code was 2.9 ± 1.0 in the OSTEO group and 3.2 ± 0.9 in the ONC group.

According to the AAOMS classification, the most fre- quent stage of MR-ONJ was stage II (38 subjects), whereas stage 0 (8 subjects 8.0%), stage I (32 subjects), and stage III (22 subjects) were less common. Furthermore, accord- ing to the SIPMO classification, MR-ONJ lesions were reported to be mainly symptomatic. Localized infections were detected in 54.0% of cases (54 subjects in stage I and II).

Complications such as fistulas were identified in 22.0% of all subjects (22 subjects in stage III).

Among all patients enrolled in the MR-ONJ cohort, 26 (72.2%) patients in the OSTEO group and 21 (32.8%) of patients in the ONC group were considered eligible for surgical treatment after receiving previous pharmacologi- cal treatment.

Quality-of-Life Scores

All patients in the cohort (n = 100) had regular follow-up visits within 10 weeks after MR-ONJ diagnosis and underwent pharmacological treatment (Fig. 1). Of these, 47 were considered eligible for surgical treatment, based on the above-mentioned criteria.

The mean score of the EORTC-H&N 35 and VAS questionnaires, administered to all patients (n = 100) enrolled in the MR-ONJ cohort at T0 and T1, as well as the corresponding total score, were stratified by primary dis- ease (ONC and OSTEO groups) and are reported in Fig. 2.

At T0, the mean score for each evaluated item and scale of EORTC-H&N 35 was higher in the ONC group than in the OSTEO group. Therefore, the mean score of GOHS for the ONC group was lower than for the OSTEO group (mean ± SD 52.0 ± 15.6 and 72.7 ± 14.2, respectively). Mean scores with regard to pain were 55.8 ± 25.0 and 64.1 ± 24.3 for the OSTEO and ONC groups, respectively, while the mean scores reflecting problems in the social sphere were 17.8 ± 16.5 for the OSTEO group and 36.7 ± 24.0 for the ONC group. Furthermore,

there was a higher consumption of analgesics in the ONC group (mean ± SD 82.3 ± 25.9) than in the OSTEO group (36.1 ± 36.8). On the 0–100 VAS scale, the mean value was 38.3 ± 12.8 for the OSTEO group and 29.6 ± 14.3 for the ONC group.

At T1, an increase in GOHS was reported in both the OSTEO group (mean ± SD 79.9 ± 15.5; ?9.9%) and the ONC group (mean ± SD 70.4 ± 20.6; ?35.4%). Phar- macological treatment appeared to be more effective in reducing pain (mean scores decreased from 55.8 ± 25.0 to 43.5 ± 32.2 for the OSTEO group and from 64.1 ± 24.3 to 35.4 ± 30.8 for the ONC group), but did not have an impact on relationships with family and friends (at T1, the mean score related to troubles with social contact reduced from 17.8 ± 16.5 to 13.5 ± 16.4 for the OSTEO group and from 36.7 ± 24.0 to 26.9 ± 21.0 for the ONC group). Similarly, a decrease in analgesic use was observed between T0 and T1 in both groups (36.1 ± 36.8 to 24.1 ± 31.5 for the OSTEO group; 82.3 ± 25.9 to 49.5 ± 35.1 for the ONC group). Mean scores of the VAS scale at T1 were 53.6 ± 29.2 for the OSTEO group (?39.9%) and 58.4 ± 28.6 for the ONC group (?97.2%), highlighting an improvement in patients' perceived QoL after pharmacological treatment.

Overall, only 47 patients (26 in the OSTEO group and 21 in the ONC group) had no marked improvement after pharmacological treatment and/or were considered eligible for surgical treatment; these were administered EORTC- H&N 35 and VAS questionnaires at T2 (Fig. 3).

A notable improvement of perceived QoL was observed at T2. Results from the OSTEO group (Fig. 3) showed an increased mean GOHS score

of 92.5 ± 4.5 (25.3%, compared with T1), while the mean VAS score was 93.8 ± 14.2 (151.5%, compared with T1). Furthermore, the mean score for the pain item reduced to 5 ± 10.5 (- 91.3%, compared with T1), the score relating to troubles
with social contact reduced to 4.6 ± 6.2 (-72.0%, in comparison with T1), and analgesic use reduced to 5.1 ± 15.5 (-84.1%, compared with T1).

Similarly, considering the ONC group, results from T2 questionnaires showed an overall improvement of the GOHS (60.2 ± 15.4; ?18.5%, compared with T1) (Fig. 3). The pain item mean score was 32.2 ± 21.0 (-50.8%, in comparison with the previous questionnaire), while that related to trouble with social contact was 30.5 ± 20.6 (- 16.4%, compared with T1). Although the mean VAS scores increased from 26.7 ± 14.3 at T0 to 29.5 ± 18.3 at T1 (10.5%), and to 73.3 ± 27.8 at T2 (59.8%), surgical treatment was not completely successful, still reporting a high use of analgesics (82.5 ± 22.7 at T2, with no improvement compared with T1) and a mean GOHS score of 60.2 ± 15.4 (18.5%, compared with T1).

Discussion

Findings in Context

To our knowledge, this is the first observational study that explored the impact of pharmacological and surgical treatment on the QoL of a

large cohort of patients with MR-ONJ. Results highlight a notable improvement in total scores and a reduction in specific items scores, such as pain, analgesic use, and trouble with social contact. The impact on QoL was much more evident after surgical treatment.

Findings from the present study suggest that patient- reported, health-related QoL data are valuable, providing important information on health status, as well as playing a role in evaluating the impact of both pharmacological and surgical treatment on QoL.

Through EORTC-H&N 35, patients could give a sub- jective, reliable judgment thanks to ordinal scales, while the VAS scale allowed patients to integrate information from the multidimensional evaluation of EORTC-H&N 35 with a quantitative analysis on the perceived level of well- being.

Considering T0, the mean score for each evaluated item and scale of EORTC-H&N 35 was higher in the ONC group than in the OSTEO group, thus suggesting cancer patients had a worse GOHS than those with osteoporosis. The items associated with lower QoL by both groups were those related to pain and social contact but, in general, the evaluation of the questionnaire scores at T0, T1, and T2 allowed identifying how pharmacological and surgical treatment influenced specific items, thus suggesting a tailored treatment to the patient's needs.

QoL scores increased modestly at T1. Pharmacological treatment was effective in 53 patients with stage II or III MR-ONJ, which, thereafter, downscaled to asymptomatic stage I. These patients were stable with

bone exposure and reported an improvement in MR-ONJ clinical manifesta- tion, symptoms, and QoL.

A more notable improvement was recorded after surgi- cal treatment. Evaluations at T2 were limited to those patients experiencing major improvement after pharmacological treatment and considered eligible for surgical treatment. Surgery of MR-ONJ led to complete healing (defined as the absence of bone exposure, absence of signs and symptoms, and radiological signs compatible with the bone healing process at 12 months follow-up) in 100% of patients with osteoporosis and 18% of cancer patients. In 71% of cancer patients, surgical treatment was associated with a greater QoL improvement, while it was unsuccessful in 18%, reporting an overall worsening of both clinical conditions and QoL.

According to the AAOMS guidelines, the therapy of MR-ONJ should be stage-dependent. Stages I and II benefit from conservative management, including antimicrobial local rinses and/or antibiotic therapy, while stage III should be surgically treated with debridement or resection of the infected jaw. In addition, in case stage II is refractory to conservative management, surgical debridement of infec- ted bone is recommended to relieve soft tissue irritation [18]. Despite the AAOMS recommendations, the choice between conservative pharmacological treatment and surgery is still challenging.

The surgical strategies for MR-ONJ management performed in several centers range from conservative debridement to major resection [4, 6–9, 25]. In managing ONJ patients, the treatment goals are to preserve a

patient's QoL, to control pain and to relieve the MR-ONJ clinical symptoms, to control infection, and to prevent the extent of lesions [3]. Since ONJ treatment is controversial, with conservative and surgical modalities being equally practiced, use of the EORTC-H&N 35 questionnaire in patients undergoing pharmacological and surgical treatment may provide data on the potential benefit of the two treatment strategies [11].

The devastating impact of cancer as a primary disease introduces a general bias, worsening the perceived global health status and oral health in such a way as to make interpretation of the respective scores difficult. For this reason, although the EORTC-H&N 35 has to be used in conjunction with the QLQ-C30 core questionnaire, results from the latter were excluded from this study as the enrolled cohort considered both OSTEO and ONC patients. Kyrgidis et al. examined the diagnostic utility, validity, and reliability of the EORTC-H&N 35 questionnaire in patients diagnosed with metastatic cancer and stage 2 or 3 ONJ, confirming that this tool can be used to quantify the impact of ONJ on QoL thanks to its psychometric properties [11].

Bisphosphonates Commonly Triggering MR- ONJ and Other Risk Factors

The most commonly used BP in the ONC group was zoledronic acid, a high-potency BP indicated for the management of solid tumors with bone metastases [26, 27] as well as for osteoporosis. In the OSTEO

group, the most common BP was alendronate, as already described in Europe [28]. The detailed drug history in the datasets
allowed us to see that some patients were treated sequentially with different BPs. BP cumulative doses and duration of exposure appeared to be the most important risk factors for MR-ONJ onset, with a higher risk after prolonged exposure to BP. MR-ONJ onset appears to be time-de- pendent, with an increased risk after long-term use of BPs, often after dental extractions. The most common potential oral trigger for MR-ONJ was dental alveolar surgery, as already described in the published literature [18, 29]. Furthermore, MR-ONJ involved the lower jaw more fre- quently than the upper or both jaws, in line with previously published data [20]. The association between smoking and/ or alcohol habits and the onset of MR-ONJ is explained by the development of chronic tissue damage [30, 31].
With regard to drug use as a risk factor for MR-ONJ in the ONC group, previous or concomitant treatment with other medications that may increase the risk of MR-ONJ were identified. The concomitant use of BPs and corti- costeroids (35.0%) was the most frequent and is an already- known risk factor for the onset of MR-ONJ [3], followed by thalidomide (prescribed for multiple myeloma). The effectiveness of the newer therapies for cancer has led to long-term disease stabilization and to a much longer pro- gression-free survival [32]. At the same time, improved survival rates of oncological patients increased the need to understand the health-related consequences of cancer therapies [33]. Patient's perceived QoL is significantly affected

by persistent health-related problems, especially those regarding oral health, as it is well known that multiple myeloma, and breast, prostate and lung cancer are complicated by ONJ [34, 35]. On the other hand, BPs are the first-line therapy for osteoporosis due to their efficacy in reducing osteoporotic fractures [36], but the long-term therapy required by such a chronic disease results in potential adverse reactions, such as MR-ONJ [37].

Finally, another risk factor for MR-ONJ relates to periodontal disease, a commonly occurring condition that can easily and quickly be treated if caught early, thus reducing the risk of MR-ONJ [38]. This was confirmed by findings from the present study from the DMFT and CPITN indices, which suggest that both OSTEO and ONC patients required periodontal care, the latter having an overall worse oral health condition.

MR-ONJ: Changes in Clinical Definitions and Regulatory Implications

In general, MR-ONJ pathophysiology is not yet completely known [30, 39]. The most valid hypothesis potentially explaining the localization to the jaws are infection or inflammation, microtrauma, altered bone remodeling or resorption, inhibition of angiogenesis, soft tissue drug toxicity, or vitamin D deficiency [30, 40–43]. The risk of

MR-ONJ depends solely on drug utilization, being higher in patients receiving long-term oral BPs for osteoporosis (21 cases per 10,000 patients) and in cancer patients treated with intravenous zoledronic

acid or denosumab (55–110 and 70–190 cases per 10,000 patients, respectively) [43–49].

Studying MR-ONJ is a challenge given the several changes that have taken place regarding the clinical defi- nition of MR-ONJ, as well as changes in the AAOMS classification of MR-ONJ, and the development in the availability on potentially MR-ONJ-triggering drugs on the market.

The definition of MR-ONJ changed over time. Initially, this related to only antiresorptive medications approved for the management of osteoporosis and metastatic bone dis- ease (BPs), but was then expanded to include denosumab and medications targeting angiogenesis (i.e. bevacizumab and sunitinib) [50]. For this reason, the original acronym BR-ONJ (BP-related ONJ) was replaced by MR-ONJ [3].

As highlighted above, other important changes have taken place in the context of MR-ONJ. For example, the AAOMS classification used in this study has recently been revised by the SIPMO in order to easily recognize the clinical variant of MR-ONJ with non-exposed bone. According to SIPMO recommendations, the severity of ONJ (i.e. the extent of bone disease) can be correctly identified if measured by a CT scan, allowing a more accurate diagnosis than by clinical inspection only and providing helpful information for ONJ management [15]. MR-ONJ stage classification of patients included in the cohort was therefore assigned retrospectively according to patient's medical

history, clinical features, and CT scans, using the most updated classifications.

Even though the diagnostic criteria changed slightly during the study period, the treatment approach has not changed since the same symptomatic and imaging criteria were used to diagnose MR-ONJ during the whole study period. Therefore, classification updates did not influence patients' enrollment in the early years, as in the last years, of the study.

Another change in the backdrop of MR-ONJ relates to a development in the Italian drug regulatory setting, i.e. the approval of denosumab, a monoclonal antibody that acts by preventing osteoclast formation, for the management of osteoporosis in 2011 and for bone metastases in 2013 by the Italian Medicines Agency.

In theory, patients may have presented with MR-ONJ triggered by denosumab use. However, no cases of ONJ due to such medications were observed during the enroll- ment period. At least one patient very recently presented at the Center for Treatment of the Osteonecrosis of the Jaw (School of Dentistry, University of Messina) without a history of BP administration and was diagnosed with MR-ONJ due to denosumab. Nevertheless, this patient was identified after the end of the study period, therefore the corresponding data were not included in this study.

Strengths and Limitations

The main strength of this study is its novelty in exploring the impact of pharmacological and surgical treatment on QoL in a cohort of patients with MR-ONJ. The QoL evaluation using specific questionnaires gave a reliable understanding of how patients responded to treatment, whether pharmacological or surgical. Furthermore, these evaluations were carried out in clinical practice, with the qualitative results from this study reflecting the impact of current management approaches used in the treating center. Finally, since MR-ONJ is a very rare disease, the cohort of 100 patients can be considered large.

However, this study also has some limitations. Although the definition of ONJ has changed slightly over time, including other antiresorptive agents and medications tar- geting angiogenesis, only cases of ONJ related to BPs were included in the study due to the enrollment period. Addi- tionally, only data from patients with at least 12 weeks of follow-up were included in the study. Consequently, the results cannot be generalized to persons who are not compliant with scheduled medical check-ups at the treat- ment center. Results can also not be generalized to persons whose prognosis was so negative that they would not have survived 12 weeks, or who would not have been eligible for treatment.

The diagnostic criteria of MR-ONJ were updated during the study period, but the treatment approach did not change since the same clinical and imaging criteria were used to diagnose MR-ONJ during the whole study period. There- fore, classification updates did not influence patients' enrollment during the entire study period.

Conclusions

Overall, a relevant increase in the perceived QoL of patients was observed after pharmacological and surgical treatment, together with an improvement in specific item scores, such as pain, analgesic use, and trouble with social contact. The change in QoL was much more evident after surgical treatment (except for the lack of a reduction in analgesic use in the ONC group), suggesting surgical treatment may offer benefits to selected patients with MR- ONJ.

This study contributes to the current knowledge of MR- ONJ clinical course and may help the clinician to take QoL into consideration when considering treatment options and evaluating treatment outcomes. MR-ONJ-related QoL is also important in order for patients to be provided with treatment options that target and improve their status globally.

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TABLES AND FIGURES

Fig. 1

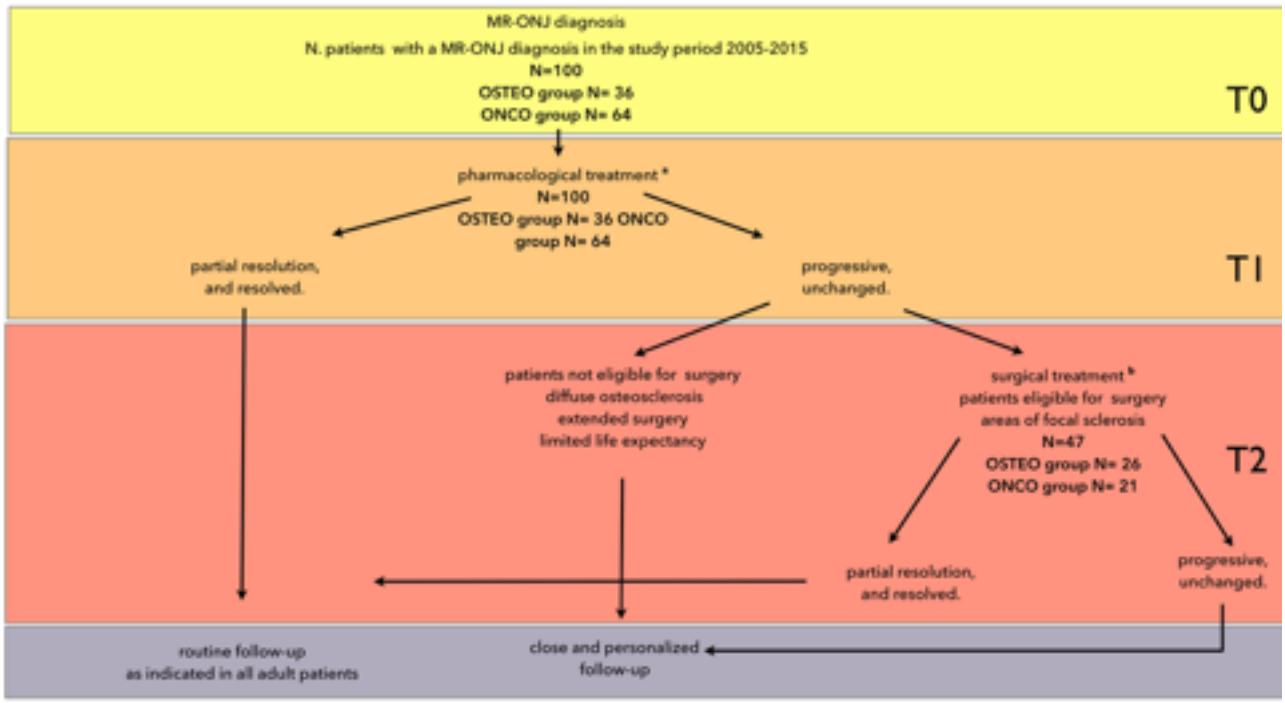

Fig. 1 Adopted workflow for MR-ONJ patient management. MR- ONJ medication-related osteonecrosis of the jaw, T0 diagnoses of medication-related osteonecrosis of the jaw, T1 pharmacological treatment, T2 surgical treatment, OSTEO osteoporosis group, ONC oncologic group.

[a]All patients were prescribed 0.20% chlorhexidine oral rinse and, in cases of bone exposure, irrigation with povidone- iodide applied with a disposable sterile syringe, to be performed daily throughout the period of initial therapy. In the presence of pain, swelling, and other signs of infection, supportive treatment, including oral antibiotics, was administered as follows: amoxicillin ? clavu- lanic acid 1 g capsules (one capsule twice daily) and metronidazole 250 mg tablets (two tablets twice daily) for 10 days. Alternative antibiotic treatments such as macrolide drugs were administered in cases of moderate to severe intolerance or allergy to penicillins.

[b]Medical status was evaluated through blood examinations. For patients receiving chemotherapy, the therapeutic window was carefully evaluated. When the patient was receiving chemotherapy, the recommendation was to check the hematologic status and to schedule surgery carefully. After oral surgery, at least 7–10 days of healing were considered before the patient received oncological therapy. All surgical procedures were performed using an intra-oral approach under local anesthesia. Surgery consisted of resection of all infected and necrotic bone using a piezoelectric device. Resection margins

were determined by the clinical appearance of bleeding bone. No segmental resections were performed because no indications were found in the considered sample of patients. Primary wound closure was achieved by using a bi-layered suturing technique. Only absorbable sutures were used. Surgical therapy was combined with a standardized perioperative adjuvant treatment starting 3 days before surgical therapy, and continued postoperatively for a recommended period of 17 days. We recommended the use of mouthwashes with an antibacterial solution (chlorhexidine 0.20%) three times daily. Considering the antiangiogenic properties of bisphosphonates, post- operative discontinuation of bisphosphonate therapy was chosen in order to counteract the effects on soft tissues, preserve blood supply and promote better healing. As for pharmacological treatments of comorbidities, such as when patients were receiving anticoagulation, the therapeutic scheme was defined in accordance with the general practitioner.

Table 1 Characteristics of patients affected by MR-ONJ, stratified by primary disease requiring bisphosphonate therapy

	Osteoporosis [n = 36] (%)	Cancer [n = 64] (%)	Total [n = 100] (%)
Age, years (mean ± SD)	72.8 ± 10.1	67.7 ± 9.6	69.5 ± 10.0
Males	4 (11.1)	19 (29.7)	23 (23.0)
Smoker[a]	10 (27.8)	35 (54.7)	45 (45.0)
Drinks alcohol[a]	1 (2.8)	12 (18.8)	13 (13.0)
Exposure to bisphosphonates			
Zoledronate (intravenous)	–	63 (98.4)	63 (63.0)
Dosage (mg)[b]	–	4.0 ± 0.0	4.0 ± 0.0
Cumulative dose (mg)[b]	–	114.2 ± 123.1	114.2 ± 123.1
Pamidronate (oral)	–	8 (12.5)	8 (8.0)
Dosage (mg)[b]	–	90.0 ± 0.0	90.0 ± 0.0
Cumulative dose (mg)[b]	–	5805.0 ± 5312.3	5805.0 ± 5312.3
Alendronate (oral)	26 (72.2)	2 (3.1)	28 (28.0)
Dosage (mg)[b]	70.0 ± 0.0	70.0	70.0 ± 0.0
Cumulative dose (mg)[b]	22,537.3 ± 13,096.4	4,900.0	21,277.5 ± 13,433.3
Neridronate (oral)	1 (2.8)	–	1 (1.0)
Dosage (mg)[b]	25.0	–	25.0
Cumulative dose (mg)[b]	3,900.0	–	3,900.0
Risedronate (oral)	4 (11.1)	–	4 (4.0)
Dosage (mg)[b]	55.0 ± 23.1	–	55.0 ± 23.1
Cumulative dose (mg)[b]	25,515.0 ± 23,063.7	–	25,515.0 ± 23,063.7
Ibandronate (oral)	6 (16.7)	2 (3.1)	8 (8.0)
Dosage (mg)[b]	150.0 ± 0.0	150.0	150.0 ± 0.0
Cumulative dose (mg)[b]	31,900.0 ± 26,604.9	13,500.0	27,300.0 ± 24,619.9
Clodronate (oral)	6 (16.7)	4 (6.3)	10 (10.0)
Exposure to non-bisphosphonate drugs potentially related to MR-ONJ			
Corticosteroids	–	35 (54.7)	35 (35.0)
Capecitabine	–	12 (18.8)	12 (12.0)
Thalidomide	–	10 (15.6	10 (10.0)
Epirubicine	–	9 (14.1)	9 (9.0)
Lenalidomide	–	8 (12.5)	8 (8.0)
Docetaxel	–	8 (12.5)	8 (8.0)
Fulvestrant	–	7 (10.9)	7 (7.0)
Paclitaxel	–	6 (9.4)	6 (6.0)
Comorbidities[c]			
Cardiovascular disease	23 (63.9)	29 (45.3)	52 (52.0)
Anxiety and/or depression	9 (25.0)	7 (10.9)	16 (16.0)
Diabetes	5 (13.9)	10 (15.6)	15 (15.0)
Lipid disorders	8 (22.2)	7 (10.9)	15 (15.0)
Potential oral trigger	24 (66.7)	34 (53.1)	58 (58.0)
Oral surgery (mean ± SD)	1 (2.8)	2 (3.1)	3 (3.0)
Dental extraction	22 (61.1)	29 (45.3)	51 (51.0)
Periodontal disease	1 (2.8)	1 (1.6)	2 (2.0)
Dental prothesis	–	2 (3.1)	2 (2.0)
DMFT index (mean ± SD)			
Decayed teeth	2.0 ± 2.9	2.2 ± 2.8	2.1 ± 2.8
Missing teeth	16.1 ± 10.4	14.2 ± 9.4	14.9 ± 9.8
Filled teeth	1.8 ± 2.9	2.3 ± 3.1	2.2 ± 3.0
CPITN	2.9 ± 1.0	3.2 ± 0.9	3.1 ± 0.9

	Osteoporosis [n = 36] (%)	Cancer [n = 64] (%)	Total [n = 100] (%)
Anatomic location of MR-ONJ			
Lower jaw	29 (80.6)	45 (70.3)	74 (74.0)
Upper jaw	6 (16.7)	11 (17.2)	17 (17.0)
Both jaws	1 (2.8)	8 (12.5)	9 (9.0)
AAOMS classification of MR-ONJ[d]			
0	4 (11.1)	4 (6.3)	8 (8.0)
I	18 (50.0)	14 (21.9)	32 (32.0)
II	11 (30.6)	27 (42.2)	38 (38.0)
III	3 (8.3)	19 (29.7)	22 (22.0)
SIPMO classification of MR-ONJ[d]			
I a	9 (25.0)	8 (12.5)	17 (17.0)
I b	12 (33.3)	10 (15.6)	22 (22.0)
II a	1 (2.8)	6 (9.4)	7 (7.0)
II b	11 (30.6)	21 (32.8)	32 (32.0)
III a	1 (2.8)	4 (6.3)	5 (5.0)
III b	2 (5.6)	15 (23.4)	17 (17.0)
No. of patients eligible for surgical treatment	26 (72.2)	21 (32.8)	47 (47.0)

MR-ONJ medication-related osteonecrosis of the jaw, *SD* standard deviation, *DMFT* decayed, missing, filled teeth, *CPITN* Community Periodontal Index of Treatment Needs, *AAOMS* American Association of Oral and Maxillofacial Surgeons, *SIPMO* Italian Society of Oral Medicine and Pathology

[a] Either previous and/or concomitant and moderate or intense

[b] The SD was not calculated in cases were less than three records were available

[c] Comorbidities were recorded at the time of MR-ONJ diagnosis

[d] In case of multiple locations of MR-ONJ and multiple stages, the most severe stage was considered

Fig. 2

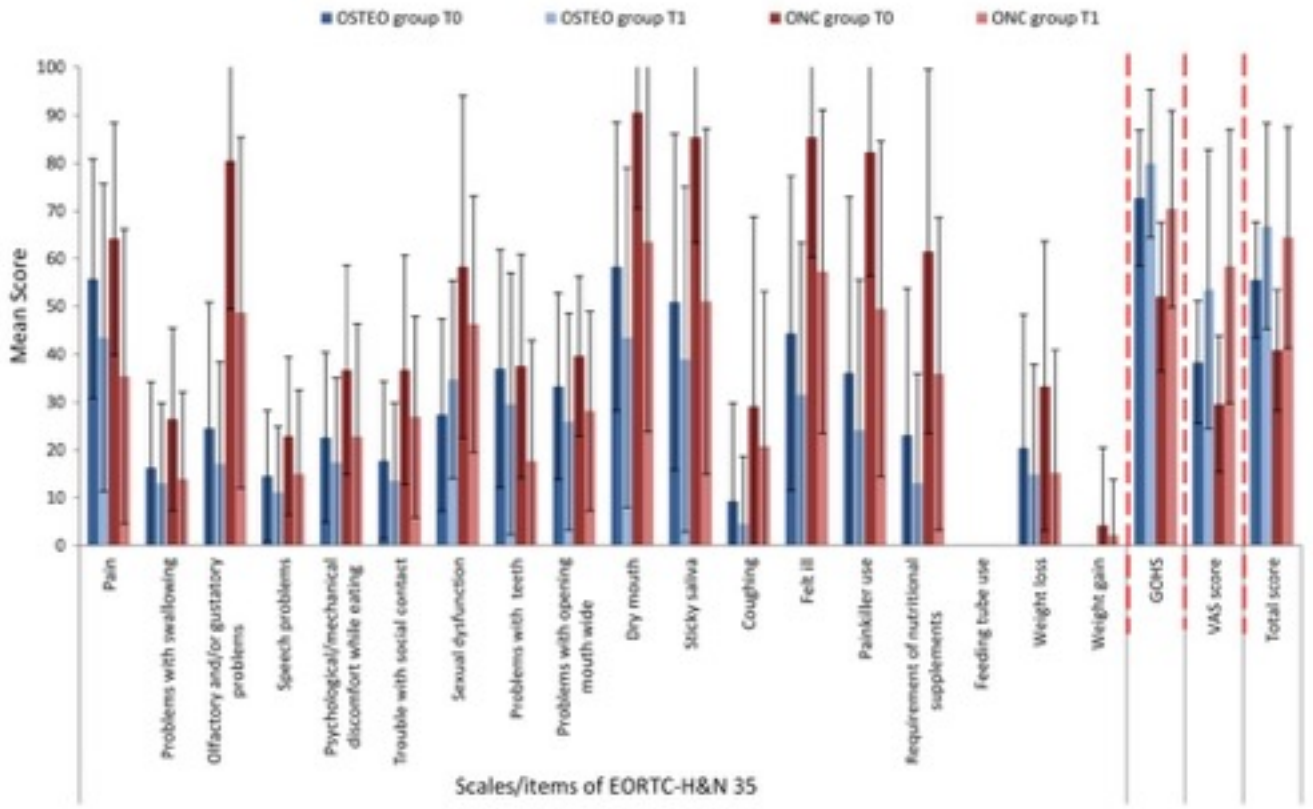

Fig. 2 Mean score of the EORTC-H&N 35 and VAS questionnaires, administered to patients (n = 100) at the time of diagnosis of medication-related osteonecrosis of the jaw (T0) and after pharmacological treatment (T1), stratified by indication of use and items. Mean scores and standard deviations are reported. *GOHS* global oral health status, *OSTEO* osteoporosis group, *ONC* oncologic group, *EORTC* European Organisation for Research and Treatment of Cancer, *VAS* visual analog scale

Chapter 2: Quality of Life of MRONJ patients

Oral-Health-Related Quality of Life After Surgical Treatment of Osteonecrosis of the Jaws

Introduction

To date bisphosphonates are considered the first-line therapy for osteoporosis, due to their established efficacy in fracture and mortality reduction[1,2]. Recent reports of drug safety have a significant impact on bisphosphonate prescription prevalence. Indeed, the alert about the potential risks of long-term therapy with bisphosphonates determined a decreasing trend in their use [3].

Next to atypical femur fracture and esophageal cancer, the osteonecrosis of the jaws (ONJs) is reported as a serious side effect of the use of bisphosphonates for long-term treatment of osteoporosis [4]. In early 2009, the possibility of a link with esophageal cancer was raised by a report of 54 adverse reaction clinical reports received by the US Food and Drug Administration from the United States, Europe, and Japan. Related adverse gastrointestinal effects are common among people who take oral bisphosphonates for the prevention and treatment of osteoporosis; they range from dyspepsia, nausea, and abdominal pain to erosive esophagitis and esophageal ulcers [5,6].

This pathologic situation is common to a wide number of drugs adopted in oncologic and osseo-dysmetabolic patients and recently the

American Association of Oral and Maxillofacial Surgeons (AAOMS) defined it as medication-related osteonecrosis of the jaw (MRONJ). It is described as ‘‘an area of exposed bone or bone that can be probed through an intra-oral or extra-oral fistula (e) in the maxillofacial region that has persisted for more than eight weeks, with current or previous treatment with anti-resorptive or anti-angiogenic agents and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws” [7].

To date MRONJ prevalence in cancer patients has been the focus of the majority of papers, whereas the impact of the disease in patients with dysmetabolic bone disease is less known [8,9].The estimated prevalence of MRONJ in noncancer (mainly osteopo- rotic) patients may range from 0.02% to 11% [10-14].

It must be a concern of the specialized centers to promote awareness about the efficacy of the treatment strategies for MRONJ, in order to validate the safety of long-term bisphosphonates therapy.

Starting from this purpose an observational cohort study was designed in order to evaluate whether osteoporotic patients affected by MRONJ, nonresponding to conservative treatment, may benefit by using the marginal osseous resective surgery and to determine the outcome of the surgical treatment by means of quality-of-life (QoL)-based questionnaires.

The QOL assessment is an appropriate tool for evaluating the effectiveness of the performed treatments [15,16].Therefore, The EORTC QoL questionnaire (QLQ) is an integrated system for assessing

the health-related QoL of cancer patients participating in international clinical trials. EORTC appropriates for self-admin- istration. The content areas covered by the questionnaire reflect the multidimensionality of the QoL construct. EORTC QQ-C30 Core questionnaire and EORTC QOL Module for Head and Neck Cancer (EORTC-H&N 35) are used in conjunction, the latter one is strictly related to oral health and although referring to patient's emotional discomfort, impact of the disease on the patient's social life and interpersonal relationships focuses on some specific aspects, such as pain, swallowing, senses (taste and smell), speech, social eating that allow a better identification of the treatment-related changes, perceived by patients, regarding pain and QoL [17].

According to this view, EORTC QQ-C30 and QLQ-HN35 appen- dices in conjunction with a visual analog scale (VAS) were chosen among the most validated QoL surveys and administered to patients for the evaluation of the maxillary surgery-related changes in QOL [17-20].

Methods

Forty-one patients with an established diagnosis of dysmetabolic bone disease, complicated with MRONJ in an early stage, were included in the study and consecutively treated, from January 2005 to December 2015, at the Oral Surgery Unit, School of Dentistry, University of Messina.

During the diagnostic phase, demographic data, use of medica- tions related to ONJs, and their cumulative dose were collected.

The MRONJ staging was identified according to the updated AAOMS classification.[18] Moreover, a further disease staging was performed following the classification proposed by the Italian Society of Oral Medicine and Pathology and Italian Society of Maxillo-Facial Surgery [21-23].

All selected patients were affected by focal disease (osteone- crotic lesion limited to the alveolar bone and not involving basal bone, maxillary sinus, or nasal floor) clinically diagnosed and confirmed with a TC examination of maxillary bones.

Local risk factors (ie, oral surgical procedures, dental-periodontal diseases) for MRONJ occurrence were evaluated [24].

Dental findings were recorded using the Decayed, Missing, Filled Teeth (DMFT) index [25].

Comprehensive periodontal evaluation was performed and assessed through the Community Periodontal Index of Treatment Needs (CPITN) during clinical examination and from patient's radiographs [26].

All patients were initially treated with professional oral hygiene procedures and prescription of antimicrobial treatment (0.20% chlorhexidine oral rinse and irrigation with povidone–iodide).

In presence of pain, swelling, and other signs of infection, supportive treatment with oral antibiotics was administered (amoxicillinþ

clavulanic acid 1 g caps 1 cap, twice a day plus metronidazole 250 mg tabs 2 tabs, twice a day for 10 days) [7,27,28].

Because of all patients had not a complete response to medical treatment, surgical procedure was performed using an intraoral approach under local anesthesia. Surgery consisted in piezoelectric marginal resection of necrotic bone areas detected with a TC examination. The electromedical device Surgysonic II, with 3 specific saw inserts, was adopted in all patients (Esacrom s.r.l. 40026 Imola, Bologna, Italy) (Figs. 1 – 4).

Primary wound closure was achieved by using a bilayered suturing technique. Surgical therapy was combined with a stan- dardized perioperative adjuvant medical treatment. The use of mouth rinses with an antimicrobic solution (chlorhexidine 0.20%) 3 times a day and postoperative discontinuation of bisphos- phonate therapy was recommended [7].

Patients were included in a continuing postoperative follow-up program, based on a 2-month schedule. Clinical outcome was evaluated at 12 months and successful treatment was defined as complete mucosal healing, absence of swelling and suppuration, and no clinical and radiologic signs of recurrence of osteonecrotic bone exposure[28-36] (Figs. 5 – 6).

The MRONJ-related changes in symptoms and side effects of treatment were assessed using the EORTC QQ-C30 and its QLQ- HN35 appendix. This assessment method was adopted because already administered in previous studies to ONJ patients[18].

The head and neck module comprises 35 questions assessing symptoms and side effects of treatment, social function, and body image/sexuality. The module HN35 incorporates 7 multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. There are also 11 single items. For all items and scales, high scores indicate more problems. Scales consist of 1 to 4 items and describe either symptoms or functions. Scores from the EORTC-H&N 35 surveys were calcu- lated according to the official scoring procedure to assess symptoms and side effects of treatment [37].

Moreover, a perceived oral health VAS was administered, before (at the time of diagnosis of MRONJ) and after surgery (at least 6 months) [17-20].Numerical values' scales ranging from 0 (worst state of health) to 100 (best state of health) were used to assess the well- being state [38].

All the above-cited clinical data, routinely collected in the daily practice of the Oral Surgery Unit, were fully anonymized and extracted from the database for statistical processing. Paired t test and relative change were applied after score calculation.

Statistics

Descriptive statistics were calculated for patient characteristics, demographics, bisphosphonate use, anatomic location of MRONJ, and local risk factors for MRONJ occurrence. To evaluate the effect of

surgical treatment, the preoperative and postoperative scores of EORTC survey and VAS were compared using Student t test.

Results

Patient's characteristics are summarized in Table 1. Mean age of patients was 72.97 years. Female gender was prevalent (37 females and 4 males).

In relation to the type of Biphosphonate (BP) used, the most common one was Alendronate administered to 30 patients, followed by Ibandronate (8 patients), Clodronate (7 patients), Risedronate (5 patients), and Neridronate (1 patient).

According to the clinical histories, some patients have been treated sequentially with different bisphosphonates; therefore, the overall percentage exceeds 100%.

Median onset of MRONJ was 85 months since the beginning of bisphosphonate therapy.

The mean cumulative dose reported at the moment of the diagnosis was 22.422 mg when Alendronate was administered and 26.400 mg in patient with Ibandronate administration. Risedronate administration was frequently associated with Alendronate (2 patients), with Alendronate and Clodronate (2 patients), or with Clodronate (1 patient). When Risedronate was administered alone (2 patients) the mean cumulative dose reported at the moment of the diagnosis was 10.935

mg. Neridronate was administered in a single patient in association with Ibandronate, for a cumulative dose of 3.900 mg.

All selected patients were affected by focal disease (osteone- crotic lesions limited to the alveolar bone and not involving basal bone, maxillary sinus, or nasal floor).

As to the anatomic location of MRONJ 34 patients appeared in the mandible and 7 patients in the upper maxilla.

Local risk factors for MRONJ occurrence were evaluated and are summarized in Table 2.

Twenty-five patients reported dental alveolar surgery performed prior to MRONJ occurrence. The results showed an average of decayed 1.97, missing 15.38, and filled 2.43 teeth. Patient popula- tion, on average, needed comprehensive dental care as assessed through CPITN index. Mean probing reported was 4.96 mm, which corresponds to a Code 3 of CPITN index assessing that the majority of patients were in need of oral hygiene, dental extraction, scaling, and root planning including elimination of plaque retentive margins (scores II and III).

After surgery (at 12 months), complete mucosal healing was achieved in the 100% of the patients and no bone exposure recurrence was observed.

Results of QLQ-HN35 appendix (Table 3) are expressed as a score calculated according to the official procedure.

The items ‘‘Pain,’’ ‘‘Trouble with social contact,’’ and ‘‘Cough- ing’’ showed a statistically significant variation ($P < 0.05$).

The score reduction concerning items ‘‘Teeth,’’ ‘‘Opening mouth,’’ ‘‘Dry mouth,’’ ‘‘Sticky saliva,’’ and ‘‘Felt ill’’ was of even greater significance ($P<0.01$).

The average score reported for the symptom ‘‘pain’’ downscaled from 57.52 to 4.06 (92.93%).

Patients experienced problems in swallowing solid foods. The severity of the problem decreased from 17.07 to 4.67 (72.61%). Sense problems decreased from 20.32 to 1.21 (94%). The symptom ‘‘felt ill’’ score went from 38.21 to 13.82 (63.82%). All patients experienced with symptoms described in ‘‘troubles with social eating’’ and ‘‘social contact’’ items. A reduction of these troubles was reported after surgery (64.70% and 77.45%,

respectively).

Results presented in Table 4 represent the average values on a scale from 1 to 4 assigned to each single response. The mean score of perceived oral health VAS increased from 36.09 to 91.95 (Table 5).

Discussion

The current study aimed to analyze the clinical and patient-centered outcomes of osseous resective surgery in 41 patients with MRONJ in the early stages, by evaluating the change in QoL after surgical therapy. Although the definition of ONJ has been updated in 2014, including RANK inhibitor bone-antiresorptive agents for treatment of

osteoporosis, our study included only patients treated with bisphosphonates [39].

For a correct interpretation of the results the characteristics of the cohort were examined. Osteonecrosis of the jaw appears to be time-dependent with higher risk after long-term use of bispho- sphonates (85 months on average) being the initial visit date defined as the time of MRONJ occurrence [7,23].

When long-term therapy is administered, the collection of a detailed patient's history may be difficult. For 2 patients of the cohort, data related to cumulative dose and duration in months of bisphosphonate therapy were not available (NA). One patient who
has been subsequently administered Alendronate and Risedronate did not remember the exact duration of Alendronate therapy; for this patient, the reported duration in months refers only to the administration of Risedronate. The same way a patient treated with Alendronate did not remember the cumulative duration of administered treatment.

Accordingly with literature, among the considered sample, the presence of decayed untreated teeth, periodontal inflammation, probing depths, and attachment loss highlighted by DMFT index and CPITN, revealed poor oral conditions. Moreover, the most frequently reported potential oral trigger for MRONJ occurrence was dental alveolar surgery [7].

The choice between medical and surgical treatment of MRONJ remains a critical issue [40].

According to the AAOMS guidelines, the therapy of MRONJ is stage dependent, Stages I and II benefit from conservative management, including the use of oral antimicrobial rinses and/or antibiotic therapy while stage III should be treated with surgery, including debridement or resection of the infected jaw. In addition, if stage II is refractory to conservative management, the AAOMS recom- mends surgical debridement of infected bone for relief from soft tissue irritation.[5]

The surgical strategies for MRONJ management performed in several specialized centers range from conservative debridement to major resection [4,8,9,11,40-42].

Stanton recommended to be limited to a conservative debridement [33].

Carlson and Basile advise to offer definitive surgery to patients with MRONJ, also in the most extensive patients and at the cost of a radical surgery [34].

Graziani supports conservative curettage of the necrotic lesion in more advanced patients (stages II and III) and major resection of the necrotic portion (stage I) [30].

Bodem et al suggest that early stages (BRONJ 0 and I) might be sufficiently managed by conservative treatment only, and surgical treatment should be restricted to advanced stages (BRONJ II and III) or after failure of the conservative approach to treatment [29].

Voss et al state how even a conservative management the problem still not remains successfully treated allowing the bone defect to worsen[31].

In managing ONJ patients, the treatment goals are to preserve patient's QoL, to control pain and relieve the clinical symptoms of MRONJ, to control infection, and to prevent the extension of the lesions and the development of new area of necrosis [7].

Results from the treated patients highlight that the outcome of the surgical treatment of the early stages of MRONJ is predictable, confirming the results of previous studies [31,34-37]; all patients showed complete mucosal healing, without complications, report- ing a significant improvement in perceived symptoms and main- taining clinical stability at follow up. A crucial aspect is considered the presence of a focal lesion with margins clearly detected by the use of a TC of maxillary bones [22].

Since the treatment of ONJ is controversial, the use of EORTC instruments in patients treated for ONJ might demonstrate a poten- tial benefit of either modality [16,18].

Patient-centered outcome was obtained by evaluating the administered H&N 35 appendix of EORTC and a VAS [17,20,21].

The use of instruments for QoL assessment is validated by the international literature and it is recommended as an useful tool for the daily management of patients [15].

Measuring head and neck functioning and related well-being from patient's perspective is as important as the clinically meaningful changes for determining improvement in the clinical management of MRONJ patients.

According to the results of the current study, MRONJ affects QoL of patients suffering of this disease. Patient well-being scored before surgery showed an overall presence of pain/discomfort. Referring to the self-report of the QoL questionnaires almost no patients did answer to questions inherent to sexual activity (proba- bly for the age-related lack of interest).

Most recommendations for treatment of MRONJ are based on clinical series and clinical reports, while evidence-based treatment paradigms are lacking [7,27-37].

This study is part of the number and aims to present the experience of a single center of southern Italy to which are referred not only cancer patients, as in most of the patients, but also patients affected by dysmetabolic bone disease.

In agreement with other authors who support surgical approach reporting surgery to be successful in some settings [29-37,42], osseous- resective surgery has been performed taking to account the patients general medical condition and life expectation.

Based on the observation of the 41 patients of the cohort, marginal resection was shown to yield successful results in the present survey and should be indicated for osteoporotic patients with symptomatic MRONJ early stage, to whom resolution of acute infection and pain

together with improvement of perceived QoL has to be the main goal of treatment.

Conclusions

This study results confirmed how the usefulness of the EORTC tools in the understanding of patients' problems and in determining the extent of self-perceived changes in oral health-related QoL gained with the specific treatment.

In the recorded patients with the present investigation, because of the improvement of perceived QoL together with the resolution of clinical symptoms such as swelling or suppuration, the marginal resection of the necrotic jaw bone seems to be an effective strategy in osteoporotic patients affected by localized MRONJ.

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TABLES AND FIGURES

Table 1

Characteristics of patients affected by MR-ONJ

MRONJ observed patients	41

Median Age	72,97
Gender	N. (%)
Male	4 (9.75)
Female	37 (90.24)
Anatomic location of MR-ONJ	
Lower jaw	34 (82.92)
Upper jaw	7 (17.07)
Type of Bisphosphonate Used	
Alendronate (oral)	30 (73.17%)
Ibandronate (oral)	8 (19.51%)
Risedronate (oral)	5 (12.19%)
Neridronate (oral)	1 (2.43%)
Cumulativedose of the administered BPs at MR-ONJ onset (mg)	MD
Alendronate (oral)	22422.5
Ibandronate (oral)	26400
Risedronate (oral)	21364
Median duration of BPs therapy at MR-ONJ onset (months)	85

Legend: MR-ONJ= medication-related osteonecrosis of the jaws; MD= average value; DMFT= Decayed-Missing-Filled Teeth; CPITN= Community Periodontal Index of Treatment Needs.

Table 2

Local risk factors for MRONJ occurrence

	N.(%)
Dental/Oral surgery prior to MRONJ occurrence	25
DMFT index	MD

Decayed teeth	1,97
Missing teeth	15,38
Filled teeth	2,43
Pocket probing	4,96
CPITN index code	3
CPITN index score	II

Legend: MR-ONJ= medication-related osteonecrosis of the jaws; MD= average value; DMFT= Decayed-Missing-Filled Teeth; CPITN= Community Periodontal Index of Treatment Needs.

Table 3

Scores from the EORTC-H&N 35 survey.

Symptom	Score pre-op	Score post-op	Δ %	P
Pain	57,52	4,06	-92,93	0,032
Swallowing	17,07	4,67	-72,61	0,090
Senses problems	20,32	1,21	-94	0,351
Speech problems	15,17	3,79	-75	0,135
Trouble with social eating	13,82	4,87	-64,70	0,086
Trouble with social contact	16,58	3,73	-77,45	0,024
Less sexuality	27,43	18,51	-32,50	
Teeth	37,39	17,88	-52,17	0,000
Opening mouth	35,77	15,44	-56,81	0,000
Dry mouth	58,53	26,82	-54,16	0,000
Sticky saliva	53,65	10,56	-80,30	0,000
Coughing	4,06	7,01	-72,45	0,044
Felt ill	38,21	13,82	-63,82	0,000

Legend: Score pre-op=pre-operative; Score post-op=post-operative.

Table 4

EORTC-H&N 35 Average values on a scale from 1 to 4 assigned to each single response (Q31-60). Percentage of positive response (Q61-65).

Question	Pre-op	Post-op	Δ %	Question	Pre-op	Post-op	Δ %
Q31	3,41	1,17	-65,68	**Q50**	1,12	1,07	-4,46
Q32	3,39	1,17	-65,48	**Q51**	1,39	1,27	-8,63
Q33	2,63	1,12	-57,41	**Q52**	1,48	1,04	-29,73
Q34	1,46	1,02	-30,13	**Q53**	1,95	1,73	-11,28
Q35	1,09	1,02	-6,42	**Q54**	1,51	1,12	-25,82
Q36	1,24	1	-19,35	**Q55**	1,22	1	-18,03
Q37	2,19	1,41	-35,61	**Q56**	1,53	1,12	-26,79
Q38	1,51	1,12	-25,82	**Q57**	1,70	1,24	-27,05
Q39	2,12	1,46	-46,22	**Q58**	1,09	1	-8,25
Q40	2,07	1,46	-29,46	**Q59**	1,8	1,55	-13,88
Q41	2,75	1,80	-34,54	**Q60**	1,84	1,55	-15,76
Q42	2,61	1,31	-49,80	**Q61**	68,2 %	12,19 %	-82,12
Q43	1,24	1,02	-17,74	**Q62**	46,34 %	17,07 %	-63,16
Q44	1,97	1,04	-47,20	**Q63**	NA	NA	NA
Q45	1,12	1,02	-8,92	**Q64**	51,21 %	4,87 %	-90,49
Q46	1,14	1,07	-6,14	**Q65**	NA	31,70 %	NA
Q47	2,14	1,41	-34,11				
Q48	1,92	1,19	-38,02				
Q49	1,65	1,19	-27,87				

Legend: Q=question; Pre-op=pre-operative; Post-op=post-operative; NA=Not Available.

Table 5

Results of perceived oral health VAS scale. Value range from 0 (worst state of health) to 100 (best state of health).

Patient	VAS pre-op	VAS post-op	Patient	VAS pre-op	VAS post-op
P1	30	90	**P22**	20	90
P2	40	100	**P23**	50	100
P3	20	90	**P24**	50	100
P4	30	100	**P25**	30	100
P5	30	100	**P26**	40	100
P6	50	100	**P27**	20	60
P7	20	90	**P28**	40	70
P8	20	70	**P29**	50	100
P9	20	100	**P30**	10	90
P10	40	100	**P31**	60	100
P11	40	100	**P32**	50	100
P12	50	100	**P33**	60	100
P13	40	60	**P34**	30	100
P14	50	100	**P35**	40	100
P15	60	100	**P36**	40	100
P16	30	50	**P37**	50	100
P17	50	100	**P38**	20	100
P18	50	100	**P39**	30	90
P19	20	90	**P40**	30	100
P20	10	80	**P41**	40	70
P21	20	80			

Legend: P=patient; VAS pre-op=pre-operative; VAS post-op=post-operative.

FIGURE 1. Maxillary osteonecrosis of the jaw at time of diagnosis.

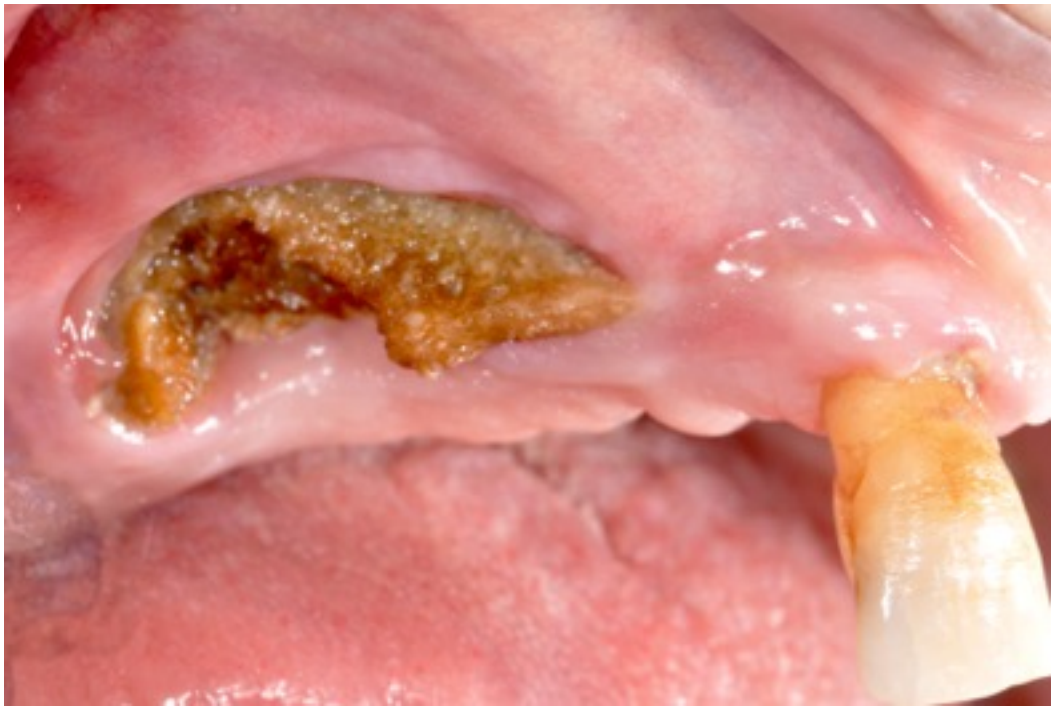


FIGURE 2: X-ray computed tomography showing the necrotic bone extension.

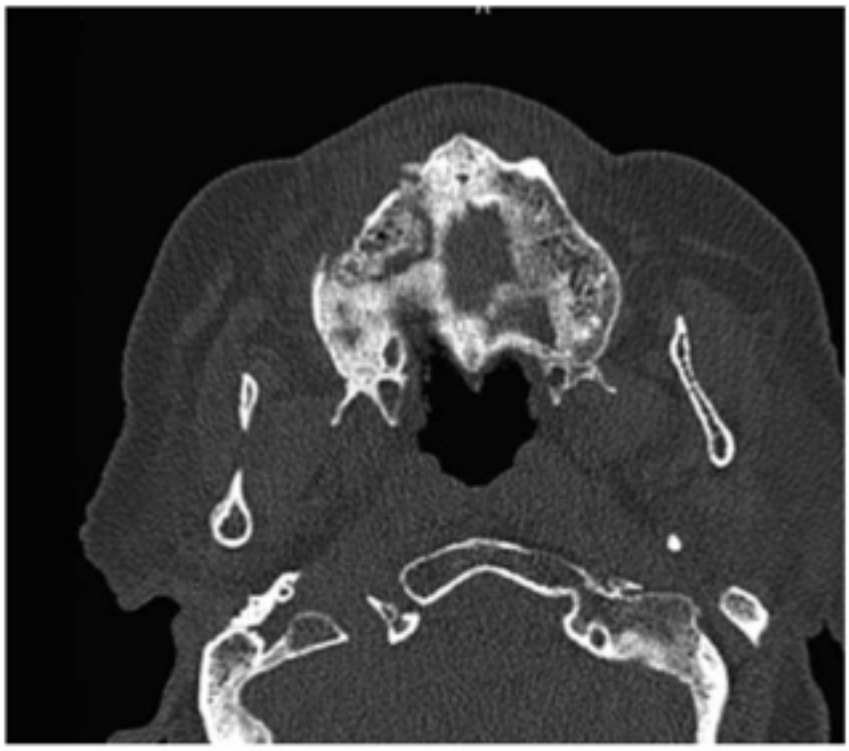


FIGURE 3: Intraoperative aspect of the piezoelectric resective surgery.

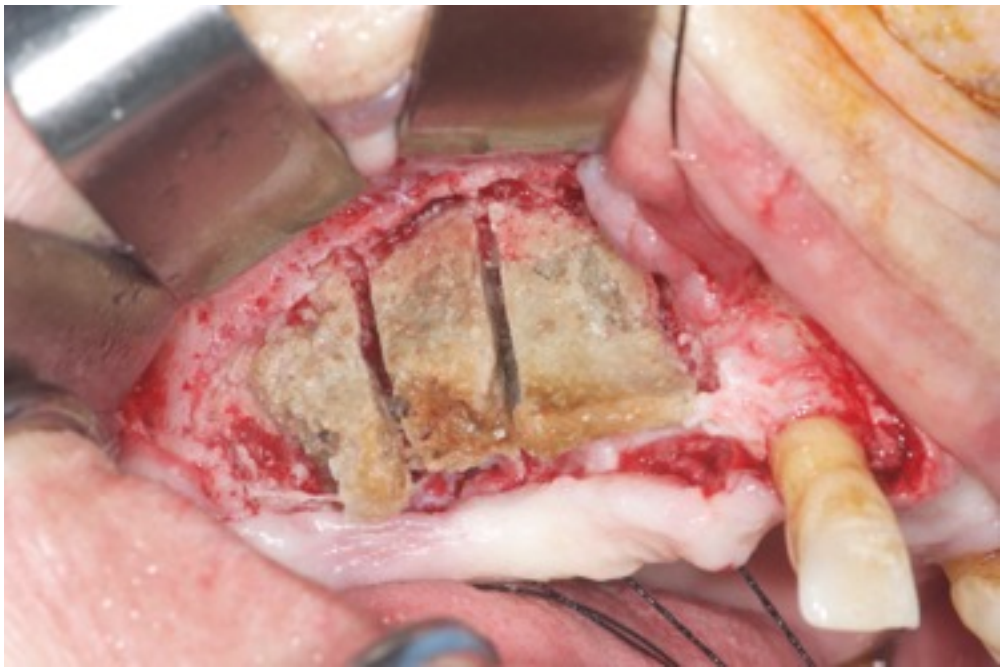


FIGURE 4. Intraoperative aspect after the removal of necrotic bone.

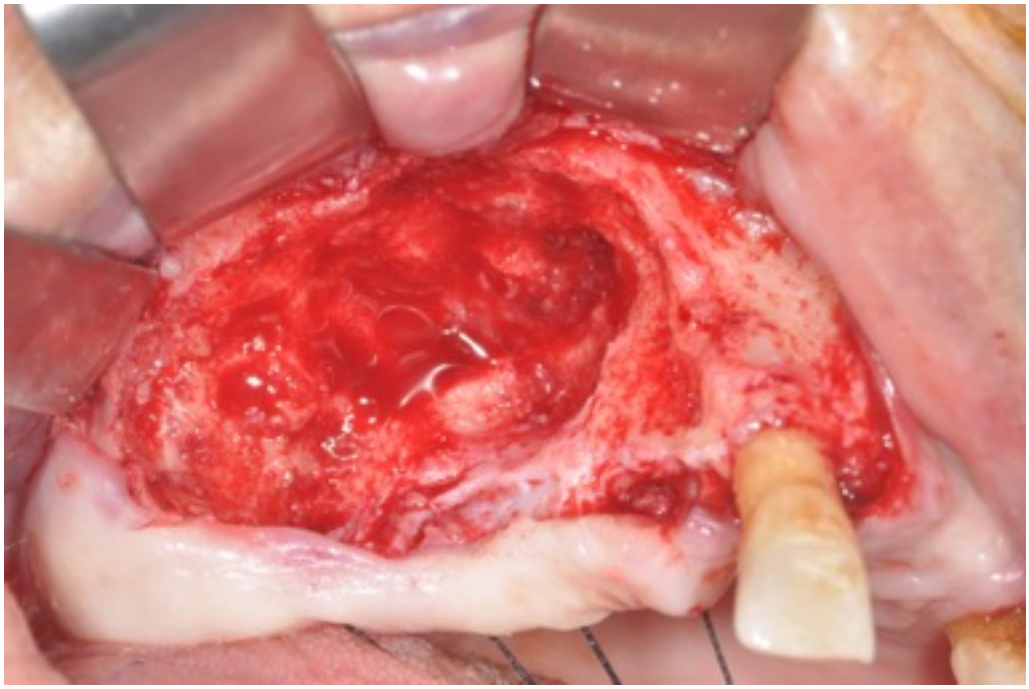
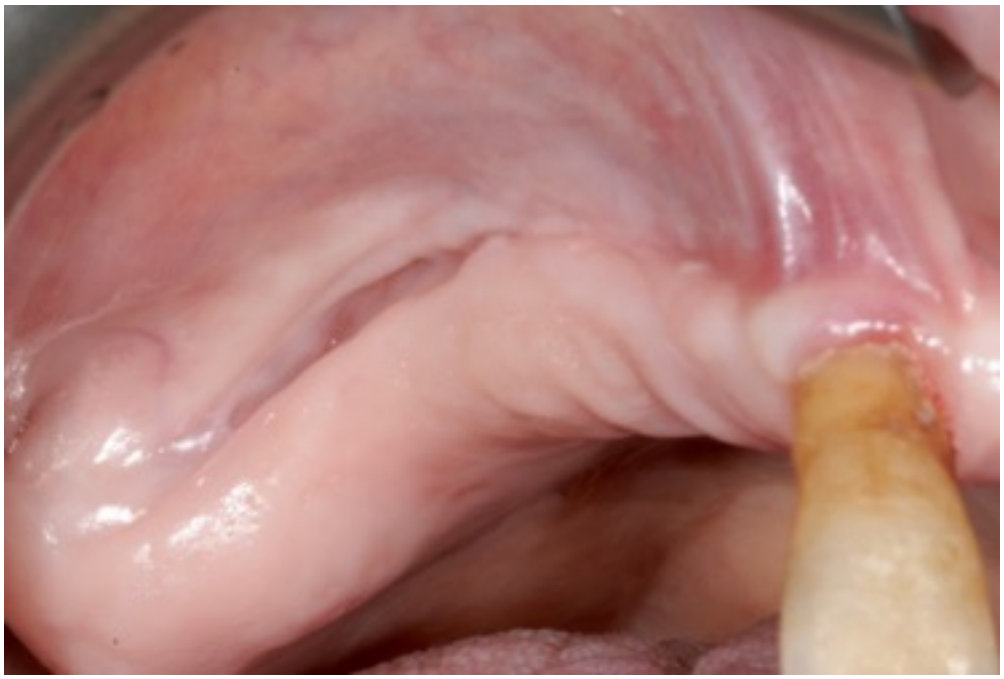


FIGURE 5: Evidence of mucosal healing 12 months after surgery.



Chapter 3: Risk factors for MRONJ and etiology

Conventional risk factors

The antiresorptive medications Zometa® and Xgeva® prescribed to prevent skeletal-related events associated with solid tumors-related bone metastases and with lytic lesions associated to multiple myeloma have been associated to MRONJ in view of their effect of inhibition of osteoclastic bone resorption and remodeling.

MRONJ has been also associated to some antiangiogenic medications such us bevacizumab (Avastin ®) because of its inhibition of the endothelial growth factor (VEGF) signaling cascade [1].

Although exposure to the above mentioned antiresorptives and antiangiogenics is the primary risk factor for MRONJ in cancer patients additional factors have been associated with MRONJ but for most of these their contribution in the co-occurrence of the adversity remains unclear [2].

Risk factors for MRONJ are mainly classified into systemic and local and are usually further divided according to:

- MRONJ-related drug type: antiresorptive (e.g. bisphosphonates, denosumab) and antiangiogenic (e.g. bevacizumab, sunitinib) drugs.
- MRONJ risk patient category: cancer patients and non-cancer patients.
- Types and timing of dental treatments (for example before, during or after drug administration) [3].

Both intravenous and oral of bisphosphonate can induce osteonecrosis of the jaws, although there is a higher risk for the intravenous route of administration [2].

Cumulative dose and duration of exposure appear to be the most important risk factors for this complication with a higher risk after prolonged bisphosphonate intake. MRONJ appears to be time-dependent, with increased risk after long-term use of bisphosphonates, often after tooth extractions [3].

Data available in the literature suggest that 27.5% of people exposed to anti-resorptive agents can develop MRONJ [2].

In a 2009 literature review, the median / minimal time to onset of MRONJ was identified between 10 months and 1.8 years for zoledronic acid, and between 1.5 and 2.8 years for pamidronate, but cases of MRONJs that appear after a few bisphosphonate infusions (often after extraction of one or more teeth) [4].

Zoledronic acid appears to cause a statistically higher risk of MRONJ than pamidronate, despite the absence of randomized studies [5,6] and ibandronate as well compared to zoledronic acid appears to have a lower risk [7].

Clodronate (a non-nitrogenous bisphosphonate, used mainly in patients with myeloma) has a lower risk of MRONJ compared with zoledronic acid, which is likely due to a different mechanism of action, as well as the frequency of use [8].

The combined use of anti-angiogenic agents (such as bevacizumab, sunitinib and sorafenib) and bisphosphonates has been associated with an increased risk of developing MRONJ [6,9-11].

MRONJ incidence may be influenced by the malignancy type/severity as well as by the contemporaneous intake of anti-cancer drugs [12,5,8,14-17].

Cancer type seems to play an important role in the incidence of MRONJ.

In the SWOG0702 trial analysis by cancer type demonstrated a higher 3-year risk in multiple mieloma patients (4.3 versus 2.9% for prostate cancer, 2.7% for lung cancer, and 2.4% for breast cancer) [18].

In a report by Rugani et al the weighted prevalence of medication-related osteonecrosis of the jaw was 2.09% in the breast cancer group, 3.8% in the prostate cancer group, and 5.16% for multiple myeloma patients [19].

Recently, an incidence of about 0.8% in breast cancer patients has been observed [20].

Walter et al also reported a lower prevalences in breast cancer patients compared to prostate cancer and multiple myeloma patients [21].

It has been reported that patients with prostate cancer have a three-fold higher risk of denosumab- associated MRONJ as compared to those with other cancer types [22-25].

Qi et al reported that the prevalence of denosumab-related MRONJ in patients with prostate cancer was higher compared with that in

patients with non-prostate cancers relating that to the longer median follow-up period for prostate cancer compared with other tumor type suggesting that the variability in the prevalence of ONJ in the different cancer types may be due to this variation [26].

In the recent study by Ikesue et al with 374 patients examining the patient characteristics between the denosumab and zoledronic acid groups the distribution of cancer types was significantly different between groups ($P < 0.001$) [27].

The increased risk of MRONJ in these patients may be attributable to the dose and frequency of administration.

Other co-morbid conditions beside cancer have been reported to have a strong positive association with MRONJ development [28].

Nevertheless when a chronic condition is under effective control, it is not a risk factor predisposing to the development of MRONJ [29].

Ardine et al hypothesized that hypocalcemia, hyperparathyroidism and bone mineralization disorders may be contributing conditions for the development of MRONJ, after administration of bisphosphonates [30].

Furthermore a strong association between osteomalacia and MRONJ has been identified [31].

The potential contributing effect of vitamin D deficiency, secondary hyperparathyroidism and bone mineralization defects has been discussed [32,33].

Oral factors predisposing to development of MRONJ are receiving attention, and oral management is recommended for prevention since it proved effectiveness in reducing the incidence of MRONJ [34-36].

There is general consensus that dentoalveolar surgery and simple tooth extraction, in particular, are the most significant risk factors associated with MRONJ in cancer patients taking anti-resorptive drugs [37] thus is considered a critical risk factor for the development of MRONJ.

In the majority of reported MRONJ cases, recent dento-alveolar trauma was the most prevalent risk factor [38] indicating tooth extraction as a surgical procedure that predisposes to the development of MRONJ [7].

Increasing evidence in the literature suggests that avoiding surgical trauma and jaw bone infection can minimize the risk of MRONJ, but there are still a significant number of individuals who develop MRONJ in the absence of these risk factors [2].

The relationship between dental implants and MRONJ development. has been explored. Dental implant placement is considered a potential trigger for MRONJ in cancer patients [39,40].

For patients taking denosumab for the prevention and management of postmenopausal osteoporosis and cancer induced bone loss the level of risk is uncertain [3].

A significant correlation has been documented between the use of removable prostheses and the development of MRONJ in a population of metastatic cancer patients treated with high-dose intravenous bisphosphonates [7,41].

The use of dentures increases the risk of developing MRONJ [7].

The presence of infections in periodontal and peri-implant dental sites has been highlighted as one of the main local risk factors for the development of MRONJ, often being the main reason for surgical dental extraction or implant removal procedures [3].

Dental and periodontal infection significantly increases the risk of MRONJ in cancer patients exposed to anti-resorptive therapy [42,43].

Being periodontal disease diagnosed in the 84% of cases in a large sample of patients with MRONJ [44].

Furthermore it has been hypothesized that the concomitant administration of chemotherapeutic agents could be considered a factor capable of allowing a more rapid worsening of clinical manifestation through the exacerbation of soft tissue defects [45].

During the use of these drugs, mucositis, stomatitis and severe gingival ulcerations may occur which could represent a local factor that predisposes to the onset of MRONJ, because the epithelial damage of gingival inflammation with multiple persistent ulcerations, involves a entry for infection to the bone [46,47].

Skin toxicities are among the most frequently observed adverse events associated with most targeted therapies and biologics, these toxicities are well characterized while oral mucosal changes induced by oncological therapies are less well described and are generally referred to using a terminology that does not specify “stomatitis” [46].

Oral mucosal toxicities described in a review by Vigarios et al include: stomatitis associated with m-TOR inhibitors and protein kinase

inhibitors; stomatitis, benign migratory glossitis and mucositis induced by EGFR inhibitors (Epidermal Growth Factor Receptor; used alone or in combination with radiotherapy and / or chemotherapy for head / neck diseases); injuries associated with BRAF inhibitors; pigmentation changes and lichenoid reactions secondary to imatinib and explore the first available structured data on oral toxicity induced by the new monoclonal antibodies to PD-1 and could be related to MRONJ onset [46].

Based on the previous considerations the pathogenesis of MRONJ is likely to be multifactorial and can involve a synergistic effect between exposure to denosumab or bisphosphonates which is the primary risk factor for MRONJ, some other systemic determinant factors and a triggering events (dental extraction, periodontal infection, ill-fitting prostheses).

The following hypothesis has been formulated for MRONJ onset: (1) a direct local effect represented by the epithelial damage [48-52] and (2) an indirect systemic effect exerted by the immunosuppressive action of anti-cancer treatments [53,54].

The new concept of osteoimmunology [55]_indeed had been recently added to the previous etiopathogenetic theories on MRONJ development [56] and lastly (3) the hypothesis that new anticancer drugs may play a role in osteoclast differentiation additionally affecting the RANKL-mediated cell cycle arrest as supported by recent in vitro and in vivo data [57,58].

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Chapter 3: Risk factors for MRONJ and etiology

Anticancer medications related to MRONJ

Cancer patients receive multiple agents that interfere with bone metabolism and may, therefore, cause or benefit the development of osteonecrosis [1-5].

Among the secondary drugs that possibly contribute to MRONJ development. hormonal therapy has been indicated as a confunding factors [6].

Neha et al reported that the signal generated for aromatase inhibitors associated osteonecrosis of jaw in the Food and Drug Administration Adverse Event Reporting System database can be false positive since upon removing the reports of concomitantly administered drugs (bisphosphonates and denosumab), signal strength for letrozole, anastrozole and exemestane respectively drastically decrease [6,7].

Regarding the utilization of chemotherapy MRONJ is associated with anti-cancer agents including classic chemotherapy agents [8,9].

The review by Shim et al summarizes fifty-four reported cases of osteonecrosis associated with chemotherapy in cancer patients [10],

as the presence of an immunosuppressive status poses a high risk of developing infection and chemotherapy has a cytotoxic effects on bone metabolism and vascularization [11,12].

In patients with multiple myeloma the use of thalidomide increased the risk for MRONJ by 2.4-fold (P = 0.043) [13].

Patients with prior multiple chemotherapy regimens should be monitored for early symptoms of MRONJ [10].

In addition to well-known medications, MRONJ may be a major adverse reaction to several new-generation anticancer drugs due to unknown mechanisms [14,15].

To date, several medications have been somehow implicated with MRONJ on the basis of the experience gained through isolated data, case series reports and literature review [16-20]

Recent reports have suggested a relatively high MRONJ risk in patients with a combined administration of bisphosphonates and targeted drugs [21,22].

In a study conducted between January 2010 and May 2016, 7 cases associated with target therapy (TT) (3.4%) were recorded on a total of 204 patients with MRONJ. Four patients received TT alone, while three were treated concomitantly with bisphosphonates and / or denosumab. TT regimens included: sunitinib (Sutent) (n = 1), everolimus (Afinitor) (n = 1), erlotinib (Tarceva) (n = 1), bevacizumab (Avastin) (n = 3), dasatinib (Sprycel) (n = 1) and imatinib (Glivec) (n = 1). The case of MRONJ associated with dasatinib, the authors say, is the first reported in the literature [23].

The combination of VEGF and bisphosphonates has been reported to increase the risk of MRONJ [20, 24,25].

Similarly, it was well confirmed that mTORs inhibitors have a strong immunosuppressive effect which can lead to delayed healing of oral soft tissues and persistent infections favoring the onset of the osteonecrotic process [26,27].

Monoclonal antibodies have been implicated too in the development of MRONJ [3,28-34] .

Although no definitive conclusions has been reached regarding the influence of anti-cancer drugs on MRONJ development these may represent an additional risk factor for the occurrence of MRONJ.

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Chapter 3: Risk factors for MRONJ and etiology

In the previous paragraphs of this chapter we focused on the different risk factors associated with MRONJ onset.

From the observation of our retrospective patient cohort it emerged that the high incidence of oral lesions and inflammation of the mucous membranes recorded among the adverse effects of the new anti-cancer therapies could favor the development and progression of MRONJ.

This finding led us to formulate the hypothesis that the concomitant administration of chemotherapy and target therapies together with the antiresorptives could possibly allow a more rapid worsening of the clinical manifestation of MRONJ through the exacerbation of soft tissue defects.

Thus a case-control study was designed for a comparative evaluation of the MRONJ event in a population of patients with current or previous treatment with zoledronic acid and / or denosumab administered for the treatment of bone metastases and conducted in order to identify new anticancer drugs. at risk of MRONJ and / or alongside bisphosphonates and denosumab, and provide risk stratification among ONJ-related drugs in the cancer patient population by evaluating associated cancer treatment regimens.

Could the Combined Administration of Bone Antiresorptive Drug,Taxanes, and Corticosteroids Worsen Medication Related Osteonecrosis of the Jaws in Cancer Patients?

Introduction

Medication related osteonecrosis of the jaws (MR-ONJ) constitutes an important issue in the eld of oral medicine and surgery as it is regularly encountered in oral pathology services. e majority of MR-ONJ cases are associated with the high-risk cancer patients [1, 2]. Osteonecrosis of the jaws in patients undergoing treatment with antiresorptive and/or antiangiogenic agents appears to be caused by the combination of a vascular supply de cit and a remodeling and bone regeneration de cit [3]. Bisphosphonates (BPs), denosumab but not immunosuppressive or chemotherapy drugs, are the major cause of MR-ONJ [4–6]. Nevertheless it has been reported that the simultaneous administration of chemotherapy drugs increases the severity of the disease, especially the incidence of so tissue defects [7]. e capacity of antineoplastic drugs to accelerate MR- ONJ is likely attributed to their ability to block endothelial cell migration and proliferation [8, 9]. In a study by Bi et al. mice treated with bisphosphonates and dexamethasone all devel- oped osteonecrosis. In this in vivo experimental model the authors found that administration of zoledronic acid (ZA), dexamethasone, and docetaxel leads to bone necrosis and intense in ammation within the extracted alveolar socket

well beyond the period of natural wound healing. e authors found that injections of zoledronate, dexamethasone, and docetaxel developed signi cantly larger areas of dead bone at both 3 and 12 weeks when compared with mice treated with zoledronate and dexamethasone [7].

MR-ONJ is strongly related to the long-term use of bisphosphonates and mechanical trauma [10]. Recent ret- rospective analyses of human MR-ONJ cases demonstrate a correlation among the use of chemotherapy drugs and immunosuppressive agents and the development of MR-ONJ [7].

Bisphosphonates and denosumab are drugs widely used on a worldwide scale with clear bene ts for oncological patients that have been clinically proven. ey result in a quality of life improvement for oncological patients with bone metastases but, on the other hand, the appearance of osteonecrosis of the jaws dramatically aspects general health and quality of life of patients suffering of this complication with high morbidity. Quality of life values significantly decrease with worsening MR-ONJ [11–13]. To hold in consideration the oral health quality of life (OHQoL) is recommended by e WHO to assess the subjective and objective functional status of an individual's oral health and the impact of oral complications on daily living and QoL [14].

To pay greater attention to predisposing risk factors translates into better prevention strategies. erefore the objective of this study was to report about the observation of cancer patients treated with taxanes, bisphosphonate, and denosumab plus corticosteroids who developed osteonecrosis of the jaws.

Methods and Materials

The study protocol was approved in date 03.27.2017 by the Ethical Committee of the Academic Hospital of Messina (n. 38/17). e les of the two Italian osteonecrosis of the jaws treatment centers, who are based at the University of Messina and at the University of Palermo, served as a source of material for this study. Files were systematically searched for cases of MR-ONJ in metastatic cancer patients treated with taxanes during a 10-year period (2006–2016). Cancer patients prior to start, undergoing or with a history of previous treatment with bisphosphonates or denosumab for the treatment of bone metastases, are regularly referred to the dental specialists at these MR-ONJ treatment centers, by the chief oncologist and/or primary care physician.

As part of the clinical care routine medical anamnesis is collected in order to analyze patients' medical history as well as oral examination and dental radiographs taken and local risk factors are analyzed.

A total of 58 MR-ONJ patient data were consecutively analyzed. Patients characteristics, demographic data, fre- quency of cancer location, lines of therapy, frequency of oncologic drugs, oral conditions, number, site, and staging of jaw osteonecrosis were reported. Zoledronic acid duration and cumulative dose were evaluated. Previous and concur- rent cancer treatments with antineoplastic agents including denosumab and bevacizumab and

corticosteroids were also reported. Registered MR-ONJ features (location and number of MR-ONJ lesions, stage, presence of suppuration, and referred oral trigger) were analyzed.

MR-ONJ stage was classi ed according to the Italian Society of Oral Medicine and Pathology (SIPMO) approach.

Results

Patients characteristics are summarized in Table 1 including details in relation to gender, frequency of cancer location frequency of oncologic drugs other than zoledronic acid, frequency of MR-ONJ location, presence/absence of oral trigger, and presence/absence of suppuration among subjects who developed osteonecrosis of the jaws. Female gender was prevalent representing 60% of patients. e most frequent cancer type was breast cancer (65,5%) followed by prostate cancer (27,5%). In the registry, we found 3 patients who were given antiresorptive therapy for metastatic lung cancer (5%) and 1 patient diagnosed with nasopharynx cancer.

Of the 58 patients in the registry, all the patients received corticosteroids; all the patients but two received zoledronic acid, two patients received denosumab as the only antiresorp- tive treatment for bone metastasis, and 15,5% of the patients received both zoledronic acid and denosumab.

Docetaxel was found to be administered in 65,5% of the patients while in 43% of the patients paclitaxel was the administered taxan, and ve

patients were treated sequen- tially with docetaxel and paclitaxel. 24% of the patients were given bevacizumab.

In relation to MR-ONJ features, the most common location of MR-ONJ was the mandible (n = 43 [74%]), followed by the upper maxilla (n = 10 [18%]). Furthermore 5 cases involving both jaws (9%) were observed. MR-ONJ lesions were reported to be mainly symptomatic due to the presence of suppuration, and localized infections were detected in 64% of cases (9 subjects in stage I [16%] and 28 in stage II [48%]). e presence of a potential oral trigger was recorded in 6 (62%) patients.

According to the SIPMO classi cation, the most frequent stage of MR-ONJ was stage II (37 subjects), whereas stage I (13 subjects) and stage III (8 subjects) were less common (Table 2).

Mean age was 63,43 years. In relation to the length of exposure, the average duration of antiresorptive therapy until the moment of the diagnosis was 17,58 months (ranging from 2 to 48 months), corresponding to 67,46 mg if expressed as average cumulative dose (Table 3).

Patients were mostly receiving rst-line (28%) or second- line (29%) cancer therapy, more patients received third- line chemotherapy (21%), a less percentage of patients who undergo advanced (greater than third) chemotherapy lines was reported, and fourth- and h-line therapy were used in 17% and 5% of the patients, respectively (Table 4).

Discussion

MR-ONJ is a severe adverse drug reaction consisting of progressive bone destruction in the maxillofacial region of patients. MR-ONJ can be caused by several pharmacological agents, mainly antiresorptive (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand inhibitors) and antiangiogenic [15, 16].

A major obstacle in elucidating the pathophysiology of this disease is the simultaneous use of multiple therapeutic drugs in cancer patients, which are required to control both tumor growth and its related skeletal complications [17–20]. e study highlighted the role of taxanes (docetaxel and pacli- taxel) a second-line monotherapy or combination therapy which is an e ective option in the treatment of patients with metastatic breast cancer a er failure of prior chemotherapy [21]. Indeed results reported that in the majority of the patients (29%) MR-ONJ occurred while receiving a second- line cancer therapy.

Docetaxel targeting endothelial cells inhibits endothelial cell proliferation and tubule formation in a dose-dependent fashion [9]. Taxanes have remained a cornerstone of breast cancer treatment [21] particularly in triple negative subsets [22].

In this study, we investigated the role of taxanes, in a broader sense of chemotherapeutic agents in the develop- ment of this serious side e ect. In this case series of 58 patients who were concurrently given taxanes and zoledronic acid/ denosumab, MR-ONJ occurred mostly in

advanced stages (di use osteonecrosis with presence of infection in the 64% of the cases).

MR-ONJ involved the lower jaw more frequently than the upper or both jaws and the presence of a potential oral trigger was identi ed in the majority of the cases, results in line with previously published data [2].

MR-ONJ stage was classi ed according to the Italian Society of Oral Medicine and Pathology (SIPMO) approach, based on the extent of bone disease, i.e., whether it is focal or di use assessed through CT scan and the clinical ndings of presence/absence of suppuration [23–26].

The findings show that patients who are given taxanes and corticosteroids for metastatic cancer while undergoing zoledronic acid or denosumab treatment are prone to developing MR-ONJ.

Nevertheless, the development of MR-ONJ under bone metastasis treatment may be associated solely with the dura- tion of ZA/ denosumab treatment. e concurrent adminis- tration of docetaxel could have eventually allowed a faster worsening of the clinical manifestation through the exacer- bation of so tissue defects due to chemotherapy drugs.

Moreover during the administration of taxanes, the systematic premedication with antihistamines and corticos- teroids before standard infusions is used to prevent infusion adverse reactions. Consequently, all the patients assumed a considerable dose of corticosteroids and these medications are associated with an

increased risk for MR-ONJ develop- ment [27, 28]. A er all in the literature, it has been already hypothesized that combining bisphosphonates with other medications such as antiangiogenic agents may induce MR- ONJ more frequently than using bisphosphonates alone [29].

In a literature review by Mcgowan et al., 11 dental risk factors for MR-ONJ development were reported, among these infections/abscesses, although no statistical analysis of the signi cance of each of these factors was possible [30].

According to the ndings from the present study, there was a higher percentage of cases in advanced stages of osteonecrosis, frequently complicated with infection (48% of the patients with di use IIB stage disease).

MR-ONJ symptomatology is characterized by dull and ceaseless pain, in advanced stages, and the exposure of necrotic bone is evident, which is frequently associated with purulent secretions and foetor oris [31].

e presence of suppuration was registered in 64% of the patients suggesting the use of targeted antibiotic therapy due to the opportunistic characteristics of the bone suprainfection [31].

Adequate di erential diagnosis of microorganisms in the oral cavity prior to therapeutic attempts is of great importance to prevent the spread of MR-ONJ since pharmacological treatment is considered essential in order to control pain and bone infection and preserve patient quality of life [11, 17].

Various other novel antineoplastic and bone-targeting therapies that can also cause jaw necrosis have recently become available [27].

Agents such as corticosteroids, erythropoietin, angio- genic inhibitors (e.g., thalidomide, sunitinib, bevacizumab, and lenalidomide), and tyrosine kinase inhibitors, which are essentially administered as adjuvants in the treatment of cancer patients, have been shown to increase the risk of MR-ONJ when used concomitantly with bisphosphonates or denosumab [32, 33].

In bone metastatic cancer patients, the introduction and increase of the use in combination with bone antiresorptive therapies of a range of chemotherapies and biological targeted therapies are associated with an increase of treatment-related oral toxicities [34].

Oral injuries such as mucosal in ammation and stom- atitis go hand in hand with the lack of patients compliance to oral hygiene that can increase the risk of developing MR-ONJ [35]. In the author's opinion, the combination of zoledronic acid and taxanes, plus corticosteroids, may have some synergy of e ect and a particularly detrimental in uence on the severity of MR-ONJ. e observation of these patients represents a starting point for re ection to stimulate the attention of the community to look a er the patients treated with bone targeted therapies in combination with other agents and maximize their mouth care [36, 37].

Limitations of the Study

The authors consider it worth underlining that in their opinion studies conducted in a osteonecrosis of the jaws treatment center are biased since they do not represent the true frequency of MR-ONJ because this institute serves mainly as a referral center for oncologists and mainly problematic cases are submitted for consultation.

e best source to obtain information on the true relative frequency of MR-ONJ is from the records of a large cancer center.

Information gained from the les of such an institution is invaluable and represents the only large source of data for a case and control study on the relative frequency of MR-ONJ.

Conclusions

This study evaluated data obtained from patients with metastatic cancer, whose les and treatments were regularly followed up in the osteonecrosis of the jaws treatment centers of the University of Palermo and Messina. A multicentric case and control study has already been designed for a comparative evaluation of MR-ONJ occurrence matching the case group with a population of cancer patients with current or previous treatment with the same type of medication (zoledronic acid and denosumab) for metastatic bone disease and had not developed MR-ONJ. In the absence of data from a case and control study, no rm conclusion can be drawn about the synergistic e ect of combined ZA/denosumab and chemotherapeutic agents in developing MR-ONJ. Anyhow in patients receiving bone targeted therapies in

combination with cancer therapies asso- ciated with oral complications, intense clinical observation is even more recommended.

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FIGURES ANF TABLES

Table 1: Patients characteristics: gender, frequency of cancer loca- tion, frequency of oncologic drugs other than zoledronic acid, frequency of MR-ONJ location, presence/absence of oral trigger, and presence/ absence of suppuration among subjects who developed osteonecrosis of the jaws.

	n (%)
Gender	
Female	36 (62%)
Male	22 (38%)
Cancer location	
Breast cancer	38 (65,5%)
Prostate cancer	16 (27,5%)
Lung cancer	3 (5%)
Nasopharynx cancer	1 (2%)
Other therapies	
Docetaxel	38 (65,5%)
Paclitaxel	25 (43%)
Bevacizumab	14 (24%)
Denosumab	9 (15,5%)
ONJ location	
Mandibular	43 (74%)
Maxilla	10 (18%)
Mandibular/Maxilla	5 (9%)
Oral trigger	
Absence	22 (38%)
Presence	36 (62%)
Suppuration	
Absence	21 (36%)
Presence	37 (64%)

Table 2: MR-ONJ stage.

MR-ONJ stage	*n* (%)
IA	7 (12%)
IIA	6 (10%)
IB	9 (16%)
IIB	28 (48%)
III	8 (14%)

Table 3: Patients age and description of zoledronic acid therapy regimen.

	Min	Mediana	Media	Max	SD
Age	43	64	63,43	84	10,24
Cumulative dosage ZA	8	62	67,46	192	37,8
Therapy duration	2	16	17,58	48	10,08

Table 4: Lines of cancer therapy.

Line of cancer therapy	*n* (%)
1	16 (28%)
2	17 (29%)
3	12 (21%)
4	10 (17%)
5	3 (5%)

Chapter 3: Risk factors for MRONJ and etiology

From the enlargement of the previous cohort, a further possibly noteworthy aspect has been explored.
The following case series was collected in response to the need to define whether an unidentified trigger exists for spontaneous MRONJ. It takes into account a conceivable cumulative effect of zoledronic acid and/or denosumab during CDK inhibitors administration in medication related osteonecrosis of the jaws (MRONJ) onset.
Clearly no statement can be made without the appropriate study design and statistics.
Nevertheless our main aim is to convey the message of a possible relationship between new anti-cancer therapies and a probable co-occurrence of adversity which should be addressed in the future since individualized MRONJ prevention strategies can only come from a thought understanding of risk factors.

Medication-Related Osteonecrosis of the Jaws and CDK4/6 Inhibitors: A Recent Association

Introduction

The discovery of various driver pathways and targeted small molecule agents/antibodies have revolutionized the management of metastatic breast cancer. Currently, the major targets of clinical utility in breast cancer include the human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) receptor, mechanistic target of rapamycin (mTOR) pathway and the cyclin-dependent kinase 4/6 (CDK4/6) pathway [1]. Palbociclib and abemaciclib are approved in combination with an aromatase inhibitor or fulvestrant for HR+ MBC. Abemaciclib

is also approved as monotherapy for pretreated patients [2]. Palbociclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor approved by the Food and Drug Administration (FDA) for the HR-positive, HER2-negative advanced or metastatic breast cancer in 2015 in combination with an aromatase inhibitor (AI) and letrozole [2].

Abemaciclib is another CDK4/6 kinase inhibitor but more potent against CDK4. It was approved by the FDA in 2017 for the treatment of the postmenopausal woman with the HR-positive, HER2- negative advanced or metastatic breast cancer in combination with fulvestrant [2]. The toxicity profile of the CDK4/6 inhibitors has been detailed in the clinical trials for each drug in the class (palbociclib- PALOMA; ribociclib-MONALEESA; abemaciclib-MONARCH) and postmarketing reports [3–6]. Stomatitis was a common (15.3%) adverse reaction reported in palbociclib-treated patients in randomized clinical trials. Stomatitis includes the following: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, inflammation of the mucous membrane, oral pain, oropharyngeal disorder, oropharyngeal pain and stomatitis [3]. Stomatitis/mucositis could eventually be implicated in medication-related osteonecrosis of the jaw (MRONJ) development due to breaking of the mucosal lining in the mouth and exposure of the underlying bone to bacteria [7,8]. The purpose of the present study was to estimate the prevalence of CDK4/6 inhibitors use among the cancer patients from the MRONJ cohort of the University of Messina.

The described work has been carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For the characterization of this study group, we retrospectively reviewed the records of all patients with either intravenous bisphosphonates or denosumab-related MRONJ reported in the electronic health records (EHRs) of the Unit of Oral Surgery, School of Dentistry, University of Messina between the first quarter of 2018 and the first quarter 2020. Inclusion criteria were: (a) MRONJ diagnosis performed on the basis of the Italian Society of Oral Pathology (SIPMO) definition and staging system, (b) CDK4/6 inhibitor treatment and (c) zoledronic acid and/or denosumab use for bone metastasis treatment. In the SIPMO staging system, the clinical signs and symptoms (pain and inflammation/ infection) were used to distinguish between the asymptomatic and symptomatic manifestations within the same stage [9]. In the clinical routine of the Osteonecrosis of the Jaw Treatment Center, School of Dentistry, University of Messina, this classification is currently adopted since it helps to better define the therapeutic needs of patients related to exacerbations of the infectious process and treatment is planned in accordance [10]. All patients' medical records (including radiographic findings such as orthopanthomography and/

or cone beam computed tomography for MRONJ diagnosis confirmation and staging) have been evaluated. The patients' anamnestic features (primary disease, comorbid conditions, i.e., hypertension, diabetes and lipid disorders) and the local risk factors were analyzed. Suspected medications (zoledronic acid and/or denosumab) and their cumulative dose as well as the concomitant cancer medications supposed to have a synergic effect in MRONJ development were analyzed. Anatomic location and numbers of exposed maxillary necrotic bone areas were described and evaluated. MRONJ management was investigated and divided into two types of intervention: (1) medical treatment and (2) surgery. The clinical course of MRONJ was registered, and outcome has been stratified into the following groups: healed (with the addition of the specific case spontaneous expulsion of sequestrum), partially healed, unchanged and progressive. Data of cancer patients diagnosed with MRONJ in the same period were extracted for comparison.

Results

This report described six consecutive cases of MRONJ in patients assuming CDK4/6 inhibitors concomitantly with intravenous bisphosphonates and/or denosumab among a total of 16 patients diagnosed with MRONJ between the first quarter of 2018 and the first

quarter 2020 at the Unit of Oral Surgery, School of Dentistry, University of Messina in the same period. Characteristics of the six CDK4/6 inhibitors related MRONJ and of the 16 cancer patients enrolled for the purpose of comparison are illustrated in Table 1.

All the six cases of MRONJ associated with CDK4/6 inhibitors assumed concomitantly with intravenous bisphosphonates and/or denosumab had breast cancer. Three patients received denosumab and two patients received zoledronic acid, whereas one patient was subsequently treated with zoledronic acid and denosumab. Average duration of therapy at time of MRONJ diagnosis was 24 months. On average, MRONJ occurred after 35 administrations of zoledronic acid and after 10 administrations of denosumab. The CDK4/6 inhibitors registered were palbociclib (n = 5) and abemaciclib (n = 1). No cases of MRONJ that occurred during ribociclib administration were registered in the EHRs of the Unit of Oral Surgery, School of Dentistry, University of Messina in the study period. Data of cancer patients diagnosed with MRONJ in the same period were extracted for comparison. Two patients had breast cancer, five had prostate cancer and three had multiple myeloma. Among these patients, six received denosumab and nine received zoledronic acid, whereas one patient was initially treated with zoledronic acid and then switched to denosumab therapy. On average, MRONJ occurred after 30.3 administrations of zoledronic acid and 19.4 administrations of denosumab. The cancer medications reported for the other MRONJ cases were: abiraterone (n = 2), leuprorelin (n = 1), GnRH agonist (n = 1) and radium-223 for

metastatic prostate cancer, fulvestrant (n = 1) and everolimus (1) for advanced-stage breast cancer and lenalidomide (n = 3) to treat multiple myeloma. Among patients enrolled in the MRONJ cohort, the most frequent comorbidity was heart disease (n = 11), followed by lipid disorders (n = 6), osteoporosis (n = 5), diabetes (n = 3) and diabetes (n = 3). MRONJ features such as disease stage, location, treatment, surgical procedure and outcome are summarized in Table 2.

All MRONJ stages except for stage IIIa were included: stage Ia (n = 1), Ib (n = 2), stage IIa (n = 1), IIb (n = 1) and stage III b (n = 1). The comparative assessment with this group of patients showed a similar distribution of MRONJ stages ranged between Ia (n = 1), Ib (n = 3), IIa (n = 2), IIb (n = 5) and IIIb (n = 5). The adopted therapeutic strategies have been reported for patients taking CDK4/6 inhibitors and for other cancer patients of the cohort as well. In total, 10 patients were eligible for surgical treatment (Figures 1–7) whereas for 6 patients, surgery was contraindicated, and disease control was obtained through medical treatment only.

The course of the disease in patients with CDK4/6 inhibitor-associated MRONJ and cancer from the cohort was registered. Six patients healed completely. Two patients healed partially with symptoms improvement but unchanged clinical manifestation. One patient remained stable with bone exposure and prolonged local antiseptic therapy, but the disease worsened in one patient. Among the six patients with CDK4/6 inhibitor-associated MRONJ, five patients healed

completely. In one of these cases, the spontaneous exfoliation of the sequestrum after medical therapy was observed. In one patient, the disease worsened, developing extraoral fistula.

Discussion

MRONJ prevalence in cancer patients stands around 2.09% in breast cancer, 3.8% in prostate cancer and 5.16% in multiple myeloma patients [11]. In the considered cohort, half of the patients with osteonecrosis had breast cancer. Although comorbid conditions under effective control were not a risk factor predisposing for the development of MRONJ, the prevalence of comorbid conditions in MRONJ patients was evaluated in view of the average age of the cohort, and the results confirmed the increasing prevalence of multimorbidity among older adults [12]. The increasing awareness of the risk for MRONJ among patients assuming novel molecules for cancer treatment [13] and/or multiple medications with synergy effect has already been described [14,15]. It has been reported that the combination of bisphosphonates and antiangiogenic factors may increase the risk of MRONJ [16]. Osteonecrosis of the jaw associated with multitargeted kinase inhibitors of the VEGF and platelet- derived growth factor (PDGF) receptors has been described in a review by Vigarios et al. [17]. Seven cases of MRONJ associated with targeted therapies (TTs) as monotherapy and in combination with antiresorptives have been described in literature [14]. Several case

reports and patient series have described the occurrence of MRONJ in patients taking protein kinase inhibitors in association with bisphosphonates as well as in patients without a history of drugs related to the event osteonecrosis of the jaws [18–23]. A case of MRONJ in a patient receiving imatinib plus bisphosphonates has been reported, which recurred after denosumab administration [24]. The case of a woman aged 59 years with metastatic colorectal cancer was reported describing a necrotic bone exposure in the upper jaw with pain and soft tissue inflammation after 22 months of regorafenib treatment [25]. MRONJ was observed in a 51-year-old woman with medullary thyroid cancer receiving cabozantinib, a new tyrosine kinase inhibitor with antiangiogenic activity [26]. There was also a case of MRONJ in a cancer patient receiving lenvatinib with no history of antiresorptive treatment [27]. Data on oral toxicities induced by the recent Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved cancer medications suggest that even if a causal relationship is difficult to establish, MRONJ could be the consequence of anticancer therapies acting as a contributing factor to the occurrence of the disease in patients exposed to intravenous bisphosphonates or denosumab. Based on available randomized trials, data on MRONJ development during treatment with palbociclib and abemaciclib are not available since this event was not reported. Nevertheless, the studies evaluating palbociclib showed a low occurrence of stomatitis, being 30% vs. 14% and 28% vs. 13% in the PALOMA-2 trial and in the phase III PALOMA-3 trial, respectively [28].

In the MONARCH-2 trial, the incidence of all-grade oral mucositis (OM) during abemaciclib administration was low (15% vs. 10%), being 1% ≥ G3 OM [29,30]. Understanding the debilitating side effects, including mucosal injury and MRONJ as a secondary effect of anticancer treatment, is an important area of clinical research. Clinical presentation and severity of reported symptoms are influenced by patient-related risk factors, systemic and local (oral), and by patients' subjective evaluation which within an overall record of primary disease and adverse events can be underestimated. In the light of these considerations, as already reported in the case of several targeted therapies (TTs) administered in combination with antiresorptives [8], also for CDK4/6, the risk of developing MRONJ due to oral toxicity may be increased.

Between the first quarter of 2018 and the first quarter of 2020, out of 16 cancer patients diagnosed with MRONJ at the Unit of Oral Surgery, School of Dentistry, University of Messina, 6 consecutive cases have been reported in patients assuming cyclin-dependent kinase (CDK) 4/6 inhibitors. We interestingly noticed that approximately 37.5% of the reported cases of MRONJ were breast cancer patients assuming cyclin-dependent kinase (CDK) 4/6 inhibitors. This finding was surprising.

As an observational study type, our investigation has a lot of weaknesses because of the fact that within our EHRs database, only MRONJ cases are reported, so it is not possible to estimate the true incidence of MRONJ in subjects taking these medications, because of

the limited number of the subjects in this study cohort, and moreover, because cancer patients with MRONJ are usually treated with multiple drugs concomitantly or subsequently.

Despite its limitations, this is the first study, to our knowledge, to estimate the prevalence of CDK4/6 inhibitor use among MRONJ patients, and we would like to call for more detailed reporting of oncological therapeutic schemes in the adverse reaction reporting forms together with the suspected drugs.

Conclusions

The degree of risk for MRONJ in patients taking these new classes of cancer medications is uncertain but warrants awareness and close monitoring. As already reported in the case of several targeted therapies (TTs) administered in combination with antiresorptives, also for CDK4/6, the risk of MRONJ may be increased.

Oral/dental follow-up with personalized schedule should be planned for patients assuming CDK4/6 inhibitors and antiresorptive medications since these cancer treatments may represent an additional risk factor for the occurrence of medication osteonecrosis of the jaws [31].

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FIGURES AND TABLES

Table 1. Characteristics of patients with cyclin-dependent kinase (CDK) 4/6 inhibitor-associated medication-related osteonecrosis of the jaw (MRONJ) and cancer in the cohort.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Total of the CDK 4/6 inhibitors cases N=6**	**Total of the MRONJ cases in the Cohort N=16**
Age (yr)								
	63	47	61	60	57	58	58 (average) 47-63 (DS)	69 (average) 47-87 (DS)
Gender								
Female	x	x	x	x	x	x	6	9
Male								7
Cancer								
Breast	x	x	x	x	x	x	6	8
Prostate								5
Multiple Myeloma								3
Co-morbidity								
Heart disease		x			x		2	11
Osteoporosis		x					1	5
Diabetes				x			1	3
Lipis disorders	x	x					2	6
Protocol								
Zometa	x					x	2	9
Denosumab		x	x		x		3	6
Zometa + denosumab				x			1	1
Duration of theraphy (months)								
	68	8	19	19	3	27	24 (average)	27,38 (average)
Cancer medication at ONJ diagnosis								
Palbociclib	x	x		x	x	x	5	

Abemaciclib			x				1	
223 Radium								1
Lenalidomide								3
Abiraterone								2
Leuprorelin								1
Fulvestrant								1
Everolimus								1
GhRH agonist								1

Table 2. MRONJ features.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Total of the CDK 4/6 inhibitors cases N=6	Total of the MRONJ cases in the Cohort N=16
Location								
Upper jaw		x	x				2	6
Lower jaw	x			x	x	x	4	8
Both jaws								2
Stage								
Ia					x		1	1
Ib		x				x	2	3
IIa			x				1	2
IIb				x			1	5
IIIa								
IIIb	x						1	5
Treatment								
Medical	x		x		x		3	6
Surgical		x		x		x	3	10
Procedure								
Debridement								3
Sequestrectomy						x	1	1
Saucerization								3
Sub-marginal resection		x		x			2	3
Outcome								
Spontaneous expulsion of sequestrum			x				1	
Healed		x		x	x	x	4	
Partially healed								
Unchanged								
Progressive	x						1	

Figure 1. Computed tomography showing mandibular medication-related osteonecrosis of the jaw.

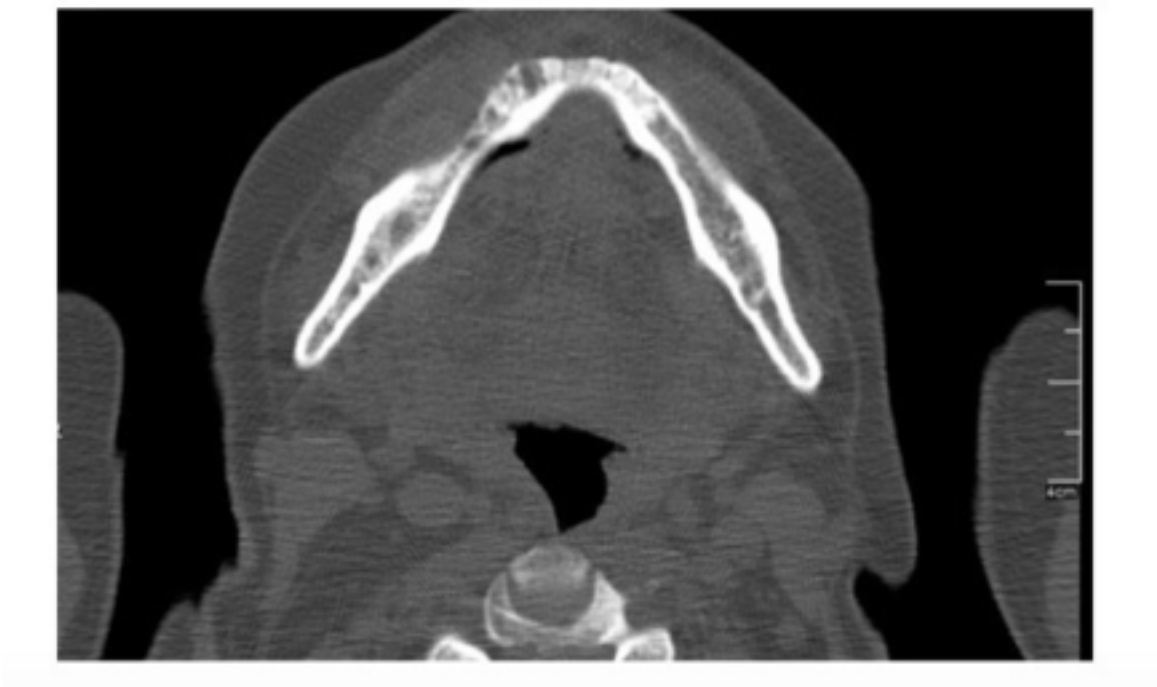


Figure 2. Clinical presentation of mandibular medication-related osteonecrosis of the jaw.

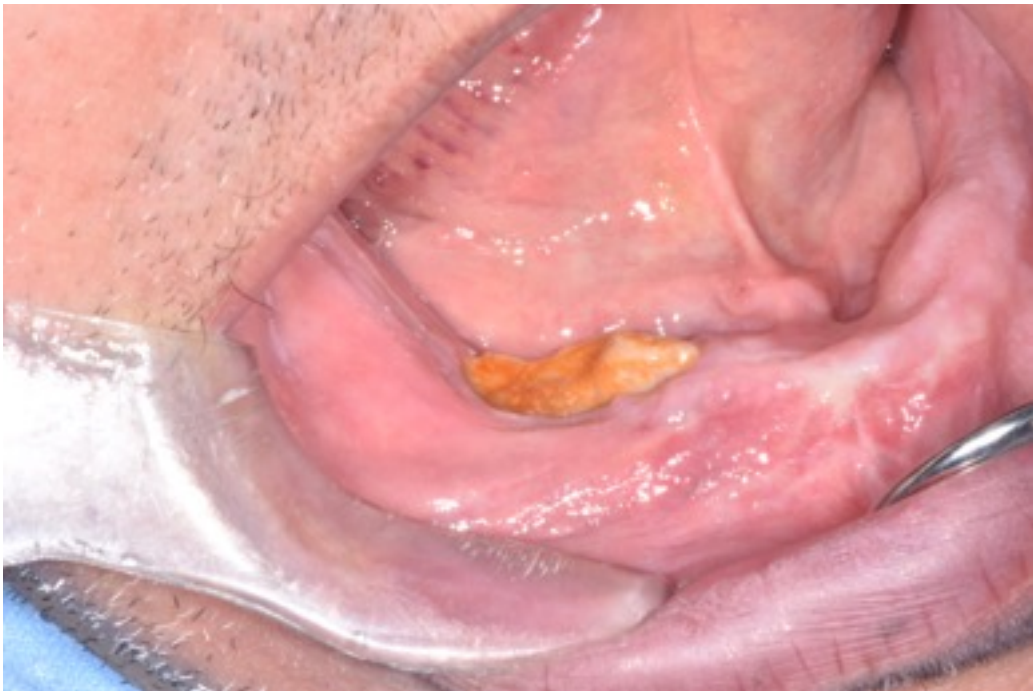


Figure 3. Intraoperative situation with necrotic bone sequestrum.

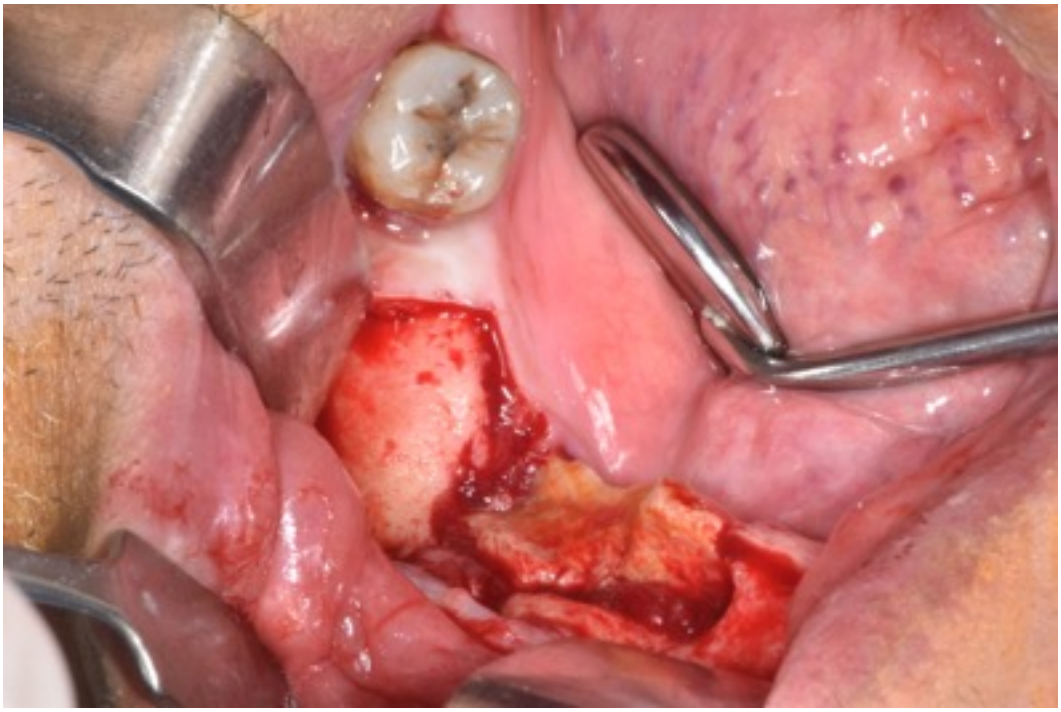


Figure 4. Removal of necrotic bone sequestrum revealing inflammatory reaction.

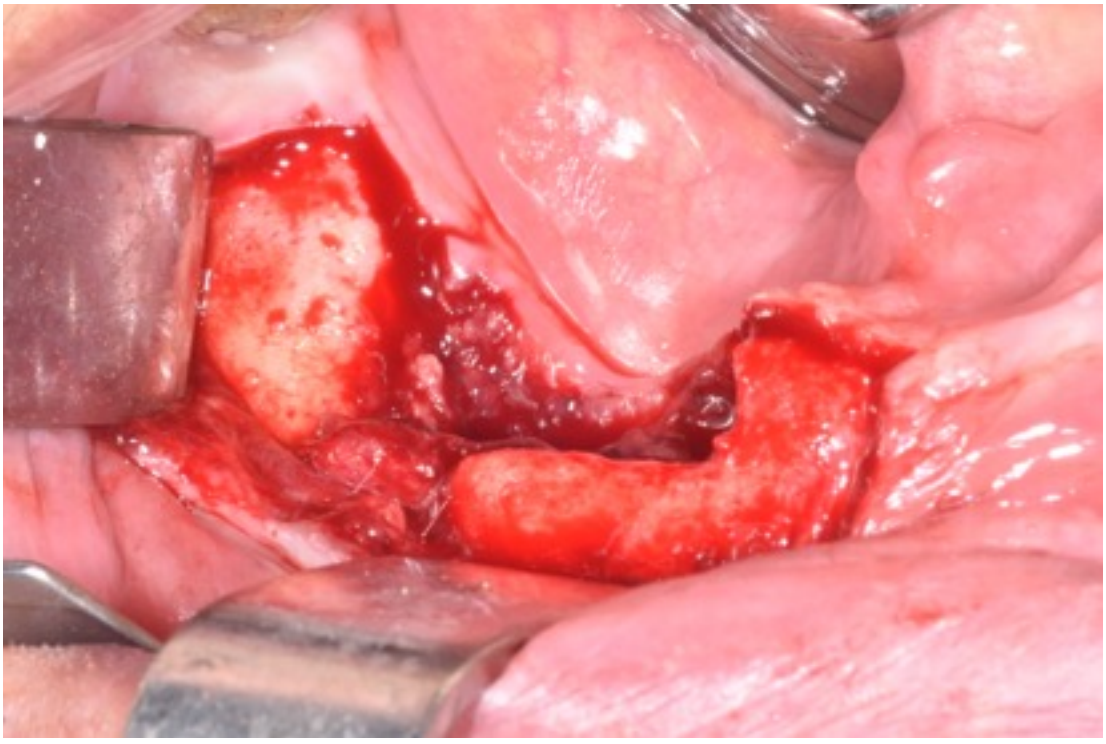


Figure 5. Healthy bleeding bone surface.

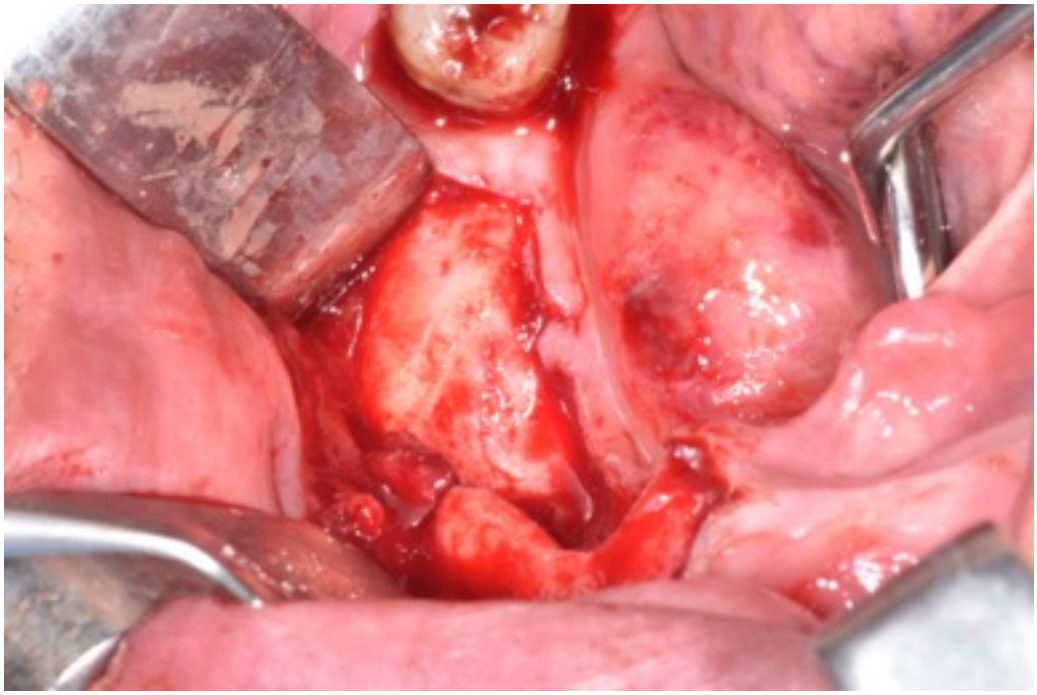


Figure 6. Primary healing

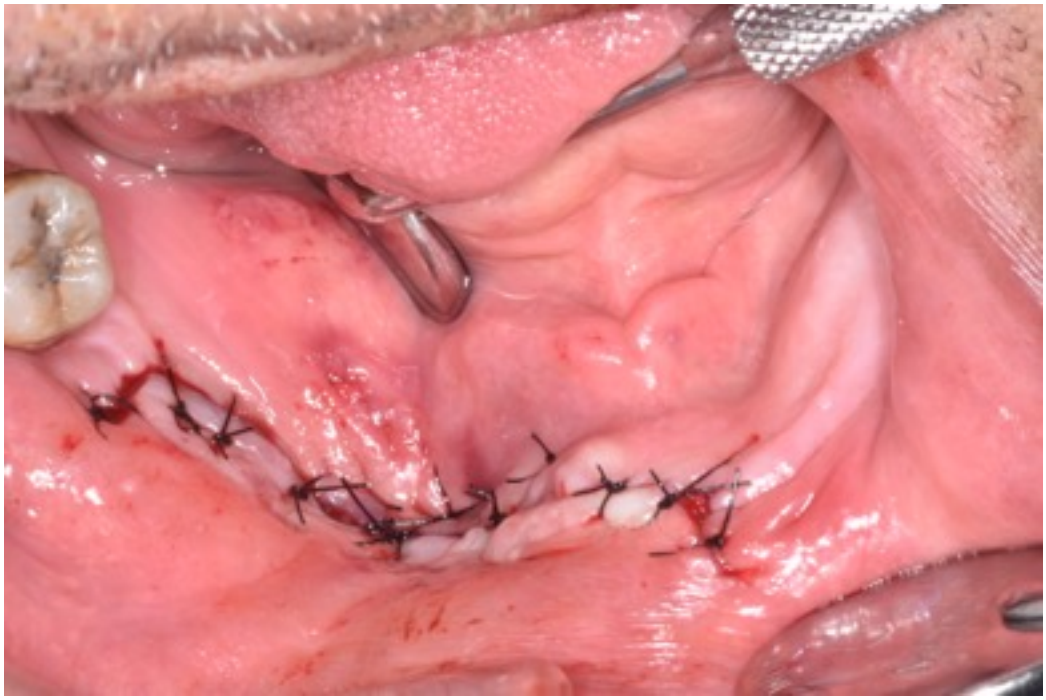
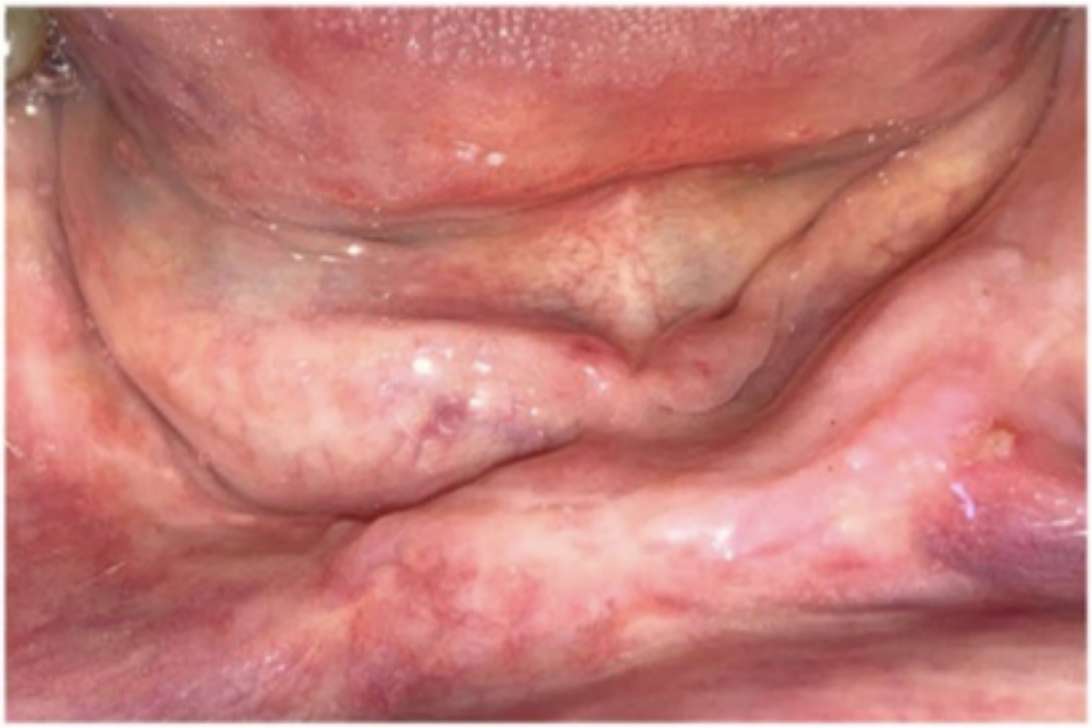


Figure 7. One-month follow-up.



Chapter 3: Risk factors for MRONJ and etiology

MRONJ predictors guide stratification of risk in the cancer patient about to initiate bone targeting agents for cancer therapy.

Individual MRONJ risk assessment for personalized prevention

Premise

Medication-related osteonecrosis of the jaw (MRONJ) is a severe oral complication of the administration of antiresorptives or antiangiogenics characterized mostly but not exclusively by an area of exposed bone in the mandible and/or maxilla that typically does not heal over a period of 6–8 weeks [1,2].

The etiology of MRONJ is multifactorial [3], as a result of the association of drug related, systemic and local factors [4].

MRONJ prevention mainly operate on local risk factors (poor oral hygiene, chronic periodontal disease, dental caries, oral surgical procedures such as tooth extraction, use of incongruous removable prostheses) [5, 6].

Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents [7].

A lot of studies have demonstrated how, prior to commencing treatment with MRONJ-related drugs, dental screening and treatments of oral diseases can significantly reduce the occurrence of this adverse event [8-10].

Patients in the pre-treatment phase are referred to the general dentist for oral/dental examination.

For these patients all typologies of dental treatments are viable and to prevent medication-related osteonecrosis of the jaw (MRONJ) questionable teeth are often extracted prophylactically before receiving bone targeting agents (BTAs) [11,12].

Nevertheless when evaluating patient that are about to initiate BTAs there are a few crucial consideration:

- An extensive prophylactic teeth extractions can compromise the patients' quality of life.
- Very often when the diagnosis of cancer is performed already in the metastatic disease a conflict arises between the need for a rapid beginning of BTAs therapy and the need for adequate timing of the oral/dental care.
- Furthermore in cancer patients, the adherence to periodontal supportive therapy (SPT), with regular attendance to follow-up visits and no interruption of more than 1 year, could not be always guaranteed, thus periodontally compromised teeth could represent a factor predisposing to the development of MRONJ.

The aim of this work is to investigate MRONJ predictors in order to support clinical decision.

Results from this study aim to design an integrated MRONJ prevention model to be applied to patients about to begin antiresorptive treatment to reflect long-term prognosis and support clinical decision-making to adapt prophylactic dental therapy to the combined evaluation of the effects on the patient's quality of life.

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Methods and materials

Study design

A case - control study has been designed.

Patients enrollment

Patients who had been diagnosed with metastatic cancer or multiple myeloma were included.

Criteria for inclusion in the study were age ≥18 years, diagnosis of bone metastases from solid tumors or multiple myeloma and use of zoledronic acid and/or denosumab. Patients with previous radiation in the head and neck area were excluded from the study.

Recruitment was a two-step process involving patients treated at the Osteonecrosis of the Jaw Treatment Center, School of Dentistry, of the University of Messina and coming from several Cancer Centers, mainly in Eastern Sicily during the years 2008-2018.

The records of all cancer patients treated with intravenous bisphosphonates- or denosumab- related MRONJ reported in the

Electronic Health Records (EHRs) of the Unit of Oral Surgery, School of Dentistry, University of Messina were collected retrospectively and used as a source of data for MRONJ group.

Controls were enrolled among patients using denosumab or zoledronic acid during the same period. Data extracted from the local Cancer Centers regarding patients diagnosed with bone metastatic cancer was used as a source of data for the control group.

At the time of enrollment , at least two pair-matched control patients were assigned to each patient case [22] through random sampling of the target population from the designated cancer centers.

A propensity score matching 1:1 was performed to adjust for confounding variables (i.e. sex and age) [23,24].

Fully anonymized data were reported in a specific dataset respecting patient's privacy.

Study variables

Information on potential risk factors relevant for the purpose of the study, were collected retrospectively.

Demographic data (i.e. age expressed as mean and standard deviation, sex expressed as percentage) and the primary cancer type were collected. The total number of zoledronic acid or denosumab administered doses was recorded and evaluated.

Concurrent cancer treatments were registered and categorized as following: a) chemotherapy, b) hormonal therapy and c) novel molecules (including target therapies, combination of chemotherapy

and target therapy, immunotherapy and radiopharmaceuticals) (See Supplementary Materials, Appendix 1).

Categorical variables referred to treatments are considered to be non mutually exclusive.

Moreover a characterization of the MRONJ cases has been added to identify MRONJ features such as anatomic location of exposed necrotic bone areas, stage of the disease ccording to our currently adopted classifications from the American Association of oral and maxillofacial Surgeons (AAOMS) and the Italian Society of Oral Medicine and Oral Pathology (SIPMO) [2,25] and potential trigger (oral/dental findings) when available.

Statistical analysis

Categorical variables are expressed as number and percentages, continuous data are summarized by mean and standard deviation. Comparison between MRONJ and control groups were performed using Chi-Squared test (with reference to categorical data) and z-test (for proportions). To investigate association between the explanatory variables (potential risk factor) and MRONJ, univariate logistic regression analysis was performed and applied to matched data by propensity score method [15,16]. Then a multiple logistic regression model was estimated in order to individuate significant independent predictors of MRONJ onset; the covariates inserted in the model were age, sex, cancer type, administration, chemotherapy, hormonal

therapy, and novel molecules. Also we included all interactions terms of first order for each treatment. Estimated odds with $p < 0.05$ was considered as significant. Statistical analysis was performed with R Studio (ver.1.3).

RESULTS

Descriptive analyses

Overall, N=75 patients affected by MRONJ were enrolled in case group and N=171 cancer patients were enrolled in control group. Female prevalence was observed in both groups (N=45 cases; 60% and N= 137 controls; 80.12%, respectively).

The mean age was 70 years (SD 64-76) and 60 years (SD 51–70) for MRONJ and control patients, respectively.

Primary cancer type has been evaluated. Among MRONJ patients N=14 (18.67%) had multiple myeloma, N= 38 (50.67%) had metastatic breast cancer, N=20 (26.67%) had metastatic prostate cancer and N=3 (4%) patients had metastatic lung cancer. Patients in the control had multiple myeloma (N=11; 6.43%), metastatic breast cancer (N=128; 74.85%), metastatic prostate cancer (N=20; 11.69%), metastatic lung cancer (N=12; 7.01%).

Concerning the studied bone metastasis treatment drugs, zoledronic acid was administered to N= 55 (73.33%) MRONJ patients and to N= 144 (84.21%) control patients.

Denosumab was administered to N=20 (11.69%) MRONJ patients vs. N= 27 (15.8%) in the control group.

Mean number of doses administered until the moment of the diagnosis was 23.5 (15.7) and 18.3 (12.6) for MRONJ case and controls respectively.

About cancer medications chemotherapy was administerd to in the MRONJ group the majority of patients had been treated with with traditional chemotherapeutic treatment schemes 42 (56.0) patients in the MRONJ group and 144 (84.2) of the control group

New anti-cancer drugs 21 (28.0) were administered to subjects in MRONJ group and 70 (40.9) control patients respectively.

38 (50.7) in MRONJ group and 116 (67.8) patients in control group received hormonal therapy.

Two patients with multiple myeloma enrolled in control group received zoledronic acid alone.

Characteristics of cases and controls are reported in **Table 1**.

Table 1. Characterization of cases and controls before and after adjustement.

	MRONJ group N = 75	Controls group N = 171	p-value	MRONJ group N =75 (after adjustement)	Controls group N = 75 (after adjustement)	p-value
Age – Mean (SD)	68.3 (9.7)	60.5 (12.7)	<0.001	68.3 (9.7)	68.8 (10.3)	0.757
Sex (%)						
Male	30 (40.0)	34 (19.9)	0.002	30 (40.0)	22 (29.3)	0.230
Female	45 (60.0)	137 (80.1)		45 (60.0)	53 (70.7)	

Primary cancer type (%)						
Multiple Mieloma	14 (18.7)	11 (6.4)	0.007	14 (18.7)	9 (12.0)	0.365
Metastatic breast cancer	38 (50.7)	128 (74.9)	<0.001	38 (50.7)	46 (61.3)	0.250
Metastatic prostate cancer	20 (26.7)	20 (11.7)	0.006	20 (26.7)	13 (17.3)	0.237
Metastatic lung cancer	3 (4.0)	12 (7.0)	0.535	3 (4.0)	7 (9.3)	0.326
Bone metastasis treatment drugs (%)						
Denosumab	20 (26.7)	27 (15.8)	0.069	20 (26.7)	11 (14.7)	0.107
Zoledronic acid	55 (73.3)	144 (84.2)	0.069	55 (73.3)	64 (85.3)	0.107
Mean number of doses administered (SD)	23.5 (15.7)	18.3 (12.6)	0.006	23.5 (15.7)	16.91 (12.6)	0.005
Cancer medications (%)						
Chemotherapy	42 (56.0)	144 (84.2)	<0.001	42 (56.0)	60 (80.0)	0.003
Hormonal therapy	38 (50.7)	116 (67.8)	0.016	38 (50.7)	47 (62.7)	0.187
Novel molecules	21 (28.0)	70 (40.9)	0.073	21 (28.0)	23 (30.7)	0.858

Characteristics of MRONJ lesions (anatomic location, clinical stage, presence of inflammation/infection and local risk factors) are reported in **Table 2**.

According to AAOMS classification of MRONJ, N= 30 (40%) patients had a stage I MRONJ, N= 32 (42.67%) had a stage II disease and N=13 (17.33%) patients had stage III MRONJ. MRONJ lesions were reported to be mainly symptomatic, with the 82.7% of patients showing clinical signs of inflammation/suppuration.

According to the SIPMO staging system N= 7 (%) patients had a stage Ia MRONJ and 23 had a stage Ib MRONJ, N= 4 (%) had a stage IIa 28 IIb disease and N=2 (%) patients had stage IIIa and 11 had a IIIb MRONJ.

Regarding to the anatomic location of MRONJ, a higher number of patients had lesions appeared in the mandible (N=52; 69.3%), followed by upper maxilla (N=16; 21.33%) and jaws (N= 7; 9.33%).

A local risk factor (oral/dental finding) potentially triggering MRONJ onset has been registered in 21 of the MRONJ (28%).

The most frequent trigger was tooth extraction (21.3%), followed by soft tissue injuries due dental prosthesis use (5.3%) and peri-implantitis (1.3%).

In the remaining cases (N= 54; 72%) the potential trigger was not identified.

Table 2. Clinical characteristics of lesions in the MRONJ group.

MRONJ staging (AAOMS classification)	**MRONJ group N (%) N = 75**
0	3
I	11
II	48
III	13
Presence of clinical signs of inflammation/suppuration at diagnosis stage	62 (82.7)
MRONJ staging (SIPMO classification)	
Ia	7
Ib	23
IIa	4
IIb	28
IIIa	2
IIIb	11
Anatomic location	
Mandible	52 (69.3)
Upper maxilla	16 (21.3)
Both jaws	7 (9.3)

Trigger	
Tooth extraction	16 (21.3)
Peri-implantitis	1 (1.3)
Soft tissue injuries due dental prosthesis	4 (5.3)
Unidentified trigger	54(72)

Abbreviations: AAOMS= American Association of Oral and Maxillofacial Surgeons

The estimates from univariate and multiple logistic regression model were reported in **Table 3** and in **Table 4** respectively.

Table 3. Univariate logistic regression models to identify potential predictors of risk of MRONJ in cancer patients

Covariate	Estimate	Std. Error	OR	CI (95%)	p-value
Age	-0.005	0.016	0.995	[0.964; 1.026]	0.755
Sex (Male)	0.473	0.346	1.604	[0.814; 3.161]	0.171
Lung cancer	-0.522	0.661	0.593	[0.162; 2.170]	0.430
Breast cancer	-0.434	0.331	0.647	[0.338; 1.239]	0.189
Multiple Myeloma	0.520	0.462	1.682	[0.680; 4.160]	0.261
Prostate cancer	0.550	0.401	1.733	[0.789; 3.803]	0.170
Administration	0.027	0.010	1.027	[1.006; 1.048]	**0.008**
Chemotherapy	-1.040	0.360	0.353	[0.174; 0.715]	**0.003**
Novel molecules	0.067	0.366	1.069	[0.521; 2.191]	0.855
Hormonal_therapy	-0.434	0.331	0.647	[0.338; 1.239]	0.189

Abbreviations: CI=Confidence Interval; OR=;Odds Ratio. In bold statistically significant p-values are reported

Using univariate logistic model we found a significant effect of Administration (OR 1.027; 95% CI= [1.006; 1.048]; p=0.008) and Chemotherapy (OR 0.353; 95% CI= [0.174; 0.715]; p=0.008) on MRONJ onset (**Table 3**).

Table 4. Multiple logistic regression model to identify indipendent predictors of risk of MRONJ in cancer patients

Covariate	Estimate	Std. Error	OR	CI (95%)	p-value
Age	-0.025	0.021	0.975	[0.935; 1.016]	0.234
Sex (Male)	0.717	0.721	2.048	[0.498; 8.416]	0.320
Cancer type (ref= Lung cancer)					
Breast cancer	2.866	1.278	17.560	[1.434; 215.05]	**0.025**
Multiple myeloma	2.799	1.227	16.281	[1.483; 181.98]	**0.022**
Prostate cancer	2.895	1.238	17.993	[1.597; 204.68]	**0.019**
Administration	0.029	0.014	1.029	[1.001; 1.058]	**0.032**
Chemotherapy	0.058	0.844	1.059	[0.202; 5.541]	0.944
Hormonal therapy	0.303	0.918	1.353	[0.223; 8.184]	0.740
Novel molecules	3.548	1.642	34.743	[1.390; 868.11]	**0.030**
Chemotherapy : Hormonal therapy	-1.408	0.993	0.244	[0.034; 1.713]	0.156
Chemotherapy : Novel molecules	-3.346	1.746	0.035	[0.001; 1.079]	0.055
Hormonal therapy : Novel molecules	-0.439	1.008	0.644	[0.089; 4.649]	0.662

Examining the results by multiple logistic regression model, we found that all examined cancer types (breast, multiple myeloma, and

prostate) involved a significantly higher risk of MRONJ onset compared to lung cancer type.

A significant association between MRONJ onset and Administration (OR=1.029; 95% CI=[1.001; 1.058]; p-value=0.032) and exposure to novel molecules treatment (OR=34.743; 95% CI =[1.390; 868.11]; p-value=0.030) was observed, too (**Table 4**).

DISCUSSION

In cancer patients MRONJ risk assessment is needed for personalized preventive strategies and to evaluate the indications and contraindications of conservative dental care and oral surgery in patient about to initiate bone targeting agents and during the treatment course.

This study was conducted in order to explore the MRONJ predictors among a cohort of cancer patients receiving zoledronic acid and/or denosumab evaluating the association between clinical characteristics and MRONJ onset.

Individual patient assessment is needed in order to guide risk stratification and plan preventive dental procedures including tooth extraction when necessary, before treatment initiation with denosumab or zoledronic acid [26-28].

Using univariate and multiple logistic model we found a significant effect of the predictor administration (number of administered doses of zoledronic acid/denosumab) confirming previous results from

literature reporting that the increase in risk related to bisphosphonates and denosumab administration is dose dependent [29] and that MRONJ incidence increases with increasing duration of exposure to antiresorptive agents, confirming the known dose-dependent fashion [30,31].

Our study showed that breast, multiple myeloma and prostate cancer patients have a significantly higher risk of developing MRONJ than patients affected by lung cancer (**Table 4**). Cancer type seems to play an important role in the incidence of MRONJ.

In the SWOG0702 trial analysis by cancer type demonstrated a higher 3-year risk in multiple mieloma patients (4.3 versus 2.9% for prostate cancer, 2.7% for lung cancer, and 2.4% for breast cancer) [32].

In a report by Rugani et al the weighted prevalence of medication-related osteonecrosis of the jaw was 2.09% in the breast cancer group, 3.8% in the prostate cancer group, and 5.16% for multiple myeloma patients [33].

Recently, an incidence of about 0.8% in breast cancer patients has been observed [34].

Walter et al also reported a lower prevalences in breast cancer patients compared to prostate cancer and multiple myeloma patients [35].

It has been reported that patients with prostate cancer have a three-fold higher risk of denosumab- associated MRONJ as compared to those with other cancer types [20, 36-38].

Qi et al reported that the prevalence of denosumab-related MRONJ in patients with prostate cancer was higher compared with that in patients with non-prostate cancers relating that to the longer median follow-up period for prostate cancer compared with other tumor type suggesting that the variability in the prevalence of ONJ in the different cancer types may be due to this variation [39].

In the recent study by Ikesue et al with 374 patients examining the patient characteristics between the denosumab and zoledronic acid groups the distribution of cancer types was significantly different between groups ($P < 0.001$) [40].

The increased risk of MRONJ in these patients may be attributable to the dose and frequency of administration.

Cancer patients receive multiple agents that interfere with bone metabolism and may, therefore, cause or benefit the development of osteonecrosis [33].

To aid in interpretation in this study anti-cancer medications have been classified into three categories hormonal therapy, chemotherapy and novel molecules.

The new anti-cancer molecules considered in the present study are mostly target therapies, for which cases of MRONJ in patients taking these drugs in association with zoledronic acid/denosumab osteonecrosis of the jaws have already been reported previously [41-44].

In regard to anti-cancer medications using multiple logistic regression model, a significant association between MRONJ development and

exposure to chemotherapy and novel molecules treatment was observed.

Multiple logistics regression model showed that the risk of developing MRONJ was significantly higher in patients that received novel anti-cancer molecules and chemotherapeutic treatment vs. those treated with traditional chemotherapies alone (**Table 4**).

In this study the hormonal therapy seems not to be an independent risk factor for the development of MRONJ. Indeed among the secondary drugs that possibly contribute to MRONJ development. hormonal therapy has been indicated as a confunding factors.

Neha et al reported that the signal generated for aromatase inhibitors associated osteonecrosis of jaw in the Food and Drug Administration Adverse Event Reporting System database can be false positive since upon removing the reports of concomitantly administered drugs (bisphosphonates and denosumab), signal strength for letrozole, anastrozole and exemestane respectively drastically decrease [45,46].

Regarding the utilization of chemotherapy, MRONJ has already been associated with anticancer agents including classic chemotherapy agents [47,48].

The review by Shim et al. summarizes fifty-four reported cases of osteonecrosis associated with chemotherapy in cancer patients [49], as the presence of an immunosuppressive status poses a high risk of developing infection and chemotherapy has a cytotoxic effects on bone metabolism and vascularization [50,51].

In patients with multiple myeloma the use of thalidomide increased the risk for MRONJ by 2.4-fold (P = 0.043) [52].

For this patients with prior multiple chemotherapy regimens should be monitored for early symptoms of MRONJ [49].

In addition to the well-known medications, MRONJ may be a major adverse reaction to several new-generation anticancer drugs due to unknown mechanisms [53,54].

To date, several medications have been somehow implicated with MRONJ on the basis of the experience gained through isolated data, case series reports and literature review [12-14, 55,56].

Recent reports have suggested a relatively high MRONJ risk in patients with a combined administration of bisphosphonates and targeted drugs [57,58].

It is known, for example, that the combination of anti-VEGFR and bone antiresorptive agents may increase the risk of MRONJ [56,59,60].

Similarly, it was well confirmed that mTORs inhibitors have a strong immunosuppressive effect which can lead to delayed healing of oral soft tissues and persistent infections favoring the onset of the osteonecrotic process [61,62].

Taking into account this observations and their potential etiologies, the following hypothesis has been developed for MRONJ onset: (1) a direct local effect represented by the epithelial damage [63- 67]; (2) an indirect systemic effect exerted by the immunosuppressive action of anti-cancer treatments [68,69] since the new concept of osteoimmunology [70] had been recently added to the previous

etiopathogenetic theories on MRONJ development [71] and lastly (3) the hypothesis that new anticancer drugs may play a role in osteoclast differentiation additionally affecting the RANKL-mediated cell cycle arrest as supported by recent in vitro and in vivo data [72,73].

With the several therapeutic options to treat oncologic patients, we expect to see an increase of long surviving patients in the metastatic bone phase receiving antiresorptive drugs [74,75] and, consequently, an increase in the number of MRONJ cases in the oncologic setting [76].

Starting from these assumptions a significant portion of oncologic patients will need preventive dental care. Furthermore, dental interventions may also be required during the course of bone resorptive therapy [77].

Thus, for those who had a concurrent administration of bisphosphonates and new anti-cancer molecules, dentists should be aware of a potentially increasing risk of severe MRONJ [56].

It is the authors' opinion that risk assessment of the cancer patient about to initiate bone targeting agents should be the expression of a strategic alliance between the oral surgeon and the oncologist by introducing informations such as overall survival and performance status in a combined evaluation. Early predictors of outcome could reflect long-term prognosis and support clinical decision-making with the application of a combined paradigm that allows to tailor prevention and treatment strategies for each of our MRONJ patients.

Results deriving from this investigation could be and important contribute in the developmental literature on MRONJ, especially because individualized MRONJ prevention strategies can only come from a thought understanding of risk factors.

In this analysis, good data collection is combined with adequate statistical treatment and appropriate inferential analysis was carried out in order to investigate predictors of MRONJ development. Furthermore the present study, in addition to the existing ones, take into consideration a potential risk factor, the intake of new molecules for cancer therapy, which resulted significant.

This study also has some limitations. One above all is the sample size. We observed a statistical significance for exposure to new molecules, however we need to be very cautious about concluding that this results outline a relationship with risk increase.

A further limitation is related to patients enrollment as the included population was not homogeneously paired. This paper uses propensity score method to address the selection bias that potentially confounds the effect of the explanatory variables in observational studies.

Current clinical practice prompted us to consider a well-structured sampling design with higher numbers for future studies on the personalized risk assessment for MRONJ.

CONCLUSIONS

The pathogenesis of MRONJ is likely to be multifactorial and can involve a synergistic effect between exposure to bisphosphonates or denosumab, other anti-cancer agents and local factors.

Exposure to denosumab or bisphosphonates is the primary risk factor for MRONJ nevertheless beside the triggering events (dental extraction, periodontal infection, ill-fitting prostheses) there might be some other systemic determinant factors.

Association of chemotherapy and/or new anti-cancer molecules, in sequence or as single therapies, may contribute to MRONJ development.

Although no definitive conclusions has been reached regarding the influence of anti-cancer drugs on MRONJ development these may represent an additional risk factor for the occurrence of MRONJ.

FUTURE DEVELOPMENT

The current standard in pharmacovigilance is bivariate association analysis, disregarding the probable co-occurrence of adversity [70,78].

Based on the above, we hypothesized a cumulative risk model for MRONJ prediction.

Among the future developments there is a further patients enrollment aiming to have a population of cases and controls matched by sex and

age. Study sample should consist in at least 200 individuals diagnosed with MRONJ.

Through identification of a set of proven risk factors we will aim to thereby combine the multiple variables positively associated to MRONJ into a single index to predict the outcome and be used to schedule individualized prevention strategies for patients at risk.

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Supplementary Material

Appendix 1: Classification of identified drugs

Drug Classes	**Drugs**
	Docetaxel (Taxotere)
	Paclitaxel (Taxol)
	Doxorubicin (available as a generic drug)
	Epirubicin (Ellence)
	Pegylated liposomal doxorubicin (Doxil)
	Capecitabine (Xeloda)
	Carboplatin (available as a generic drug)
	Cisplatin (available as a generic drug)
	Cyclophosphamide (available as a generic drug)

Chemotherapy	Eribulin (Halaven)
	Fluorouracil (5-FU)
	Gemcitabine (Gemzar)
	Ixabepilone (Ixempra)
	Methotrexate (Rheumatrex, Trexall)
	Protein-bound paclitaxel (Abraxane)
	Vinorelbine (Navelbine)
	Cabazitaxel (Jevtana)
	Mitoxantrone (Novantrone)
	Estramustine (Emcyt)
	Melphalan (Alkeran, Evomela)
	Etoposide
	Carmustine (BiCNU)
	Bendamustine (Bendeka)
	Nab-paclitaxel (Abraxane)
	Pemetrexed (Alimta)
Combination of chemotherapy	AC (doxorubicin and cyclophosphamide)
	EC (epirubicin, cyclophosphamide)
	AC or EC followed by T (paclitaxel or docetaxel), or the reverse)
	CAF (cyclophosphamide, doxorubicin, and 5-FU)
	CEF (cyclophosphamide, epirubicin, and 5-FU)
	CMF (cyclophosphamide, methotrexate, and 5-FU)
	TAC (docetaxel, doxorubicin, and cyclophosphamide)
	TC (docetaxel and cyclophosphamide)
Hormonal therapy	Tamoxifen
	Anastrozole (Arimidex)
	Exemestane (Aromasin)
	Letrozole (Femara)
	Leuprolide (Lupron, Eligard)
	Goserelin (Zoladex)
	Triptorelin (Trelstar)
	Histrelin (Vantas)
	Degarelix (Firmagon)
	Abiraterone (Zytiga)

	Flutamide (Eulexin)
	Bicalutamide (Casodex)
	Nilutamide (Nilandron)
	Enzalutamide (Xtandi)
	Apalutamide (Erleada)
	Arolutamide (Nubeqa)
Targeted therapy	Trastuzumab
	Pertuzumab (Perjeta)
	Neratinib (Nerlynx)
	Ado-trastuzumab emtansine or T-DM1 (Kadcyla)
	Alpelisib (Piqray)
	Abemaciclib (Verzenio)
	Lapatinib (Tykerb)
	Bortezomib (Velcade)
	Carfilzomib (Kyprolis)
	Ixazomib (Ninlaro)
	Panobinostat (Farydak)
	Selinexor (Xpovio)
	Osimertinib (Tagrisso)
	Erlotinib (Tarceva)
	Afatinib (Gilotrif)
	Dacomitinib (Vizimpro)
	Gefitinib (Iressa)
	Alectinib (Alecensa)
	Brigatinib (Alunbrig)
	Cretinib (Zykadia)
	Crizotinib (Xalkori)
	Lorlatinib (Lorbrena)
	Entrectinib (Rozlytrek)
	Larotrectinib (Vitrakvi)
	Abrafenib (Tafinlar)
	Tremetinib (Mekinist)
	Capmatinib (Tabrecta)
	Selpercatinib (LOXO-292)
	Bevacizumab (Avastin)

Combination of target therapies	Pertuzumab, trastuzumab, and hyaluronidase–zzxf (Phesgo)
Combination of chemotherapy and target therapy	AC-TH (doxorubicin, cyclophosphamide, paclitaxel or docetaxel, trastuzumab)
	AC-THP (doxorubicin, cyclophosphamide, paclitaxel or docetaxel, trastuzumab, pertuzumab)
	TCH (paclitaxel or docetaxel, carboplatin, trastuzumab)
	TCHP (paclitaxel or docetaxel, carboplatin, trastuzumab, pertuzumab)
	TH (paclitaxel, trastuzumab)
Immunotherapy	Atezolizumab (Tecentriq)
	Pembrolizumab (Keytruda)
	Atezolizumab (Tecentriq)
	Durvalumab (Imfinzi)
	Nivolumab (Opdivo)
	Pembrolizumab (Keytruda)
	Ipilimumab (Yervoy)

Chapter 4: MRONJ surgical treatment: Learning from the experience of MRONJ Treatment Centers

Current MRONJ treatment strategies come from the pioneering efforts of multiple specialized centers which experimented the different surgical techniques, identified the treatment indications and allowed with their case series to estimate the success rate of MRONJ surgical treatment making it the first-line strategy especially in the early stages of the disease.

Analyzing briefly the noteworthy aspects, since the first years with MRONJ surgery Carlson and Basile recommend offering definitive surgery to patients with MR-ONJ, even in the most extensive cases and at the cost of radical surgery [1].

On the other hand Stanton recommended only a superficial debridement [2].

Graziani et al. they supported the conservative curettage of the necrotic lesion in the most advanced cases (stage II and III) and the major resection of the necrotic portion (stage I) [3].

Bodem et al. suggested that early stages (BRONJ 0 and I) could be sufficiently managed with conservative treatment only, and surgical treatment should be limited to advanced stages (BRONJ II and III) or after failure of the conservative approach to treatment [4].

From the cautious approaches of the early years, there has been a move towards considering surgery the first choice of treatment.

Voss et al. affirm that the only conservative management of the pathology leads to a progression of bone lesions [5].

Hoefert et al. in a retrospective analysis examined the clinical course and therapeutic outcome of 16 patients with denosumab-related osteonecrosis of the jaw (DRONJ). Ten patients underwent non-surgical treatment and six patients underwent surgical treatment (6/16) with major (5/6) or minor (1/6) surgery and included in the follow-up analysis. Complete healing was significant in patients treated with major surgery (80%) compared to the unoperated group (20%, $p < 0.035$). Major surgery demonstrated more complete healing than nonsurgical management, and discontinuation of denosumab did not improve healing outcomes [6].

Kim et al. indicated that an extensive surgical procedure has a better prognosis than a less extensive treatment. The authors conducted a retrospective cohort study of 325 osteoporotic patients with BRONJ undergoing surgical procedures in order to assess which type of procedure produces the best treatment outcomes. The surgical interventions performed were: Curettage n = 35 Sequestrectomy n = 207 Saucerization n = 78 and Mandibulectomy n = 5. Outcome was evaluated as relapse rate after surgery: Curettage n = 20 Sequestrectomy n = 60 Saucerization n = 17 n = Mandibulectomy 0. In total, 30% of patients did not recover with the first surgery and underwent a more radical surgery. In some cases, three surgeries were also required.

Hayashida et al. performed a multi-center retrospective study on 378 patients with MRONJ to study treatment technique and outcome. Of the 159 patients undergoing surgical treatment, those undergoing extensive surgery had significantly better treatment outcomes than those undergoing conservative surgery. The results indicate that extended surgical treatment should be performed as the first choice therapy for MRONJ patients [8].

Eguchi et al. performed a retrospective study comparing 28 patients undergoing surgery and 24 patients undergoing non-surgical treatment to evaluate the most effective strategy in patients with stage II MRONJ. Surgical treatment in 25 patients (89.3%) was successful, with failure in 3 patients (10.7%). Non-surgical treatment was successful in 8 patients (33.3%) and failed in 16 patients (66.7%). The results showed a significant difference between the groups with the best outcome for surgical treatment ($P < 0.01$) [9].

Zirk et al. conducted a retrospective study of 143 MRONJ stage II and III patients to study the number and type of treatments needed to achieve a stable and painless condition of the disease. The most interesting result was the statistically significant difference between the first and second surgery ($p < 0.05$) [10].

Voss et al. gaining a further surgical treatment experience compared to the previous publication reported a single center retrospective study that included all patients diagnosed with maxillary BP-ONJ and concomitant maxillary sinusitis. A total of 12 patients underwent surgical treatment with complete resection of the affected bone and

multilayer wound closure. MRONJ recurrence appeared in a patient with bone exposure but no signs of sinusitis and was treated conservatively [11].

Nisi et al. performed a retrospective analysis of 120 subjects diagnosed with MRONJ undergoing surgical treatment to evaluate its effectiveness. 84% of the injuries improved after surgery, 20 showed no changes, and one got worse. The results concluded that local resection may be the treatment of choice in BRONJ stages I and II, while the therapeutic indication of Stage III is evaluated based on the patient's systemic conditions [12].

Klingelhöffer et al. examined the outcome of surgical resection of osteonecrotic lesions and the influence of different potential risk factors on treatment success. The results of this prospective study with 76 surgeries performed on 40 patients suggest that advanced stages of MRONJ benefit from surgical treatment, while stage I patients can also be treated conservatively. Indeed, although long-term maintenance of mucosal closure was achieved in only 27.6% of cases, stage II patients regressed to stage I in 81% after surgery ($p < 0.01$) and stage III patients improved in 83% of cases (OR = 8.08; $p = 0.07$). Only 38% of stage I patients improved after surgery [13].

Pichardo et al. have published two studies on the surgical treatment of MRONJ. Out of 11 surgically treated patients with DRONJ healing was achieved in 9 cases. In a retrospective analysis of 74 BRONJ patients who underwent surgery it was successful in 93.2% of patients [14,15].

Nørholt et al. evaluated the outcome of surgical treatment of osteonecrosis of the jaws (ONJ) with the additional use of autologous platelet-rich fibrin (PRF) membranes. Complete mucosal healing with total absence of symptoms was achieved in 14 of the 15 patients (93%) [16].

Silva et al. performed a literature review to identify clinical studies on the surgical management of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in order to evaluate different surgical treatment modalities, outcomes and follow-up.

The surgical treatment modalities were: debridement, sequestrectomy, marginal resection, bone reconstruction (free flaps) and laser therapy and hyperbaric oxygenation, as adjuvant therapy to surgical treatment [17].

Ramaglia et al. performed a systematic review with meta-analyzes to outline the best therapeutic approach based on the stage of ONJ. In relation to the surgical approach, the postoperative results showed a heterogeneous success rate in all phases (stage I range 0-100%, phase II interval 52-100%, phase III interval 50-100%) [18].

Kang et al. compared the characteristics and outcomes of patients undergoing surgical treatment for drug-related stage II osteonecrosis of the jaws versus osteomyelitis. The wound healing rate was significantly higher in the MRONJ stage II group (19.1%, 14/73 cases) than in the osteomyelitis group (2.2%, 2/89 cases, $p < 0.001$) [19].

Voss et al. further implemented their treatment protocol over time performing surgery in combination with bone regeneration using mesenchymal stem cells (MSCs) taken from the bone marrow from the patient's iliac crest as a treatment modality in MRONJ therapy. In this 6-patient study, all patients showed satisfactory healing with no signs of wound infection, dehiscence or bone exposure in the surgical region with a mean follow-up of 21 months [20].

Blus et al. used ultrasonic piezoelectric bone surgery on a cohort of 18 patients treated for MRONJ; including 20 surgically treated sites. Clinical success was considered when the following criteria were met: (1) effective pain resolution, (2) exposed bone was covered with soft tissue, and (3) complete soft tissue healing in treated areas. All patients recovered and achieved complete soft tissue closure within 1 month. No repetition of symptoms was observed during this follow-up (10-54 months) [21].

Other prospective studies have evaluated the use of healing promoters beside mesenchymal stem cells (MSCs) such as, bovine lactoferrin [22], leukocytes [23], platelet rich plasma (PRP) [24] and platelet-rich fibrin (PRF)[25-27].

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Chapter 4: MRONJ surgical treament Techniques

According to the AAOMS guidelines, MRONJ therapy is stage-dependent, stages 0, I and II benefit from non-surgical management which includes the use of oral antimicrobial rinses and / or antibiotic therapy while stage III must be treated with surgery, including debridement or bone-resective surgery of the necrotic segment [1].

For stage II patients not responding to conservative management, the AAOMS recommends superficial surgical debridement to stimulate soft tissue healing [1].

No precise guidelines have been drawn on the surgical treatment of MRONJ; interventions range from conservative debridement to major resection, often without a precise definition or description of the extent of bone removal.

It is therefore necessary to reach a general consensus, defining the characteristics of the case and the details of the intervention required (for example, debridement, conservative surgery, decorticalization) to provide clear indications on the surgical treatment of MRONJ [2-4].

The extension of the necrotic bone segment determines the choice of the most appropriate surgical technique according to a stage-specific approach [5,6].

For small lesions, the treatment is curettage, which consists in the removal of the superficial inflammatory soft tissue and necrotic bone, performed under loco-regional anesthesia [3,7,8].

Another treatment strategy for small MRONJ lesions is superficial debridement of the wound or local decortication, which consists in the removal of cortical bone in an extension not exceeding the width of three teeth [4,6,8,9-13].

In the technique named decortication, also called saucerization, the removal of the cortical bone and the formation of a cup-like depression occurs [3,14].

For larger MRONJ lesions, the most suitable technique is extensive decortication, with or without sequestrectomy [3,4,14]. which consists in the removal of infected and avascular bone segments [3],

This surgical technique involves the use of manual instruments, rotary cutters and / or piezoelectric instrumentation.

Voss et al. they perform superficial debridement of the wound with bone forceps and rotary burs [12,13].

According to the experience of Blus et al. the use of piezoelectric ultrasound surgery provides excellent decontamination of the surgical site and promotes tissue healing [15].

The advanced stages of MRONJ are referred to the maxillofacial surgeon to be performed under general anesthesia and are treated with marginal or segmental mandibulectomy or maxillectomy [3,7,10,11,16].

In marginal bone resection, loss of mandibular bone continuity is avoided [2,4,5], on the other hand, in segmental bone resection the mandibular bone continuity is interrupted [2,4-6].

These surgical procedures can be followed by a reconstruction of the mandible with the use of a titanium osteosynthesis plate [2,4,6,9,16-18] or by the reconstruction of the mandibular or maxillary bone with vascularized bone grafts [9,16,18].

In all the surgical techniques listed, vital and bleeding bone must always be reached, which defines the margins of these interventions [2,4,3].

Surgical access involves an initial crestal incision possibly extended with an intrasulcular incision when there are adjacent dental elements not involved within the osteonecrotic lesion, for an optimal view of the necrotic bone, flap should be extended beyond two dental elements out of the affected segment. Vertical release incisions are made and a full-thickness flap is always elevated [12, 19].

After the removal of the necrotic segment with one of the techniques described above, if we are faced with a sufficient amount of mucosa to obtain closure by primary intention, the vestibular and lingual flaps are directly sutured onto the defect without any periosteal release [10,14].

On the other hand, in the case in which sufficient mucosa to obtain closure by primary intention is lacking, advanced mucoperiosteal flaps can be used by means of periosteal and mobilized releases to cover the surgical site for a tension-free closure of the flap [6,8-10,13,20-23-25].

Advanced mucoperiosteal flaps can be used and mobilized to cover the surgical site for tension-free closure of the surgical wound [6,9,12,13,20].

To ensure primary intention healing without dehiscences, the use of multilayer suturing techniques is recommended [19].

The technique described by Voss et al. involves a deep incision of the vestibular periosteum; the basal edge of the periosteum is mobilized and quilted with resorbable sutures under the lingual or palatal mucosa based on the location of the MRONJ lesion.

The buccal and lingual / palatal flaps are then sutured together using both detached sutures (vicryl 2-0 / 3-0) and continuous sutures (vicryl 3-0 / 4-0) [12,13].

Wild et al. use a multilayer suture technique: the vestibular mucoperiosteal flap is designed and from this a flap of connective tissue as thick as possible and with a broad base is mobilized. The same procedure is performed for the lingual flap. The two flaps of connective tissue are sutured over the surgically treated bone. The buccal and lingual flaps are then sutured to the connective tissue flap [6]. For the covering of very extensive bone defects, it is possible to use advanced surgical techniques such as nasolabial flaps, myloid and others, which provide a sufficient amount of soft tissue to obtain a flap closure without tension [9,20].

The mylohyoid flap is a myofacial flap that is accessible from the lingual border of the mandible and can be used to cover mandibular bone defects [9].

Preparation of the mylohyoid flap is performed after complete removal of the necrotic bone area.

To prepare the flap, the mucous membrane of the floor of the mouth must be carefully dissected from the muscle which is subsequently detached from the mylohyoid line [9].

During mobilization of the mylohyoid muscle, particular attention must be taken to preserve the submandibular duct, the sublingual gland and the lingual nerve, which run on the myolohyoid muscle [20].

Then the lingual nerve is delineated on the posterior edge of the flap, the sublingual gland and the submandibular gland duct are visualized extending deep between the mylohyoid muscle and the mucous membrane of the floor of the mouth [19].

After complete mobilization of the mylohyoid muscle, the flap is easily dislocated and tractioned to cover the mandibular bone defect [9,19,20].

The next phase consists in the closure of the flap and in the literature there are several techniques.

Ristow et al. make a periosteal incision on the vestibular flap posterior to the mental nerve, at the point where the nerve has entered the soft tissue. The periosteum has been detached from the muscle and soft tissue to provide a sort of periosteal loop. The mylohyoid flap is fixed to the periosteal loop with several resorbable sutures. Finally, the buccal mucoperiosteal flap was tightly sutured to the lingual mucosal flap to ensure closure of the surgical wound [19,20].

Lemound et al. and Mücke et al. implement a different technique of closing the mylohyoid flap: Once the flap is placed in a tension-free position on the surgically treated mandible, it is fixed with deep

sutures at detached points with resorbable material (Vicryl 3-0, Ethicon).

A further closure of the soft tissue mucosa is then performed [20].

Other flap described in the literature is the pedicled vestibular adipose tissue flap (PBFPF), used after MRONJ surgical treatments in the maxillary region [6,19,26-28].

This flap is used when a communication with the maxillary sinus is present, in these cases the mucous membrane of the maxillary sinus was gently cleaned and the sinus was then irrigated several times with saline solution [6,19].

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Chapter 4: MRONJ surgical treatment: Role of local flaps to achieve primary wound closure in MRONJ osseous-resective surgery

Our research group dealt with the above mentioned issue through a retrospective study designed to evaluate the most suitable surgical technique in relation to the position and extent of MRONJ and to propose a standardization of surgical procedures based on stage and location MRONJ.

Introduction

The clinical success after surgical treatment of medication- related osteonecrosis of the jaws (MRONJ) is defined as the maintenance of full mucosal coverage without signs of residual infection [1-3].

Mucosal wound closure plays a key role after surgery of MRONJ [3]. The success rate of MRONJ surgical treatment was higher when the osteotomy was performed and primary wound closure was guaranteed [4-6].

The type of flap determines the feasibility of primary closure, duration of wound healing, and has an impact on clinical outcome. Full-thickness flaps are needed as periosteum elevation is required for access to bone. In the absence of sufficient mucous tissue that ensures

a stable and tension-free closure, it is possible to mobilize a local flap to advance or rotate in the defect to be closed [3].

The use of advanced flaps and rotation flaps has widened the possibility of covering large defects after MRONJ osseous-resective surgery with local tissue. Additional layers of soft tissue promise, in addition to a better seal that prevents microbial con- tamination from the oral environment, better vascularization, and mechanical stability [3].

Objective of the use of a local flap is to provide healthy and stable tissue to prevent microbial contamination of the wound and bone and to improve soft tissue healing and vascularization of the underlying healthy bone, as well as possibly contributing to rehabilitation with additional soft tissue to support the future removable prosthesis. The presented study aims to evaluate the use of oral flaps for the monophasic coverage of surgically treated MRONJ lesions and to evaluate the most suitable surgical technique in relation to the location and extent of the affected bone through comparison of success rate between the routinely used mucoperiostal flaps and different local flaps designs.

Methods

The study is a retrospective analysis conducted at Center for Treatment of the Osteonecrosis of the Jaws (University of Messina,

Italy). The study was notified to the Ethical Committee of the Academic Hospital of Messina Prot. n. 6311-24703/2017 according to the current national law. The digital medical records of patients admitted to Day Surgery at this institution in the 2016 to 2019 period have been revised. Only anonimized individual codes that do not allow identification of the study subjects were available for the analysis.

Patients were considered eligible if currently or previously treated with bone antiabsorptive agents for the treatment of primary osteoporosis, with focal forms of osteonecrosis of the jaws or limited to the alveolar bone and not interesting basal bone, maxillary sinus or nasal floor, and without systemic contraindications to surgical treatment.

When patients attend at first examination local signs and symptoms are regularly recorded to establish a suspected diagnosis of MRONJ.

In all patients with suspected diagnosis of MRONJ a second- level radiological examination is regularly performed for diagnostic confirmation and staging of the disease. Medication-related osteo-necrosis of the jaws is staged according to the classification of the Italian Societies of Oral Medicine and Maxillofacial Surgery (the SICMF-SIPMO staging system) [7,8].

Based on the SICMF-SIPMO staging system, patients are defined as stage 1 if they have focal MRONJ that is increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: markedly

thickened and sclerotic lamina dura; persisting alveolar socket; and/or cortical disruption and in the presence of at least 1 minor clinical sign.

The minor clinical signs and symptoms are represented by: bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity; and/or hypoesthesia/paraesthesia of the lips.

Patients are classified as stage 2 if affected by diffuse MRONJ when increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oro-antral fistula is observed at com- puted tomography imaging and the same clinical signs and symp- toms as for Stage 1 are present.

Furthermore, the patients of both stages are classified in the subgroups ‘‘a’’ asymptomatic and ‘‘b’’ symptomatic based on the presence/absence of pain and purulent discharge [7].

All patients are regularly subjected to perioperative adjuvant antibiotic therapy according to the following scheme: Amoxicillin 875 mg þ ac. Clavulanic 125 mg tablets 1 cpr 2/day 1 days before and 6 days after surgery in combination with Metronidazole 250 mg 2 cpr 2/ day 1 days before and 6 days after surgery and to antiseptic therapy of the oral cavity with Chlorhexidine 0.20% mouthwash rinse 2 to 3 times a day from 7 days before surgery and until the sutures are removed.

The surgery is performed in loco-regional anesthesia with intraoral approach and consists in resection of the necrotic bone until reaching bleeding vital bone. Access to the osteonecrotic lesion is provided by a mucoperiosteal flap with total thickness sufficiently large to include the margins of the necrotic bone.

For the purpose of this retrospective analysis, the patients were divided into 3 groups based on the amount of perilesional soft tissue and in relation to the surgical technique consequently used to obtain primary wound closure.

GROUP A: mucoperiostal flaps when adequate amount of soft tissues was present and the mucoperiostal flap was sutured directly above the residual defect.

GROUP B: advanced mucoperiostal flaps or rotation flaps when insufficient soft tissues was present requiring a flap design with releasing incision which enables soft tissue advancement and rotation.

GROUP C: local flaps when insufficient amount of soft tissues to cover a large defect was present demanding for advanced surgical techniques.

Postoperative and follow-up examinations are regularly per- formed according to the following scheme:

1. one week: cleaning of the surgical wound through irrigations with physiological solution and chlorhexidine at 0.20% and plaque control and to evaluate any signs of wound infection (T1)
2. two weeks: suture removal (T2)
3. four weeks: evaluation of mucosal healing (T3)

4. twelve weeks: orthopantomography evaluation of bone healing.

The clinical result was evaluated based on the findings recorded at 12 weeks examination taking into consideration both the clinical instrumental parameter (ie, complete or partial mucosal healing, absence or presence of clinical signs as swelling, and suppuration) and the absence or presence of radiological signs of failed bone healing. Success of surgical treatment was defined as wound healing without dehiscence, without clinical signs of infection, and without radiological signs of failed bone healing.

Results

Thirteen consecutive patients were surgically treated during the examined period. Patient's demographic characteristics of the patients and systemic risk factors (cumulative dose, use of drugs related to the onset of MRONJ, duration of therapy) are summarized in Supplemental Digital Content, Table 1, http://links.lww.com/ SCS/B201.

Medication-related osteonecrosis of the jaws characteristics (staging and localization) are summarized in Supplemental Digital Content, Table 2, http://links.lww.com/SCS/B201.

The surgical technique and the result of surgical treatment is reported in Supplemental Digital Content, Table 3, http://links.lww.- com/SCS/ B201 and divided into clinical and radiological healing.

The success rate was stratified according to the surgical tech- nique used (Supplemental Digital Content, Table 4, http:// links.lww.com/ SCS/B201).

Discussion

Hard Tissue Management

The extension of the necrotic bone segment determines the choice of the most appropriate surgical technique according to a stage-specific rationale [9,10].

A variety of techniques have been described in the literature. Curettage is the removal of superficial inflammatory soft tissue and necrotic bone, sequestrectomy is the removal of infected and avascular pieces of bone, saucerization, also called decortication, is the removal of the adjacent cortical bone and formation of a saucer-like depression. Mandibulectomy is the marginal or segmental resection of the mandible, followed by reconstruction. It is the most radical type of surgical intervention [11-13].

Mandibular resections are referred to as segmental resections where mandibular continuity is broken and reconstructed with bone plates and marginal resections where the alveolus is resected without loss of mandibular continuity [9].

All surgical procedures include the removal of the necrotic bone. Intraoperative resection or decortication is performed until sound bone was reached at the margins [15,16]. The affected bone can be removed using a bur [15,16], otherwise surgical ablation can be performed with ultrasonic bone surgery device [17].

Outcome

In the experience of Carlson and Basile [9], 87 out of 95 resected sites (91.6%) healed in an acceptable fashion with resolution of disease. When surgical treatment with saucerization was performed
healing was achieved in 9 patients out of 11 cases of denosu- mab-related osteonecrosis of the jaws [18].

Surgical treatment of MRONJ appears to be more effective when resective procedures were performed. In a retrospective survey of 347 cases conducted by Graziani et al [19] improvement was observed in 49% of cases treated with local debridement and 68% of cases treated with resective surgery. Within a prospective study performed by Schubert et al. [20] surgical treatment records high success rates of over 80%. Bedogni et al. [13] assessed the effectiveness of surgical resection of the jaws reporting a cumulative recurrence rate of MRONJ in resected jaws of the 3.1% and 9.4% at 3 and 6 months after surgery. Kim et al. [11] performed a retrospective cohort study with 325

subjects, in this study after surgery, 228 patients (70%) showed treatment success highlighting how the type of surgical procedure and mode of anesthesia were the most important factors in the treatment outcome since better results were achieved when an extensive surgical procedure rather than curettage was performed with the patient under general anesthesia.

Soft Tissue Management

After removing the necrotic segment if a sufficient quantity of soft tissue to obtain closure by first intention is present, the vestibular and the lingual mucoperiostal flaps can be directly sutured on the defect without any release incision; otherwise, closure could be obtained using mucosal advancement flaps to allow for a tension-free suture [21]. For the covering of very large bone defects it is possible to use local flaps that provide a quantity of soft tissue sufficient to obtain a tension-free closure [22,23].

The Mylohyoid Flap is a myofacial flap that is accessible from the lingual edge of the jaw and can be used to cover mandibular bone defects [22].

Another flap described in the literature is the Flap of Vestibular Vestibular Tissue (PBFPF), used after surgical treatments of MRONJ in the maxillary region [3,5,9,10,20,24-26]. This flap is used especially in the presence of communication with the maxillary sinus.

The success rate of MRONJ surgical treatment proved to be higher when the osteotomy was performed and closure by first intention without tension was achieved [4-6].

Stockmann et al [4] used an advanced mucoperiosteal flap in 50 patients with a 89% success rate.

The same strip was used by Eguchi et al. [27] in 14 patients also finding a success rate of 89.3%.

Stanton and Balasanian [21] in their study compared advanced mucoperiosteal flaps with mucoperiostal flaps. Twenty-four patients were treated with advanced mucoperiostal flaps, while 14 were treated with mucoperiostal flaps. The success rate is 83.33% for the advanced mucoperiosteal flap and 78.57% for the mucoperiosteal flap [21].

Aljohani et al [5] treated 60 lesions with an advanced mucoper- iosteal flap and 76.7% were completely healed. Instead, the lesions subjected to PBFPF all showed a complete mucosal healing in 85.7% of cases [5].

Ristow et al [3] evaluate the success rates of double-layer closure techniques for MRONJ surgical treatment and in particular the vestibular fatty tissue flap pedunculate (PBFPF) and the mylohyoid muscle flap (MMF). At the time of the last follow-up (8 months after surgery), 88.0% (44 of 50 patients) of patients in the MMF group and 93.1% (27 of 29) of patients in the group PBFPF showed mucosal integrity. One year after surgery, 93.1% of patients in the PBFPF group

and 88% of patients in the MMF group had complete mucosal coverage [3].

Mucke et al [22] compared advanced mucoperiosteal flaps with myxoid flaps, with particular attention to their influence on wound healing. The authors found a success rate of 69.24% using a mylohyoid flap and 42.60% using an advanced mucoperiosteal flap. Medication-related osteonecrosis of the jaws recurrence was significantly reduced with the use of the mylohyoid flap from 29.6% to 15.4% (P 1/4 0.023) [22].

Pichardo et al [18] used a mucoperiosteal flap to favor closure by first intention, finding a success rate of 64.84%.

Wilde et al treated 28 lesions with mucoperiostal flap with bilaminar suture of connective tissue and 5 lesions with PBFPF flap. The 89.2% success rate was obtained with the mucoperiosteal flap with bilaminar suture of connective tissue flap and 80% instead with the PBFPF flap [2,10].

Instead, Voss et al treated 21 patients in 2012 using a mucoper- iosteal flap with bilaminar flap of the periosteal flap and in 2016, using the same flap, as many as 21 patients achieving a success rate of 95.2% in 2012 and 91.67% in 2016 [15,16].

Berrone et al. [25] Rotaru et al, [26] Carlson and Basile [9] have success rates ranging from 90% to 100% using the PBFPF flap.

Instead, Lemound et al for 20 MRONJ lesions used the mylo- hyoid flap obtaining 90% success from surgical treatment [26].

The localization of a well-vascularized tissue over the surgically treated bone, in addition to wound closure without tension, has improved healing rates, with a success rate of 99% after 18 months, and facilitates the postoperative course [22,23,28].

According to Gallego et al [24] and Aljohani et al [5] the PBFPF flap offers a rich vascularization in the MRONJ site, a mechanical protection, and an abundant source of adipose stem cells, favoring the healing of the surgical wound.

Although healing by primary intention is considered for most authors to be an indispensable prognostic factor for surgical suc- cess, there are experiences in the literature where it was impossible to close the surgical wound by first intention and the patients regressed in a less severe clinical stage than disease.

Eguchi et al [27] to reduce microbial contamination of the open wound use antimicrobial aids such as gauze soaked with terramycin. Instead, Kang et al [29] in cases where it is not possible to close the wound by first intention, favor the closure by second intention using a gauze soaked with furacin. They compared advanced mucoper- iostal flaps with second intention closure with gauze soaked with furacin and found 88.23% success using the advanced mucoper- iostal flap and 55% instead favoring closure by second intention
using a gauze soaked with furacin [29].

In the face of a lack of consensus treatment guidelines, different

therapeutic approaches have been employed in the management of MRONJ.

Surgical options entail conservative surgery (sequestrectomy and/or superficial debridement of sequestrum), extensive surgery (alveoloplasty, resection), and laser surgery [4,9,16,19].

Outcome after surgical treatment of MRONJ was positive in every group (GROUP A 80%; GROUP B 100%; GROUP C 100%) which is in agreement with literature percentage of success rate (GROUP A 78, 42; GROUP B 63, 18; GROUP C 87, 70) irrespec- tively to MRONJ localization and extension. This may be due to the appropriate selection of surgical procedure. Figures 1 to 3 show the surgical technique adopted for each group.

The clinical success after surgical treatment of MRONJ is defined as surgical wound healing without dehiscence and without clinical signs of infection or evidence of recurrence [1,2].

Definition of the result of surgical success is not the same for everyone in the literature.

Eguchi et al [27] consider the outcome of surgical treatment as the lack of progression of the disease to a higher clinical stage and not in a re-epithelization of the surgically treated site.

Stanton and Balasanian [21] demonstrated how the success of the treatment is instead considered as complete mucosal coverage of the surgically treated site and in the resolution of pain.

Bodem et al [30] consider the success of the treatment as mucosal healing or regression of a minor and asymptomatic clinical stage.

Pichardo et al [31] published a study which outlined the outcome of surgical treatment is considered to be lack of symptomatology and the presence of re-epithelialized mucosa.

Aljohani et al [5] identify the success of the treatment in re-epithelialization of the surgical site in the absence of pain and inflammation.

For Kim et al [11] the failure of surgical treatment is given by the manifestation of recurrence of the disease.

For Wilde et al [2] the outcome of the surgical treatment is evaluated on the complete recovery of MRONJ, without exposed necrotic bones, no residual mucosal defect, no fistula, and the absence of swelling and pain.

Instead of Schubert et al [20] the criterion for evaluating the success of the treatment was considered the absence of symptoms for at least 3 months after surgery.

Therefore, it would be more appropriate to use the terms palliative or curative with reference to the treatment of osteone- crosis of the jaws [32].

In the end it is noteworthy to mention that this case series represents the prosecution of a previous cohort of 41 patients similarly affected by focal MRONJ where mucosal healing was achieved after surgery in the 100% of the patients and no bone exposure recurrence was observed confirming, in agreement with other authors that support surgical approach, that surgery is successful in this specific subset of

patients which suffer of focal forms of MRONJ and do not have contraindication to surgical treatement [17,30,33].

Conclusions

The results obtained demonstrated that MRONJ surgical treatment, irrespective of the adopted procedure, is a reliable approach to the disease. The positive outcome reached in every surgery may be due to the appropriate selection of the surgical procedure.

About this critical issue no precise guidelines were drawn on the surgical treatment of MRONJ; interventions range from conserva- tive debridement to major resection, often without a precise defini- tion or description of the extent of bone removal.

It is therefore necessary to reach a general consensus, defining the characteristics of the case and the details of the intervention required (for example, debridement, conservative surgery, decor- ticalization) to provide clear indications on the surgical treatment of MRONJ [11,14,34].

This study proposes a standardization of surgical procedures according to MRONJ stage and localization to provide the surgeon with an algorithm of treatment with the aim of maximizing the success of surgical treatment and implementation of the SIPMO classification with an indication of management of hard and soft tissues stratified by MRONJ localization and extension.

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TABLES AND FIGURES

FIGURE 1. Surgical technique adopted in group A: (A) radiologic appearance MRONJ lesion in alveolar process of left mandible. (B) Clinical appearance of focal MRONJ lesion. (C) Radical ostectomy until bleeding bone. (D) Double layer first intention wound closure. MRONJ, medication-related osteonecrosis of the jaws.

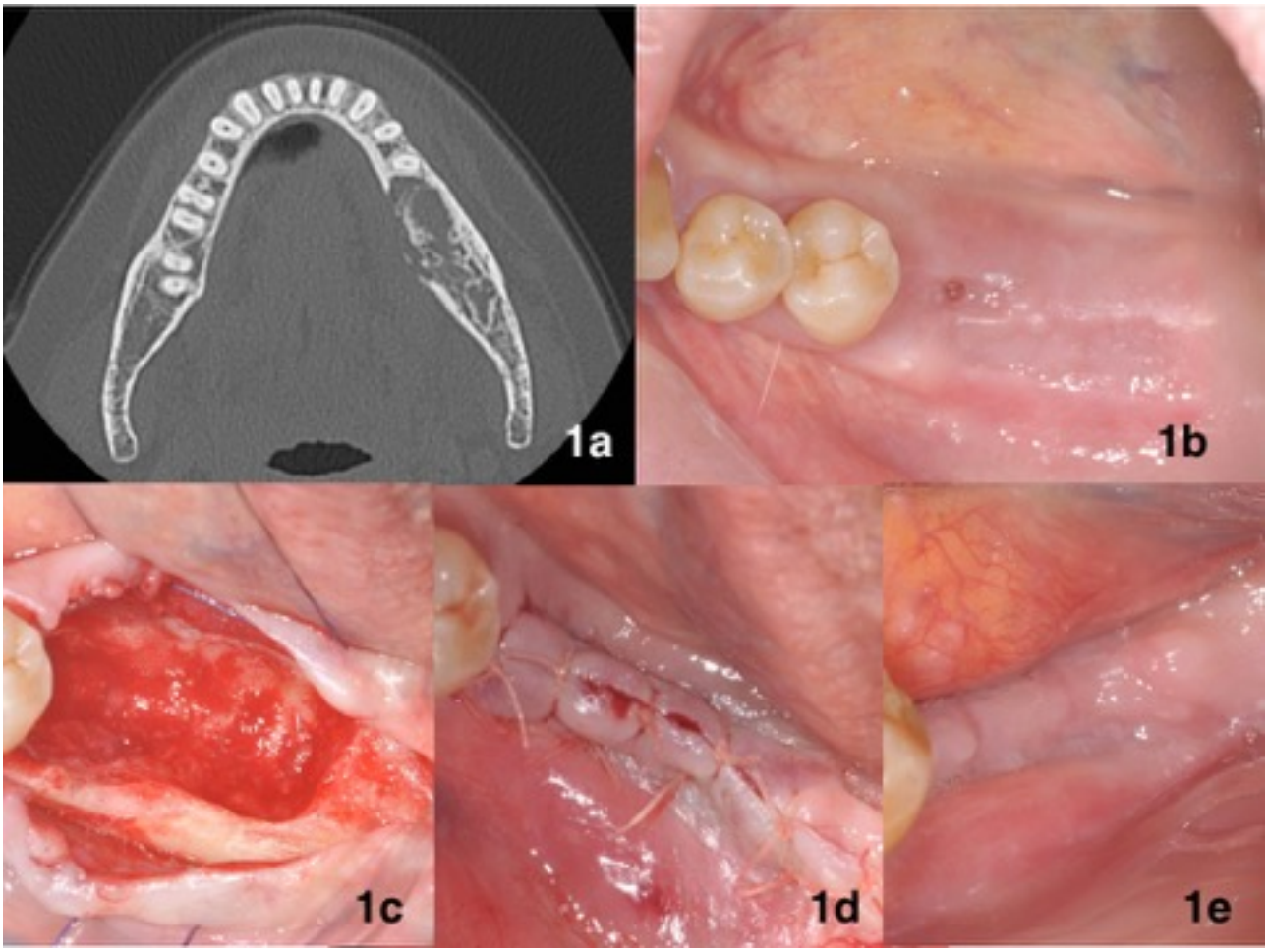

FIGURE 2. Surgical technique adopted in group B: (A,B) coronal and axial cone beam computed tomography scans of upper jaw medication-related osteonecrosis of the jaws. (C) Full-thickness flap and necrotic bone exposure. (D) Bone cavity after osseous resection. (E) Tension-free advancement mucoperiosteal flap. (F) Double layer suture to secure a primary healing.

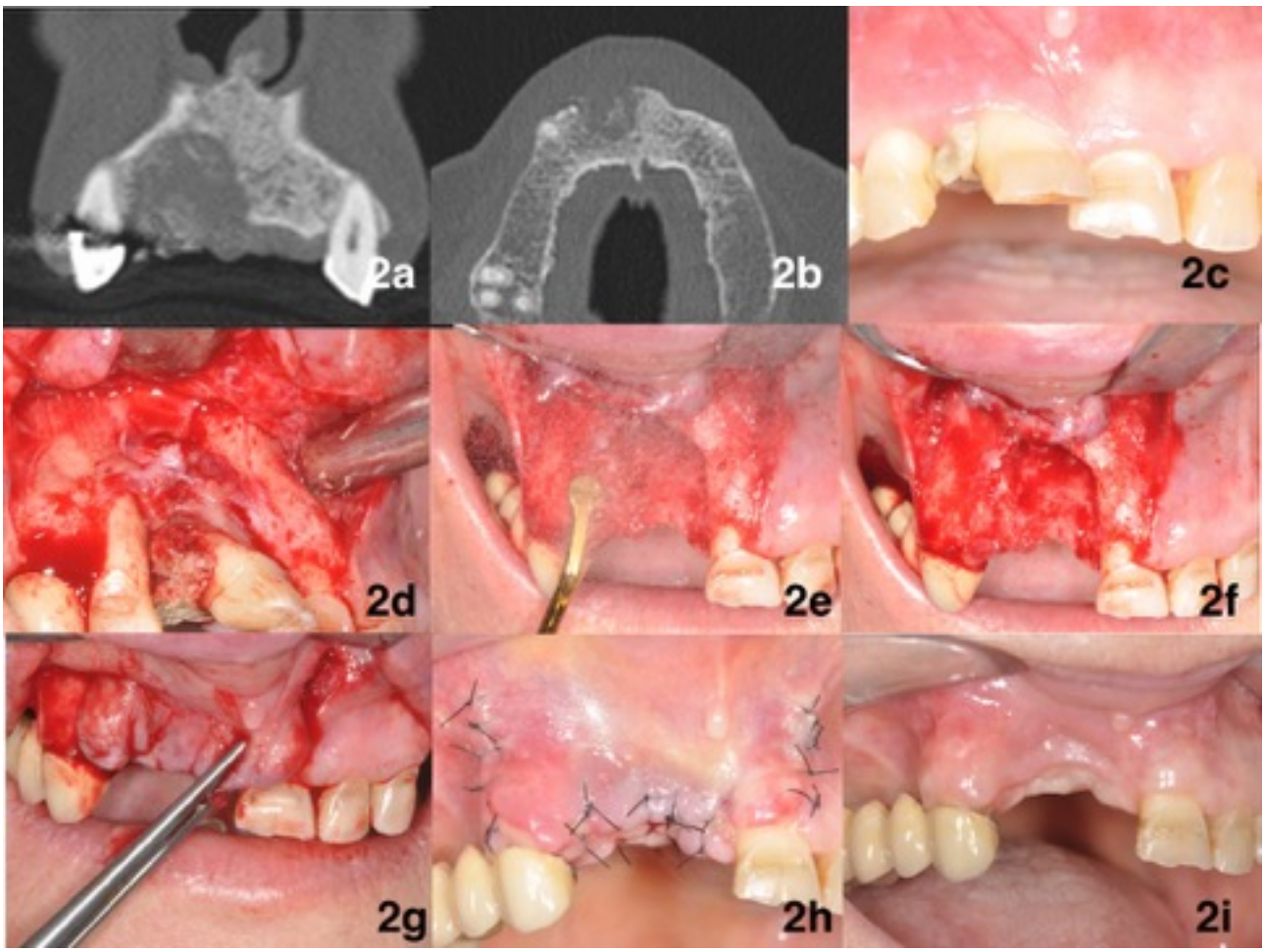

FIGURE 3. Surgical technique adopted in group C: (A) orthopantomograph of left mandible medication-related osteonecrosis of the jaws lesion. (B) Clinical appearance of necrotic bone extended to the whole left mandible. (C) Bone cavity after removed necrotic bone and implants. (D) Wound closure obtained after detachment of mylohyoid flap.

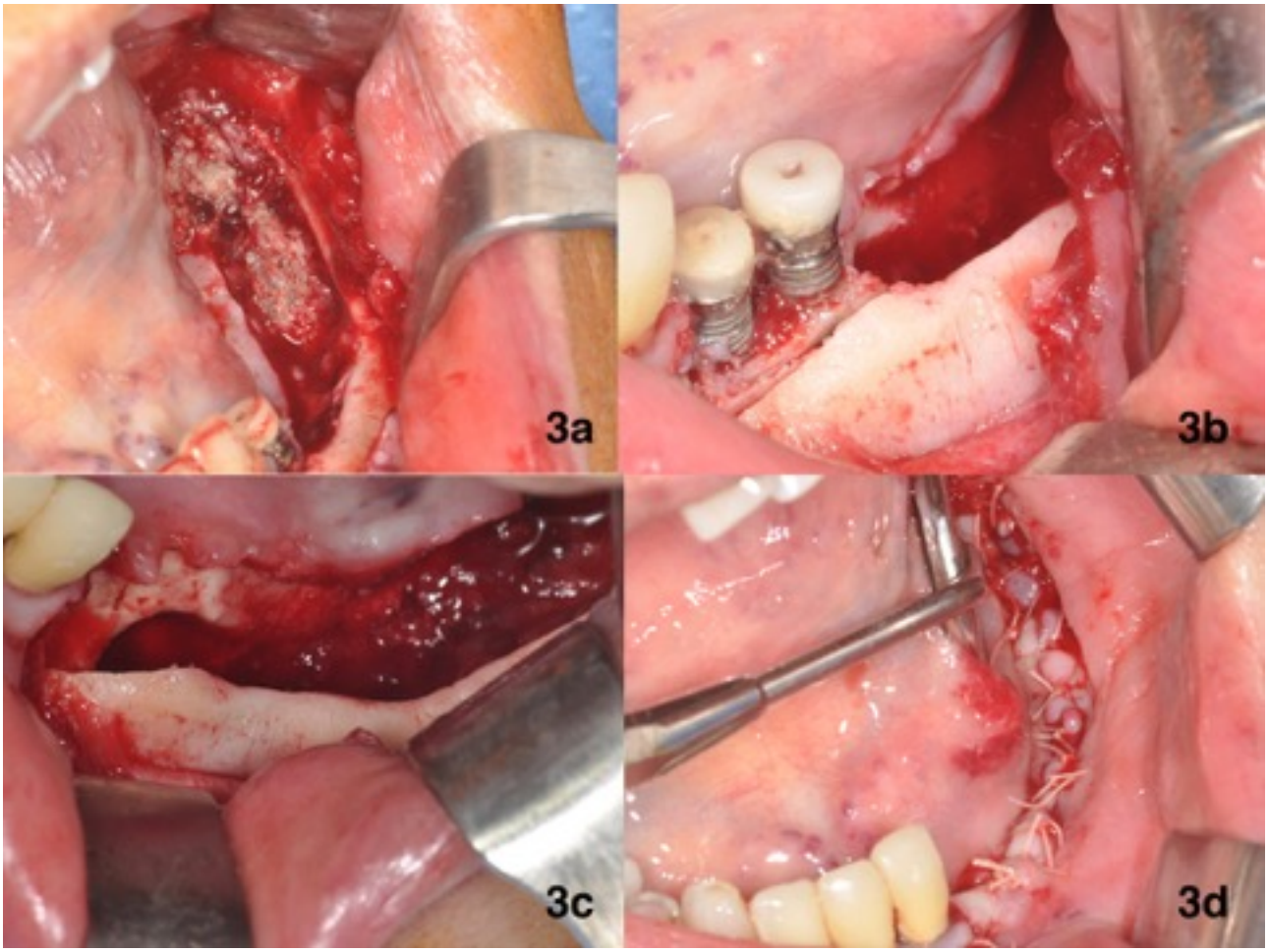

Table 1 Characteristics of patients affected by MRONJ

Patients with MRONJ	**13**
Mean age	72,25
Sex	N. (%)
Male	0 (0)
Female	13 (100%)
Administered antiresorptive drug	
Denosumab 60 mg (subcutaneous)	3 (23,07%)
Ibandronate (per os)	3 (23,07%)
Risedronate (per os)	2 (15,38%)
Alendronate (per os)	4 (30,76%)

Clodronate (i.m)	1 (7,69%)
Cumulative dose of BP at MRONJ occurrence (mg)	
Alendronate (per os)	15945
Ibandronate (per os)	12600
Risedronate (per os)	10281
Clodronate (i.m)	9600

Table 2 SIPMO classification of MRONJ and anatomic location of MRONJ site

Patient	MRONJ stage	Localization
1	2b	Mandibular
2	1b	Mandibular
3	1b	Mandibular
4	2b	Mandibular
5	1b	Mandibular
6	2b	Maxillary
7	1b	Mandibular
8	2b	Maxillary+Mandibular
9	1b	Mandibular
10	2a	Mandibular
11	1a	Mandibular
12	2b	Mandibular
13	1b	Mandibular

Table 3 Adopted surgical procedure for MRONJ management

Patient	Surgical procedure	Clinical healing	Radiological healing
1	mylohyoid flap	complete healing	No evidence of bone translucency
2	mucoperiosteal flap	complete healing	No evidence of bone translucency
3	mucoperiosteal flap	complete healing	No evidence of bone translucency
4	advanced mucoperiosteal flap	complete healing	No evidence of bone translucency
5	mucoperiosteal flap	complete healing	No evidence of bone translucency
6	pedicled buccal fat pad flap	complete healing	No evidence of bone translucency
7	mucoperiosteal flap	complete healing	No evidence of bone translucency
8	advanced mucoperiosteal flap	complete healing	No evidence of bone translucency
9	mucoperiosteal flap	partial healing	No evidence of bone translucency
10	advanced mucoperiosteal flap	complete healing	No evidence of bone translucency
11	advanced mucoperiosteal flap	complete healing	No evidence of bone translucency
12	advanced mucoperiosteal flap	complete healing	No evidence of bone translucency
13	mucoperiosteal flap	complete healing	No evidence of bone translucency

Table 4 Outcome after MRONJ surgical treatment stratified by adopted surgical technique

	GROUP A	GROUP B	GROUP C
Success [a]	4	6	2
Failure	1		

Legend: MRONJ= medication-related osteonecrosis of the jaws; BP= bisphosphonates

[a] Success of surgical treatment was defined as wound healing without dehiscence, without clinical signs of infection and without radiological signs of failed bone healing.

Chapter 4: MRONJ surgical treatment: Oral Surgical Management of Bone and Soft Tissues in MRONJ Treatment: A Decisional Tree

Premise

Reparative surgery after MRONJ radical treatment calls for complex surgical techniques to cover the residual bone defect.

Our group presented a case series of modified soft tissue reconstruction techniques using local flaps for oral reconstructive surgery after MRONJ treatment.

Optimal wound healing allows to achieve mechanical stabilization and increases healing chances enabling and supporting the necessary nutrition and defense against opportunistic infections to improve clinical outcome of MRONJ cases.

The aim of the following work was to describe in a retrospective series of MRONJ cases a range of oral surgical approaches categorized taking into consideration two variables a) hard tissue management (defined as debridement or marginal osseous resective surgery) and b) soft tissue management (flap design plus type of healing).

Secondary aim was to report the clinical outcome for each single technique in order to draw, on the basis of the highest success rate obtained, a treatment algorithm that can aid to standardize clinical decision making and maximize the success of oral surgical treatment of MRONJ.

The decisional tree developed accordingly allow clinicians to assess the degree of complexity required when selecting individual treatment approaches for MRONJ management and to plan treatment in accordance to patients need and to personal surgical skills.

Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is defined as exposed necrotic bone or bone that can be probed through a fistula in the maxillofacial region for at least 8 weeks in patients receiving an anti-resorptive medication for primary or metastatic bone cancer, osteoporosis, or Paget's disease, without history of radiation therapy to the jaw [1]. Medication-related osteonecrosis of the jaw (MRONJ)'s o cial treatment guidelines are still lacking. Although the knowledge of diagnosis and staging of MRONJ has gradually advanced, and the most recent position papers provide detailed clinical and radiological diagnostic elements, a stepwise protocol for medical and/or surgical treatment has not been o cially drawn [1,2].

To date, only a few stage-specific treatment indications deriving from the best practice of qualified centers for MRONJ prevention and treatment are available [3]. Nevertheless, these treatment protocols reported in the literature do not describe the step-by-step surgical procedures (from incision to suture techniques) to be used to favor wound-healing [4,5].

The present work aimed to critically analyze a 10-year retrospective series of surgically treated MRONJ cases, reporting the related clinical outcome and introducing a decision tree to identify the appropriate surgical approach. The purpose was either to (a) provide the surgeon with a treatment algorithm, based on MRONJ location and staging, that can aid and standardize clinical decision making; (b) increase the success rate of oral surgical treatments [6].

Materials and Methods

All study procedures were performed under the ethical standards of the Institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was notified to the Ethical Committee of the Academic Hospital of Messina (Prot. n. 6311-24/03/2017) according to the current national law. This article does not contain any studies with animals performed by any of the authors [7].

In order to provide a clear description of the stage-related surgical procedures adopted in MRONJ treatment, a 10-year retrospective cohort study conducted at the Center for Treatment of the Osteonecrosis of the Jaws (University of Messina, Messina, Italy) was carried out.

Patient inclusion in the retrospective analysis required a diagnosis of MRONJ.

MRONJ diagnosis was made according to the definition and staging system of the Italian Society of Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Oral Medicine (SIPMO) [8,9]. Diagnosis was based on the following: (a) clinical findings of MRONJ (e.g., presence of exposed bone); (b) patients' medical history reporting current or previous treatment with anti-resorptive or anti-angiogenic agents; (c) dental radiographies suggestive of MRONJ.

Patients were defined as stage I if they had focal MRONJ, that is, increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura; persisting alveolar sockets; and/or cortical disruption in the presence of at least one minor clinical sign.

According to the SICMF-SIPMO definition, the minor clinical signs and symptoms are represented by the following: bone exposure; sudden dental mobility; nonhealing postextraction sockets; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity and/or hypoesthesia/paranesthesia of the lips.

Patients were classified as stage II if a↵ected by di↵use MRONJ when increased bone density was extended to the basal bone (di↵use osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oro-antral fistula observed at computed tomography (CT) imaging and the same clinical signs and symptoms as for Stage I.

Complicated forms were defined as Stage III if extra-oral fistula and/or displaced mandibular stumps and/or nasal leakage of fluids were present, and if computed tomography findings such as adjacent bone (zygoma, hard palate) involvement and/or pathologic mandibular fractures and/or osteolysis extending to the sinus floor were present.

Furthermore, the patients of all stages were classified into the subgroups of “a”—asymptomatic and “b”—symptomatic based on the presence/absence of pain and purulent discharge [8,9].

Characterization of the MRONJ cohort was made as follows: Patient demographics data were registered (age and gender); primary disease was analyzed, patients a↵ected by metastatic malignant cancer disease (mainly carcinoma) were stratified by cancer type, i.e., breast cancer, lung cancer, prostate cancer, kidney cancer, etc. Patients a↵ected by dysmetabolic disorders were divide into two categories of osteoporosis and rheumatoid arthritis.

Suspected medications related to MRONJ onset and average duration of therapy in months have been reported.

MRONJ features such as anatomical location and stage frequency of the disease have been reported.

As previously reported [10], according to our center’s clinical routine, after MRONJ diagnosis the patients are included in a 8–10-week outpatient-based medical treatment program which includes local antiseptic administration (chlorhexidine and povidone iodide) and targeted antibiotic therapy.

Regarding discontinuation of suspected medications, individual decisions should be made for every single case, even with respect to the drug-holiday protocol [11].

At the end of this initial phase the clinical course of MRONJ is evaluated and divided into four categories: progressive, unchanged, partially resolved and resolved.

The clinical MRONJ course was categorized as reported by Watters et al. Patients were defined as progressive if they experienced an increase in swelling, discomfort, or secondary infection, or had radiographic evidence of worsening bone loss or destruction; unchanged if they continued to be symptomatic and had exposed necrotic bone with clinical or radiological results neither improving nor worsening; partially resolved if MRONJ lesions spontaneously improved or soft tissue coverage in the area was achieved with symptom improvement; and resolved when surgical wound-healing was achieved without dehiscence and without clinical signs of infection or evidence of recurrence.

On the basis of the achieved outcome after medical treatment, the appropriateness of surgery with radical intent is discussed in a multidisciplinary meeting (MDM) where the chief oncologist and/or primary care physician are present.

For patients adamantly against receiving extensive surgery or those who do not want to undergo an invasive surgical procedure, the possibility of palliative surgical treatment is also discussed in the MDM.

Patients diagnosed with MRONJ (regardless of whether or not they are surgically treated [7]) are included in a follow-up routine program and recalled for clinical and radiological examination. The duration of follow-ups varies, generally being longer for patients affected by osteoporosis and shorter for cancer patients in consideration of a more limited life expectancy.

Only patients with at least 12 weeks of follow-up were included in the retrospective analysis.

To meet the objectives of this study, surgically treated patients were categorized according to the adopted surgical procedure taking into consideration two variables: (a) hard tissue management (defined as debridement, saucerization or marginal resection surgery) and (b) soft tissue management (flap design plus type of healing).

Surgical options entail conservative bone surgery (sequestrectomy and/or superficial debridement of sequestrum) and extensive bone surgery (alveoloplasty, resection).

Patients treated with radical intent underwent radical removal of necrotic sequestrum determined through bleeding evidence of the surrounding bone (Figures 1–14) [9]. In the absence of complete mucosal coverage of the surgically treated site, reintervention was performed [12].

Conservative surgical treatment, defined as palliative therapy, is usually adopted in stage III MRONJ forms when maxillo-facial surgery is contraindicated because of poor systemic conditions, and it consists of obtaining soft tissue relief from exposed bone irritation.

The clinical outcome was reported and defined as successful when surgical wound-healing was achieved without dehiscence and without clinical signs of infection or evidence of recurrence and functional recovery, as further prosthetic rehabilitation was viable to preserve the patient's quality of life [4,5,13,14].

The decisional tree has been designed incorporating data of clinical outcomes of each single adopted procedure and following the high success rate registered. If success was obtained, the surgical procedure was suitable for that clinical scenario, and when healing was not achieved, the more appropriate surgical treatment option was defined through analysis of the re-entry procedure.

Results

For this retrospective cohort study, 103 MRONJ patients were enrolled and a total of 128 surgical procedures were performed.

Patients' clinical data were acquired, including sex, age and medical procedures to report any underlying primary diseases (cancer/ osteoporosis).

Overall, the mean age was 70.72 years old. A female prevalence was observed (N = 76 subjects).

A female prevalence was observed (N = 76 subjects).

A total of 49 patients received MRONJ-related medication for the treatment of dysmetabolic bone (N = 46 suffering of osteoporosis; N = 3 suffering of rheumatoid arthritis), and 54 were oncohematologic patients.

In detail, of the 103 patients enrolled in the cohort, 11 patients had multiple myeloma, 24 had metastatic breast cancer, 16 had metastatic prostate cancer, 1 patient had metastatic lung cancer 1 had metastatic kidney cancer, and 1 had gastro intestinal stromal tumors (GISTs).

Among the cancer patients, the most commonly administered medication was zoledronic acid (N = 37) followed by denosumab 120 mg (N = 13). Among this group of cancer patients, 1 subject was switched from zoledronate to denosumab 120 mg. Two patients consumed zoledronate plus pamidronate and one patient zoledronate plus ibandronate.

Among patients with dysmetabolic bone diseases, the most commonly administered bisphosphonate was alendronate (N = 28) followed by ibandronate (N = 9), risedronate (N = 2) and denosumab 60 mg (N = 2). One subject received clodronate. Two patients consumed alendronate and risedronate consecutively, and two were treated with alendronate followed by ibandronate. One patient with osteoporosis adopted a step-down therapy, switching from zoledronate to risedronate. One patient was treated with zoledronate followed by denosumab 60 mg. One patient consumed neridronate followed by ibandronate.

As for cancer patients, the median onset of MRONJ was after 28.70 months in the case of zoledronate administration and after 26.92 months since starting a course of denosumab 120 mg.

As for dysmetabolic patients, the average duration of antiresorptive therapy was 33.5 months in the case of denosumab 60 mg and 66.14 months in the case of alendronate, respectively.

Characterization of the medication-related osteonecrosis of the jaw (MRONJ) cohort is reported in Table 1.

MRONJ features such as anatomical location and stage are reported in Table 2. The most common site of MRONJ was the mandible (N = 74). According to the SIPMO classification, the most frequent stage of MRONJ was stage II (stage IIa N = 45 lesions; stage IIb N = 11), whereas stage I (stage Ia N = 13 and stage Ib N = 27 lesions) and stage III (N = 15 lesions) were less common.

Among all the reported surgeries (N = 128), 113 were performed with radical intent (MRONJ stage I and II), while 15 procedures were palliative treatments (MRONJ stage III).

The di↵erent surgical approaches adopted with radical intent were analyzed and categorized as the following: superficial debridement (N = 16); sequestrectomy (N = 4); saucerization alias radical decortication of the necrotic bone (N = 22); sub-marginal bone resection (N = 25); marginal bone resection avoiding the loss of bony continuity (N = 46).

Among this group, the most frequent surgery of choice was marginal bone resection.

As for soft tissue management, a mucoperiosteal flap was adopted in 29 surgical procedures; a coronally advanced mucoperiosteal flap in 57 surgeries. In advanced surgeries, to obtain tissue coverage, a

mylohyoid flap (n = 23) or a pedicled buccal fat pad flap (n = 4) was needed.

The success rate was reported. A total of 113 procedures lead to a complete resolution of the disease. In 96 cases, healing was obtained with the first surgical treatment. Sixteen patients underwent a second intervention, and one a further third treatment to achieve complete and stable mucosal coverage.

Table 3 shows hard and soft tissue management details in the surgeries performed with radical intent in stage I and II MRONJ surgical procedures, detailing hard and soft tissue management with their related success rate.

Re-entry surgical procedures are reported in Table 4.

Palliative treatment was adopted in Stage III cases. A total 13 lesions were treated with superficial wound debridement, while in 2 cases a sequestrectomy (the removal of infected and avascular bone segments) was performed. Among the palliative treatments, partial healing was observed after eight procedures. Five lesions were unchanged and two worsened after treatment (Table 5).

A decisional tree was defined, in order to address the surgical options based on the extent, location, and stage of ONJ to provide an assessment tool useful to route the surgeon alongside such treatment options for standardization of the appropriate surgical procedures, clearly addressing both hard and soft of tissue management.

Discussion

The success rate of MRONJ surgical treatment proved to be high [2,15,16].

The surgical treatment raises questions regarding the margins of bone necrotic removal and the covering of the surgical wound by oral soft tissues, thus, a positive outcome is not always achieved [17–20].

The aim of the work was to demonstrate that adequate bone necrotic maxillary removal combined with di↵erent local flaps, usually adopted in oral reconstructive surgery, may prevent wound dehiscence, increase the vascularization, and protect the healing tissues against postsurgical opportunistic infections [21].

Primary flap closure is essential to promote oral mucosa healing in MRONJ patients, creating a more favorable environment for the e↵ect of basal lamina signaling proteins [14]. These biochemical pathways resulted under-expressed in patients treated with drugs frequently involved in angiogenesis [22].

A previously reported cohort was expanded [6,12]. Moreover, oncohematologic cases were included, since all the treated patients received approval from the oncologist and underwent a safe surgery appropriate to their systemic condition. Both focal and di↵used forms were included.

For patients with cancer, a decision regarding discontinuation of medications related to MRONJ should be based on the careful

evaluation of benefits and toxicities in order to maximize their quality of life [23].

The scientific community seems to be divided.

In a large follow-up study by Memorial Sloan Kettering Cancer Center (MSKCC), there was no statistical di↵erence in the clinical course of MRONJ lesions in patients that discontinued intravenous bisphosphonates (BP) therapy when compared to those who had not suspended it [13].

Conversely, Hinson et al. reported that in case of BP administration independent of treatment modality and MRONJ stage at presentation, discontinuing BP before or at treatment initiation is associated with faster resolution of MRONJ symptoms compared to continuing the drug throughout jaw treatment. As assessed by the authors, patients should be counseled that continuing BP therapy after established MRONJ diagnosis may delay resolution of maxillofacial symptoms by approximately 4–6 months [24].

In a study by Ramaglia et al., results showed a significantly higher prevalence of completely healed sites in patients who followed the drug-holiday protocol [11].

In the experience of Hoefert et al. however, cessation of denosumab seemed to have no influence on healing outcomes in the non-surgical group and did not demonstrate any influence on surgical outcome [25].

However, all the patients of this cohort discontinued the suspected medication.

It is worth mentioning that in our country, discontinuation of denosumab is mandatory as expressly requested by the Italian Medicines Agency (AIFA) [26].

The role of radical-intended surgery using local flaps in MRONJ treatment was investigated as well as the palliative treatments. All stage I–II patients completely healed after radical surgery. Nevertheless, some cases required reintervention [27].

The analysis of the failed surgical procedures highlighted how both (a) the management of hard tissues to guarantee radical removal of necrotic bone and (b) the management of soft tissues to allow tension-free wound-healing influence the clinical outcome after surgery [28].

In every case of surgical failure, modifications to the management of soft tissue were required. Among these cases, additionally, three patients needed di↲erent hard tissue management (i.e., marginal resection instead of superficial debridement).

In stage III, when the patient was not eligible for aggressive maxillo-facial surgery, the use of palliative surgical strategies led to symptoms relief, allowing for the maintenance of maximum quality of life for the duration of their life.

Clinical experience from this case series provides important insight into MRONJ oral surgical treatment, highlighting that positive outcomes could be achieved with accurate presurgical planning. The decisional tree, based on obtained results, allows clinicians to assess the degree of complexity

required when selecting individual treatment approaches for MRONJ management, and to plan treatment in accordance with their surgical skills and the patients' needs.

Following the pathway of the decision tree (Figure 15), the surgeon must first locate the MRONJ lesion, given the di↵erent topographical anatomy of the maxillary and mandibular bone.

Subsequently, using the clinical/radiological stage, the surgeon will perform a risk/benefit assessment in terms of radicality of the intervention, deciding on a radical surgery with curative purposes in the focal and di↵use forms, and on palliative therapy in complicated forms or in patients with systemic conditions for which invasive surgery is contraindicated.

The surgical procedure most frequently used in the management of focal forms is the superficial debridement, whereas for di↵use forms, saucerization or a marginal bone resection is indicated.

In saucerization, the removal of the necrotic bone takes place using rotating drills and/or a piezoelectric device until obtaining the formation of a cup-like depression [2,29].

In marginal dental-alveolar bone resection, block removal of the pathological bone, avoiding the loss of mandibular bone continuity, is performed. This should always include an additional osteoplasty to eliminate residual bone asperity [30].

The choice between the two techniques is determined by the characteristics of the MRONJ lesion itself.

Palliative therapy through superficial debridement allows the removal of bone asperities giving relief to perilesional tissues for improved comfort of the patient; furthermore, the role of incomplete necrotic bone removal in terms of reduction in the local bacterial load in the case of suppuration refractory to antibiotic therapy has to be clarified.

The amount of perilesional soft tissue determines the choice of flap management [31].

The surgeon should perform a mucoperiosteal flap in cases with an adequate amount of soft tissues, or a coronally advanced mucoperiosteal flap in cases of insu cient amounts of perilesional soft tissues. In the advanced stages, a mylohyoid flap could be needed if the MRONJ lesion is localized in the jaw, while a flap pedicled buccal fat pad flap (PBFPF) may be needed if the lesion is located in the upper jaw [28,32].

In complicated forms, soft tissue management does not influence the clinical result, thus bone surgery with alveoloplasty and superficial debridement is performed to remove all bone asperities that generate ulcerative mucosal lesions in the patient. To promote a sense of well-being for the patient, the surgeon will opt for minimal soft tissue manipulation.

The use of platelet-rich plasma (PRP) rich in growth factors (PRGF) as well as the use of bone morpho-genetic proteins demonstrated an enhancement in vascularization and regeneration of osseous and epithelial tissues [33,34].

Nevertheless, given the high rate of successful healing achieved without any adjuvant intervention, we believe that the use of any bone stimulator, including all locally delivered growth factors such as PRP, PRGF and rhBMP, could be avoided.

Regarding the palliative treatment, this approach is adopted in Stage III cases to relieve symptoms and improve patients' quality of life. Minimally invasive surgery techniques are chosen to limit patient involvement when major maxillo-facial surgical intervention is not viable for systemic contraindications.

Within palliation strategies, the removal of mobile sequestra is not considered a proper surgical act and is categorized within the medical conservative treatments. However, some MRONJ lesions without bone exposure may evolve into a sequestrum as results of compartmentalization by surrounding hard tissue. In these cases, the elevation of a flap is needed and, subsequently, the classification among surgical treatments.

Conclusions

The results from this retrospective study show that the surgical treatment of MRONJ is a reliable approach to the disease, and they confirm that appropriate soft tissue management procedures represent an additional guarantee against wound dehiscence, favoring the release of endogenous growth factors and leading to the successful healing of MRONJ disease.

Surgery with radical intent might represent a valid option for eligible MRONJ patients. The high clinical success rate achieved in the treated cases is due to an appropriate choice of surgical procedure, adjusted to case complexity.

Addressing the importance of promoting knowledge and, above all, the awareness that a comprehensive preoperative analysis of the hard and soft tissue components is essential to maximize the clinical result.

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Tables and figures

Figure 1. Cone beam-computed tomography showing the necrotic bone extension in a panoramic view with and without zoom, 3D rendering and cross-sectional view.

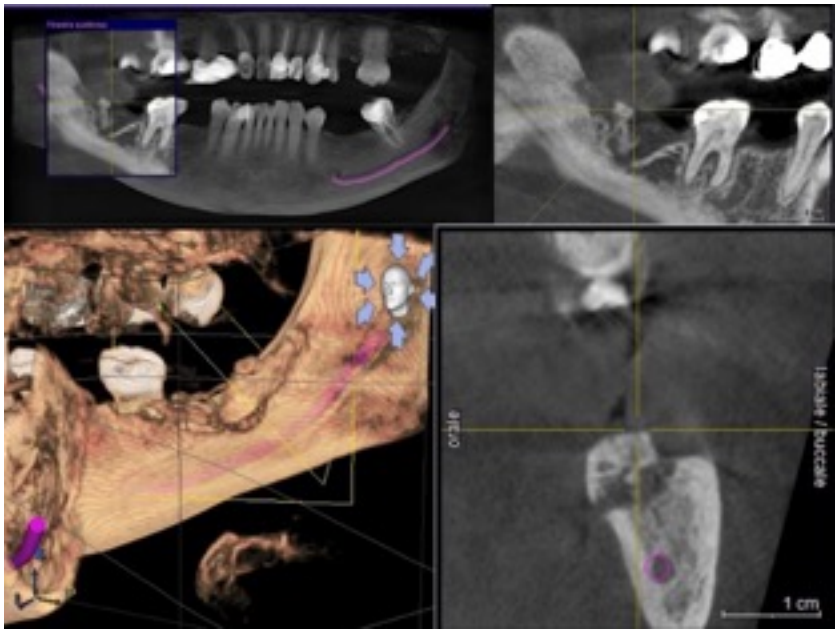


Figure 2. Clinical appearance of stage 1a MRONJ according to the the Italian Society of Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Oral Medicine (SIPMO) staging system (absence of signs of infection/inflammation).

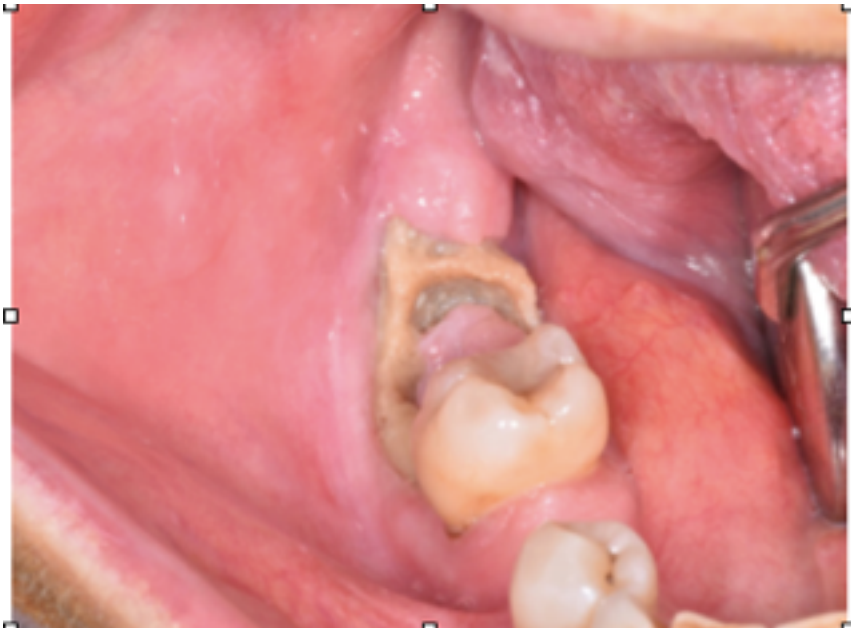


Figure 3. Sub-marginal resection performed using piezoelectric device.

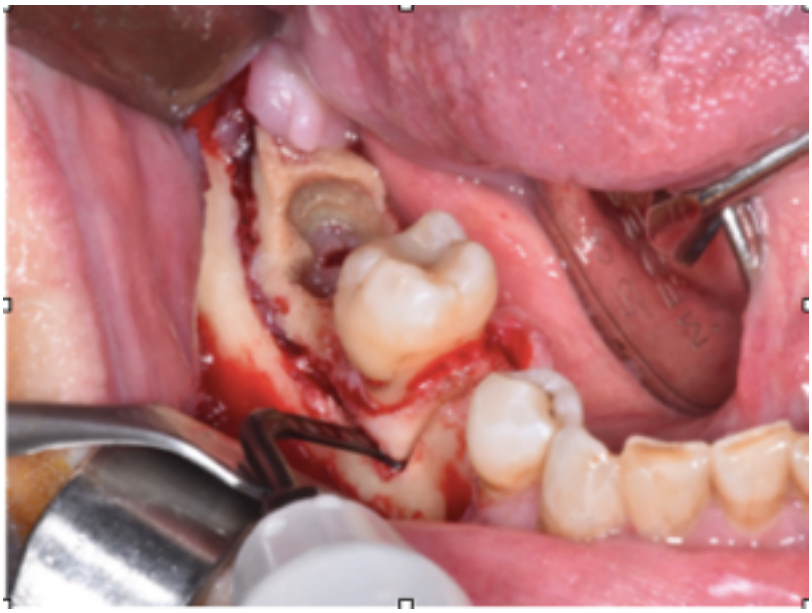


Figure 4. Revision of the cavity until observation of bleeding bone.

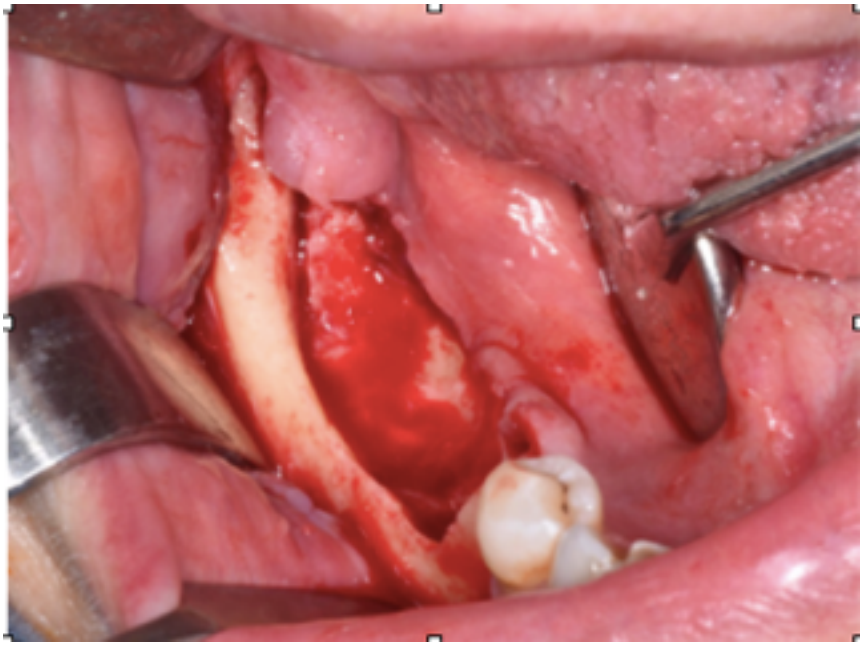


Figure 5. Resected sequestrum and extracted involved tooth.

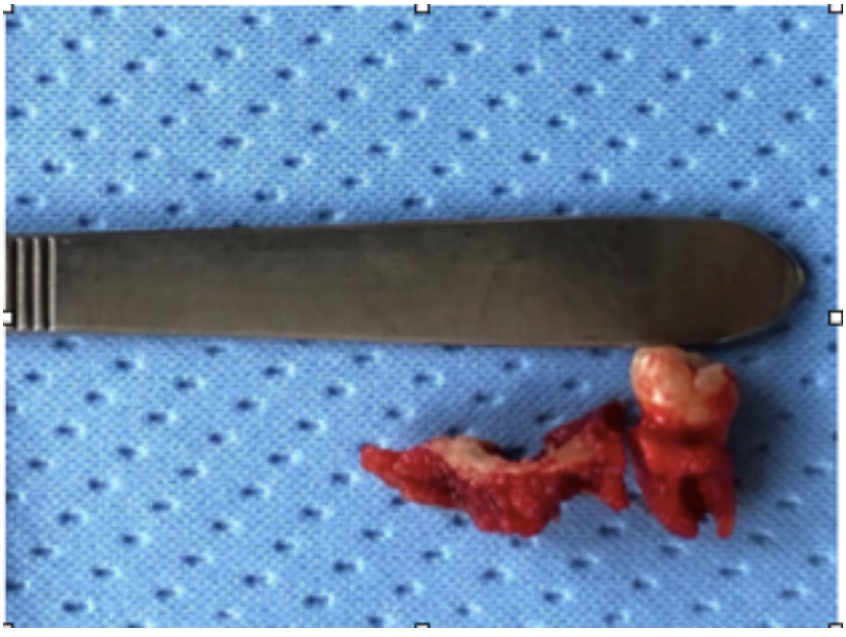


Figure 6. Suture with interrupted points to secure primary healing in order to avoid dehiscence.

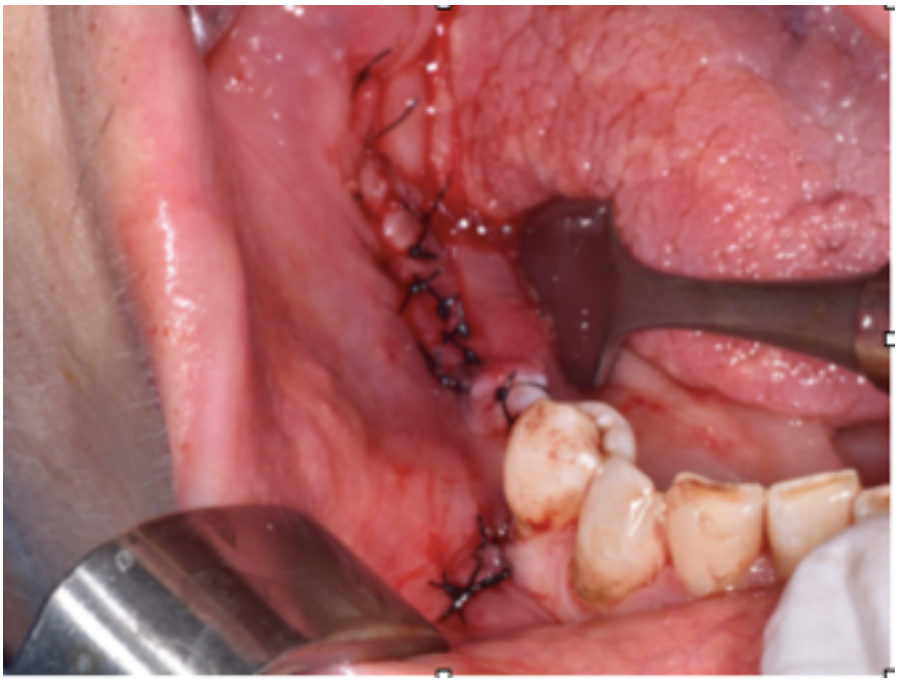


Figure 7. Healing without complications.

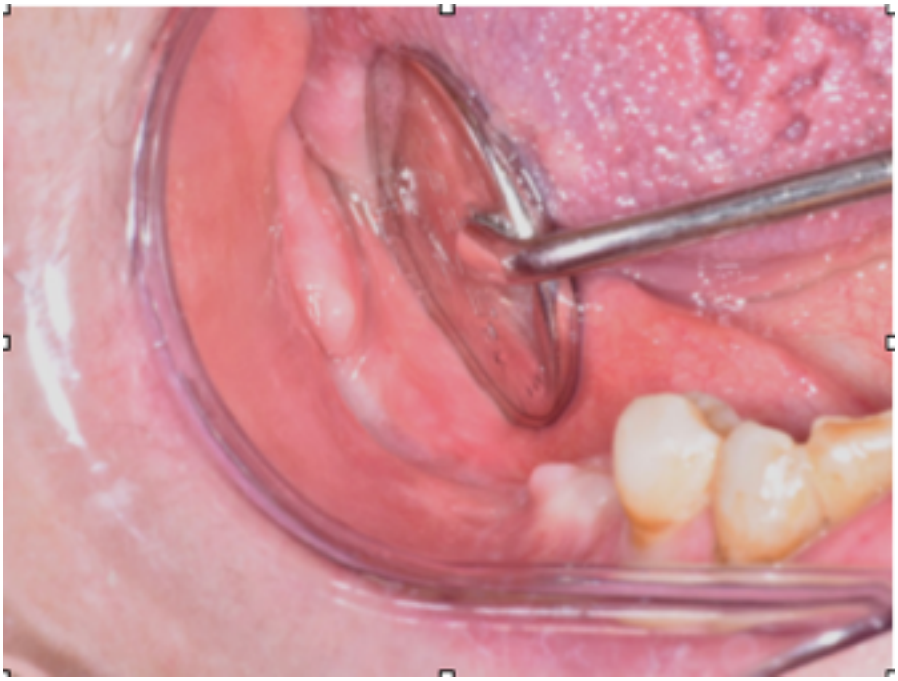


Figure 8. MRONJ "ghost socket" of the upper jaw as shown in 3D rendering, and coronal view of a cone beam computed tomography (CBCT) scan.

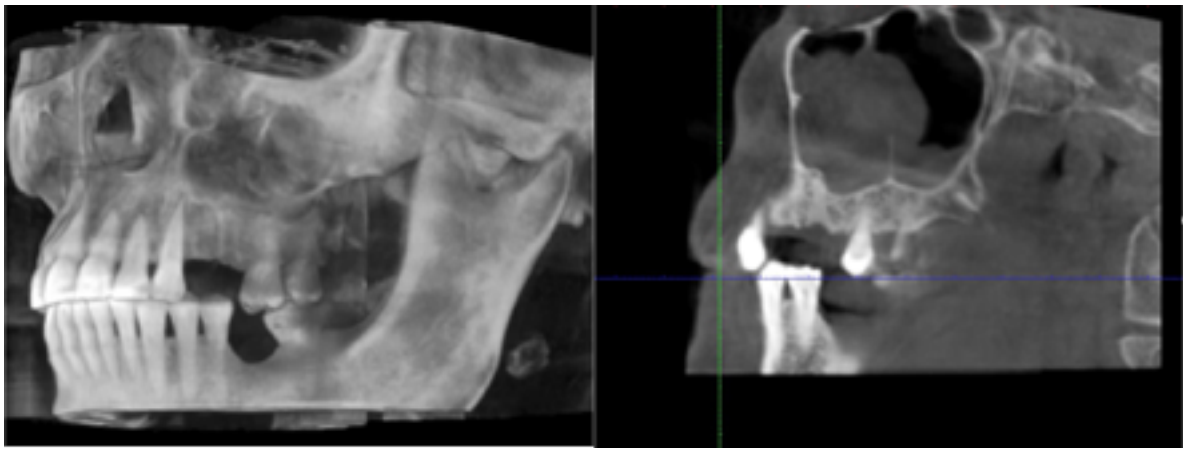


Figure 9. Maxillary osteonecrosis of the jaws at the time of diagnosis.

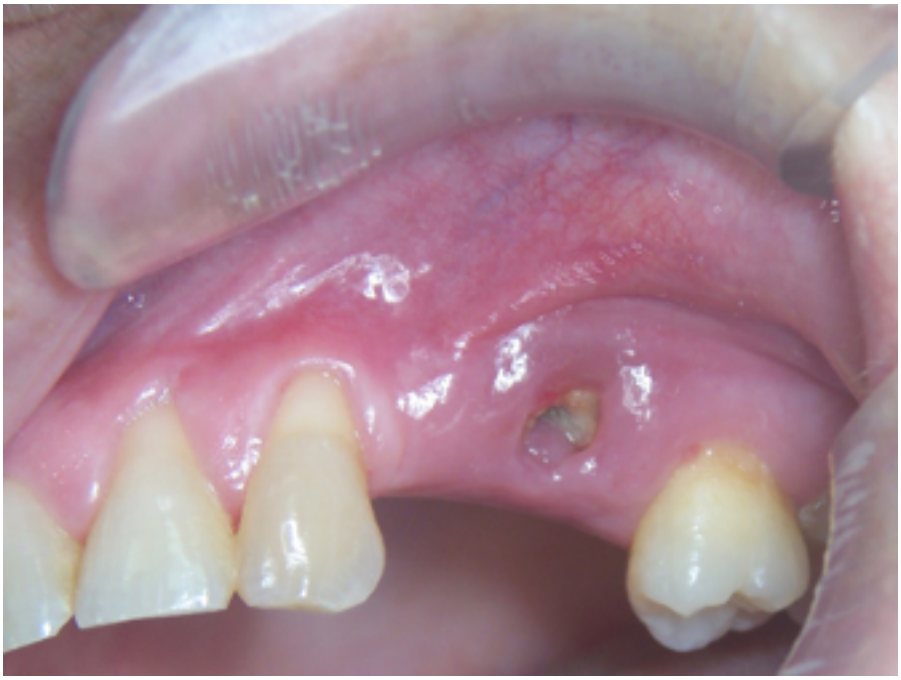


Figure 10. Intraoperative aspect.

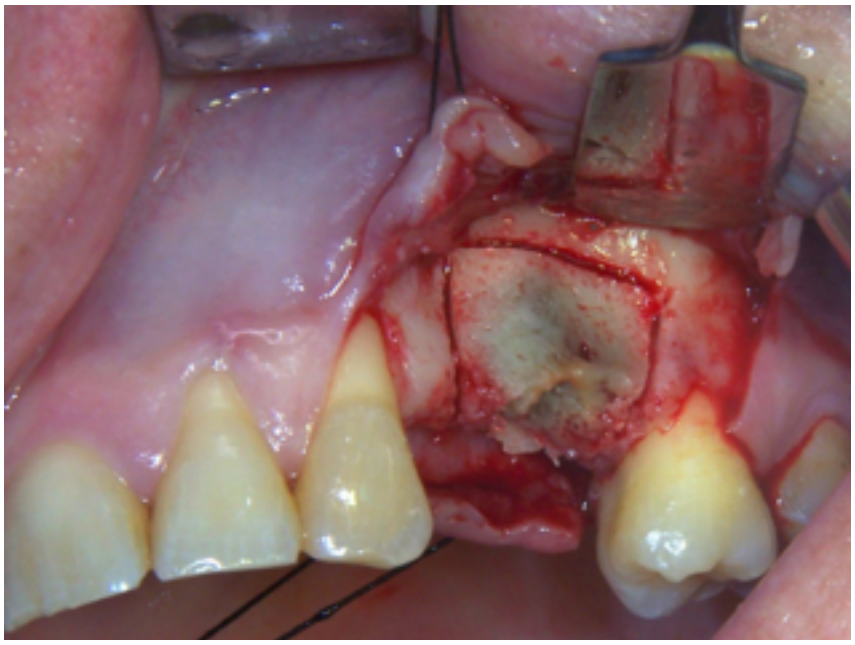


Figure 11. Intraoperative view after the removal of necrotic bone.

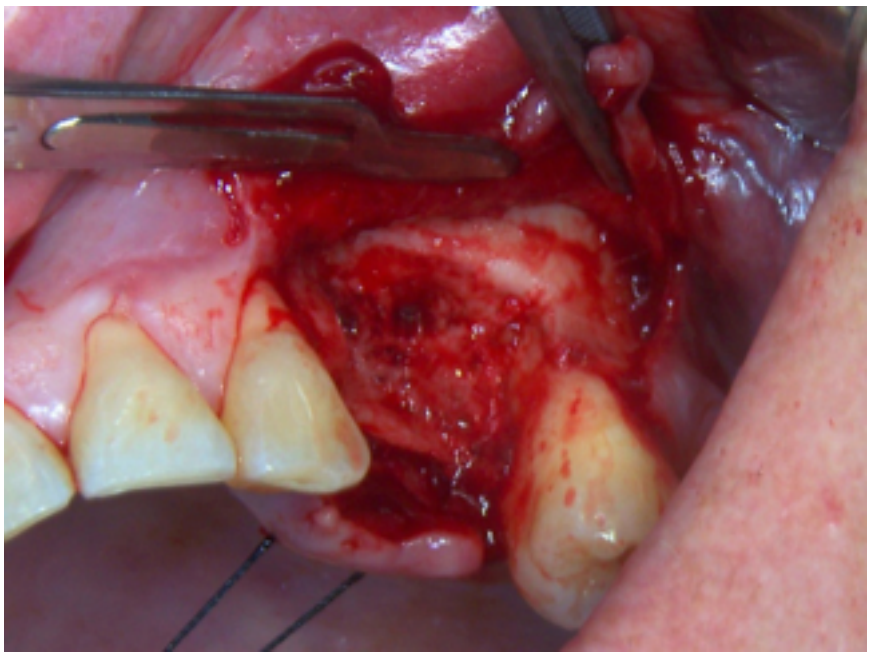


Figure 12. Resected bone segment.

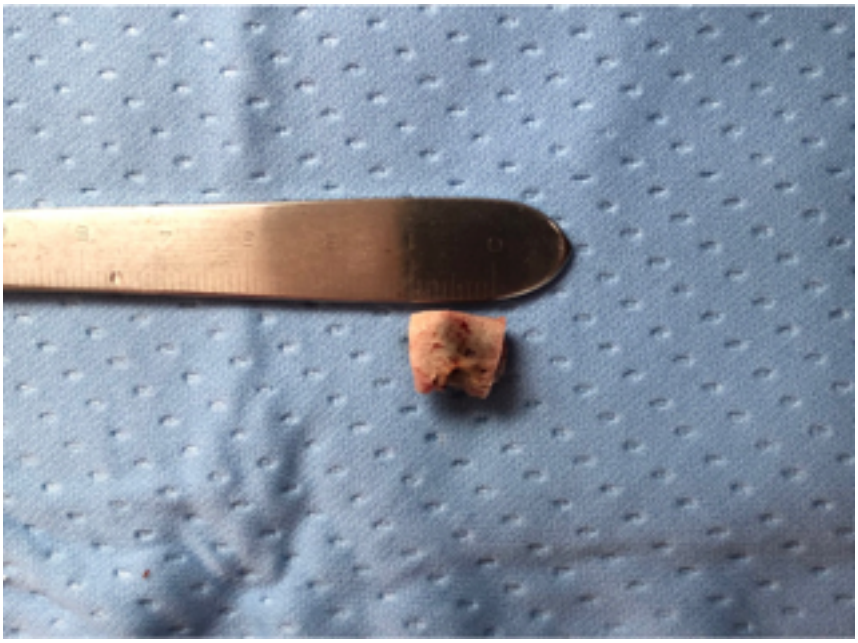


Figure 13. Tension-free advancement of the mucoperiosteal flap.

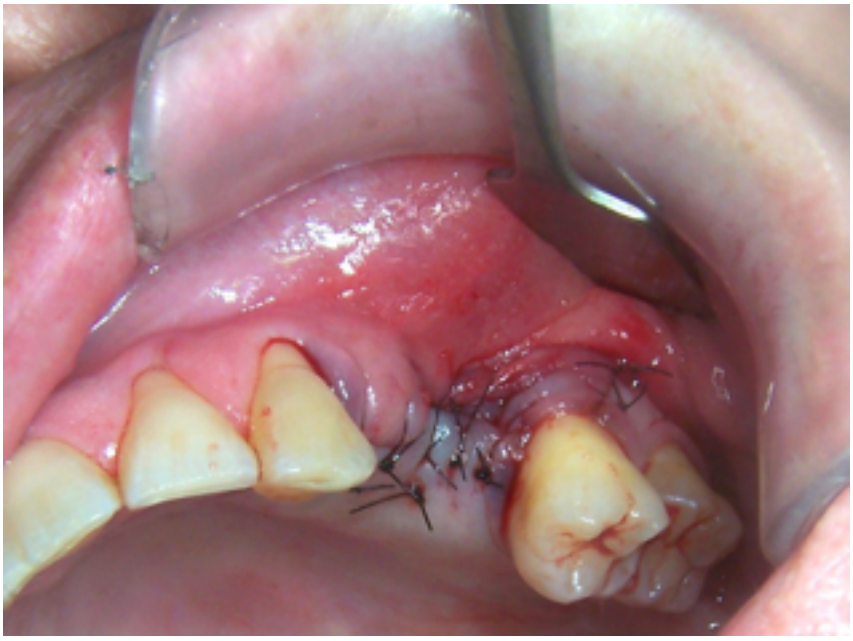


Figure 14. Evidence of mucosal healing.

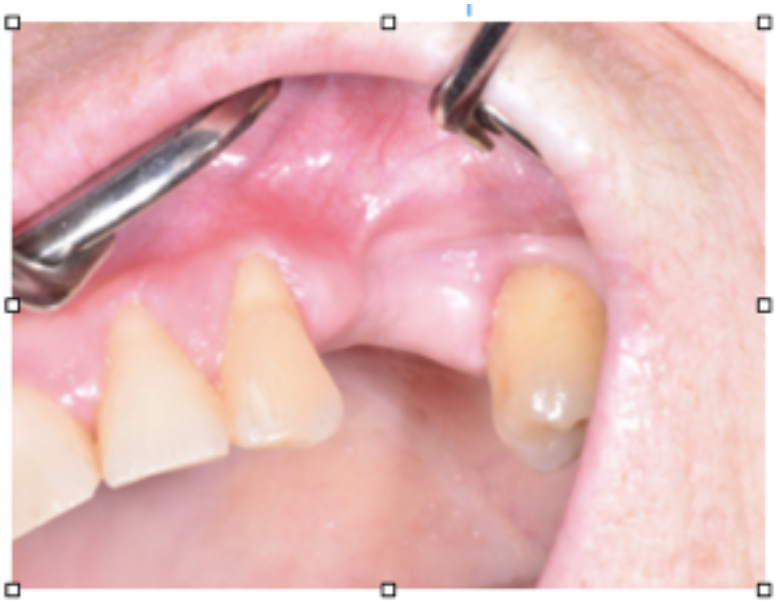


Table 1. Characterization of the medication-related osteonecrosis of the jaw (MRONJ) cohort of 103 patients.

	# (%)
Age years (mean)	70.72
Sex	
Male	27 (26,21%)
Female	76 (73,78%)
Primary Disease	
Breast cancer	24 (23,30%)
Prostate cancer	16 (15,53%)
Kidney cancer	1 (0,97%)
Multiple myeloma	11 (10,67%)
Lung cancer	1 (0,97%)
Gastointestinal stromal tumors (GISTs)	1 (0,97%)
Rheumatoid arthritis	3 (2,91%)

Osteoporosis	46 (44,66%)
Administered antiresorptive drug	
Zoledronate (i.v)	37 (68,51%)
Denosumab 120 mg (subcutaneous)	13 (24,07%)
Denosumab 60 mg (subcutaneous)	2 (4,08%)
Alendronate (per os)	28 (57,14%)
Ibandronate (per os)	9 (18,36%)
Risedronate (per os)	2 (4,08%)
Clodronate (i.m)	1 (2,04%)
Switch therapy	
Zoledronate (i.v) + Risedronate (per os)	1 (2,04%)
Zoledronate (i.v) + Pamidronate (i.v)	2 (3,70%)
Zoledronate (i.v) + Ibandronate (per os)	1 (1,85%)
Alendronate (per os) + Risedronate (per os)	2 (4,08%)
Alendronate (per os) + Ibandronate (per os)	2 (4,08%)
Neridronate (i.v) + Ibandronate (per os)	1 (2,04%)
Zoledronate (i.v) + Denosumab 120 mg (subcutaneous)	1 (1,85%)
Zoledronate (i.v) + Denosumab 60 mg (subcutaneous)	1 (2,04%)
Average duration of therapy (months)	
Zoledronate (i.v)	28.70
Denosumab 120 mg (subcutaneous)	26.92
Denosumab 60 mg (subcutaneous)	33.5
Alendronate (per os)	66.14
Ibandronate (per os)	95.11
Risedronate (per os)	78.5
Clodronate (i.m)	24
Zoledronate (i.v) + Risedronate (per os)	113
Zoledronate (i.v) + Pamidronate (i.v)	52.5
Zoledronate (i.v) + Ibandronate (per os)	65
Alendronate (per os) + Risedronate (per os)	85.5
Alendronate (per os) + Ibandronate (per os)	164.5
Neridronate (i.v) + Ibandronate (per os)	70
Zoledronate (i.v) + Denosumab 120 mg (subcutaneous)	24
Zoledronate (i.v) + Denosumab 60 mg (subcutaneous)	99

Table 2. MRONJ features (n = 103 subjects and n = 111 lesion).

	# (%)
Anatomic location	

Lower jaw	74 (71,84%)
Upper jaw	21 (20,38%)
Both jaws	8 (7,76%)
SICMF-SIPMO staging	**Total [n=111] (%)**
Stage 1a	13 (11,71%)
1b	27 (24,32%)
Stage 2a	11 (9,90%)
2b	45 (40,54%)
Stage 3	15 (13,51%)

Table 3. Surgery with radical intent in stage I and II MRONJ.

Stage and Location of MRONJ	**Bone surgery**					**Flap management**				**Surgeries # (%)**	**Success # (%)**
	SD	SQ	SAU	SMBR	MBR	MPF	CAF	MYF	FPF		
Stage I Mandibular bone	✓					✓				5 (4,42%)	4 (80%)
	✓						✓			8 (7,07%)	8 (100%)
				✓		✓				7 (6,19%)	6 (85,71%)
				✓			✓			15 (13,27%)	13 (86,66%)
	✓	✓				✓				1 (0,88%)	1 (100%)
Stage II Mandibular bone			✓			✓				5 (4,42%)	2 (40%)
			✓				✓			7 (6,19%)	6 (85,71%)
			✓					✓		4 (3,53%)	4 (100%)
					✓	✓				5 (4,42%)	2 (60%)
					✓		✓			14 (12,38%)	11 (78,57%)
					✓			✓		19 (16,81%)	19 (100%)
	✓	✓					✓			1 (0,88%)	1 (100%)
Stage I Maxillary bone	✓					✓				1 (0,88%)	1 (100%)
	✓						✓			2 (1,76%)	2 (100%)
				✓		✓				1 (0,88%)	1 (100%)
				✓			✓			2 (1,76%)	2 (100%)

	✓	✓				✓				1 (0,88%)	1 (100%)
Stage II Maxillary bone			✓			✓				1 (0,88%)	0 (0%)
			✓				✓			3 (2,65%)	3 (100%)
			✓						✓	2 (1,76%)	2 (100%)
					✓	✓				2 (1,76%)	1 (50%)
					✓		✓			4 (3,53%)	3 (75%)
					✓				✓	2 (1,76%)	2 (100%)
	✓	✓					✓			1 (0,88%)	1 (100%)

Legend: # = number; SD = superficial debridement; SQ = sequestrectomy; SAU = saucerization; SMBR = sub-marginal bone resection; MBR = marginal bone resection; MPF = mucoperiosteal flap; CAF = coronally advanced mucoperiosteal flap; MYF = mylohyoid flap; FPF = pedicled buccal fat pad flap.

Table 4. Re-entry surgical procedures.

Patient #	**1st Procedure**						**Re-entry Procedure**						
	Bone surgery				**Flap management**		**Bone surgery**				**Flap management**		
	SD	SAU	SMBR	MBR	MPF	CAF	SD	SAU	SMBR	MBR	CAF	MYF	FPF
1		✓			✓					✓		✓	
2		✓			✓					✓		✓	
3		✓			✓					✓		✓	
4				✓	✓					✓		✓	
5				✓		✓				✓		✓	
6		✓			✓			✓			✓		
7				✓	✓					✓		✓	
8	✓				✓		✓				✓		
9	✓				✓				✓		✓		
10				✓		✓				✓		✓	
11				✓		✓				✓		✓	
12				✓	✓					✓	✓		
13				✓		✓				✓			✓
14			✓		✓				✓		✓		
15				✓	✓					✓	✓		
16			✓			✓				✓	✓		

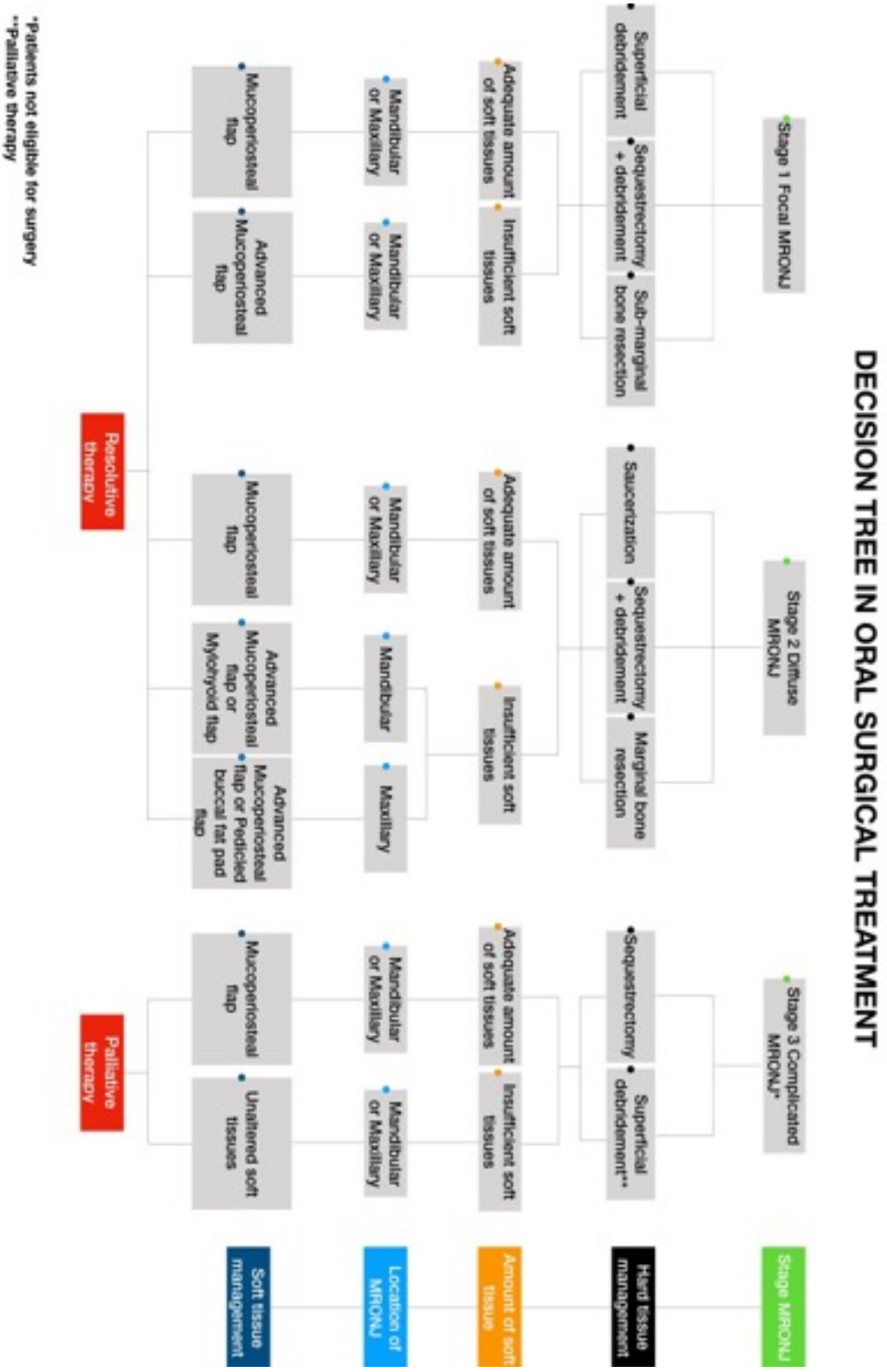
Legend: # = number; SD = superficial debridement; SAU = saucerization; SMBR = sub-marginal bone resection; MBR = marginal bone resection; MPF = mucoperiosteal flap; CAF = coronally advanced mucoperiosteal flap; MYF = mylohyoid flap; FPF = pedicled buccal fat pad flap.

Table 5. Palliative surgical therapy of stage III MRONJ not eligible for maxillo-facial surgery.

Patient	**Localization**	**Surgical Techniques**			**Outcome**
		SD	**SQ**	**MPF**	
1	Maxillary	✓		✓	Partial Healing
	Mandibular	✓			Unchanged
2	Maxillary	✓			Unchanged
3	Mandibular	✓		✓	Worsened
4	Maxillary		✓	✓	Partial Healing
5	Maxillary	✓			Worsened
6	Mandibular	✓		✓	Partial Healing
7	Maxillary	✓		✓	Partial Healing
8	Maxillary		✓	✓	Partial Healing
9	Mandibular	✓			Unchanged
10	Mandibular	✓		✓	Partial Healing
11	Maxillary	✓		✓	Partial Healing
12	Maxillary	✓			Unchanged
13	Maxillary	✓		✓	Partial Healing
14	Maxillary	✓			Unchanged

Legend: # = number; SD = superficial debridement; SQ = sequestrectomy; MPF = mucoperiosteal flap.

Figure 15. Decision tree.



Chapter 5: Prognostic impact of CD34 and CD105 expression and neovessels after radical surgery for MRONJ treatment

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is “an area of exposed bone or bone that can be probed through an intra-oral or extra-oral fistula(e) in the maxillofacial region that has persisted for more than eight weeks, with current or previous treatment with anti-resorptive or anti-angiogenic agents and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws [1]

Drug-induced avascular injury is a cause for concern because there are no prognostic markers for clinical monitoring and there is an intellectual gap in our understanding of the pathogenesis of this disease, moreover this condition strongly influences the patient’s quality of life.

Surgical treatment may offer benefits to MRONJ patients [2,3], and its indications expanded over time from being limited to advanced stage [4,5] to being considered more effective when performed in early stage [6-9]. Nevertheless surgery showed different success rate in the literature, depending on different variables which have an impact on the surgical intervention outcome [10].

About this, prognostic factors for surgical treatment failure and/or recurrence of MRONJ are not fully elucidated [11-15].

Several investigations have suggested that the underlying disease, the duration of administration of MRONJ related medications, the presence of bacterial infections as well as the adopted treatment strategies act as factors in MRONJ recurrence [11-13].

Patients affected by osteoporosis are more prone to heal in comparison to cancer patients [13,14]. It appears that this could be due to the concomitant administration of anti-cancer medications which may play a role in the occurrence of adversity [15]. Although a clinical and symptomatological remission could be still experienced by cancer patients regardless the underlying malignancy [16].

Concomitant treatment with corticosteroids or tobacco smoking are reported to be others individual factors that can inhibit the bone healing process in MRONJ patients [17]. A further relevant parameter that favor a positive outcome of surgery could be the event triggering the outbreak of MRONJ [14,15]. MRONJ localization can also affect the outcome of surgery, indeed proximity to the maxillary sinus can lead to interfering correlations with the condition of chronic sinusitis which would be detrimental to healing [14]. A crucial aspect is considered the presence of a focal lesion with margins clearly detected by the use of a TC of maxillary bones [18]. The adopted surgical technique is reported to be one of the most relevant factors that affect the outcome of the MRONJ treatment [15], according to the extent of the surgical procedures and the closure technique which strongly influences treatment outcome [11,12,19-21]. Furthermore it has been also reported that some intrinsic characteristics of the MRONJ lesion

may result in a better or worse outcome of the procedure. Mature bacterial biofilms are now identified as potential critical triggers in the pathogenesis of drug-related osteonecrosis of the jaw which can also have a negative influence on disease resolution, as well as on its onset [22]. Thus the perioperative antibiotic regimen has a significant influence on the chances of disease recurrence [23,24].

In the clinical experience of the University of Messina, despite radical surgery and targeted antiobiotic therapy, MRONJ outcome still shows difference in terms of outcome and disease recurrence [25,26].

The present study hypothesis was that the rate of neoangiogenesis may be helpful in discriminating the probability of a poor prognosis of MRONJ outcome after radical surgery.

Starting from this assumption the immunohistochemical expression of CD34 and CD105 in MRONJ specimen obtained from surgically treated patients was evaluated in order to understand the impact of the angiogenesis status on MRONJ treatment outcome.

CD34 and CD105 (also known as Endoglin) are endothelial antigens that have been choosed due to their recognized role as direct markers of the degree of vascolarization and neoangiogenesis. Specifically, CD105 is a cell membrane glycoprotein related to newly formed blood vessels, while CD34 is expressed in both mature and newly formed vessels [27,28]

Considering all the above mentioned variables the secondary objective of this study has been to investigate the different conventional factors

affecting outcome and their impact on angiogenesis in the cohort of surgically treated patients of the University of Messina.

MATERIALS AND METHOD

Study design

The study was conducted at the Department of Human Pathology of Adult and Developmental Age of the University of Messina and coordinated from the Department of Biomedical, Dental and Morphofunctional Imaging Sciences of the University of Messina.

The surgical specimens were obtained from surgically treated MRONJ patients at the Center for Treatment of the Osteonecrosis of the Jaws (University of Messina, Italy).

Biopsies were taken from the bone tissue including the necrotic area with a rim of adjacent bone [29,30]. The necrotic tissue itself was excluded from the analysis [31]. Samples were retrospectively divided according to the clinical outcome of MRONJ surgical treatment dividing patients into 2 groups “healed” and “not healed”.

“Healing” was defined as clinical wound healing without dehiscence or evidence of recurrence [32,33]. Minimun follow-up was established in 6 months.

Inclusion criteria

MRONJ diagnosis had to be performed according to the definition of the Italian Societies of Oral Medicine and Maxillofacial Surgery (the SICMF-SIPMO staging system) [34,35]. Only patients who underwent radical surgery were considered eligible for the study.

Surgery

Patients are referred to the Osteonecrosis of the Jaw Treatment Center, School of Dentistry, University of Messina mostly by their oncologist. On arriving at the center, patients are diagnosed with MRONJ based on the clinical and radiological findings in order to distinguish focal and diffused forms.

Routine procedures at first examination include oral swab and pharmacological treatment prescription with systemic antibiotics.

Initial treatment is amoxicillin plus clavulanic acid in combination with metronidazole 250 mg subsequently patients are switched to targeted antibiotic therapy on the basis of the antibiogram result.

Eight to ten weeks after the initiation of pharmacological treatment unchanged and progressive forms urdergo surgical treatment [36].

The systematic application of this work flow ensure homogeneity in the patient sample in terms of antibiotic therapy (empiric vs targeted therapy) and time to intervention (defined as time from MRONJ diagnosis to surgical procedure).

The surgical approaches were defined according to literature [10, 17,23, 33, 37,38] as previously described by our study group [25,26].

Study variables

Patient's characteristics were analyzed. Investigated variables were patient related and treatment related.

Demographic data (age and gender), primary disease (cancer or osteoporosis), type of medication (zoledronic acid, denosumab or oral bisphosphonates), duration of antiresorptive treatment (referring to osteoporotic vs cancer patients and expressed in months) were reported and analyzed.

MRONJ clinical features (localization, stage of MRONJ) were registered and analyzed.

Immunohistochemical analysis

Histomorphometrical analyses were performed in a blinded fashion without knowledge of the clinical features and treatment outcome of the patients corresponding to individual biopsies [29].

Four micrometer-thick consecutive sections were cut from the paraffin blocks and submitted to the immunohistochemical procedures against CD105 and CD34.

For the CD105 epitope retrieval, specimens were treated with proteinase K (S3020, DAKO Cytomation) at room temperature for 15

min, while CD34 antigen was unmasked by microwave oven pre-treatment in 10 mM, pH 6.0 sodium citrate buffer for 3 cycles × 5 min.

Then slides were incubated at 4°C overnight with the primary monoclonal antibodies against CD105 (DAKO Corporation, Denmark, clone SN6 h, w.d. 1:50) and CD34 (DAKO Corporation, Denmark, clone QBEnd10, w.d. 1:50); a sheep anti-rabbit immunoglobulin antiserum (Behring Institute; w.d. 1:25) was used and the bound primary antibody was visualized by avidin–biotin–peroxidase revealing by the Vectastain Rabbit/Mouse Elite Kit, according to the manufacturer's recommendations.

To reveal the immunostaining, the sections were incubated in darkness for 10 min with 3–3′ diaminobenzidine tetra hydrochloride (Sigma Chemical Co., St. Louis, MO, USA), in the amount of 100 mg in 200 ml 0.03% hydrogen peroxide in phosphate-buffered saline solution (PBS).

Nuclear counterstaining was performed by Mayer's haemalum. Specificity of the procedure was confirmed by omitting the primary antiserum or changing it with normal rabbit serum/phosphate buffered saline solution (PBS pH 7.4). In addition, samples of human placenta was applied as a positive control for CD105.

The quantification of microvessels was performed according to the procedure elsewhere described [39].

Necrotic areas were excluded. In detail, the three most vascularized areas detected by CD105 were firstly selected (hot spots) under 40× field. Microvessels were then counted in each of these areas under a

400× field. Single endothelial cells or cluster of endothelial cells, with or without a lumen, were considered to be individual vessels.

The mean value of three ×400 field (0.30 mm2) counts was verified as the microvessel density (MVD) of the slide. Successively, the MVD value was converted into the mean number of microvessels/mm2 for statistical investigations.

The vessels were evaluated using a Nikon microscope by two independent observers blinded to the clinico-pathological data. The same procedure was carried out for CD34 expression on equivalent slides.

Statistical analysis

Statistical analysis was performed to assess if neovessels could influence treatment outcome in patients undergoing radical surgery.

Data are presented as means ± standard deviation (SD). Student's t test for means and Fisher's exact test ($p < .05$) for the other values for low numbers were used to

compare means between two different groups. A p-value below 0.05 was considered statistically significant.

RESULTS

Among the MRONJ cases referred to the Center for Treatment of the Osteonecrosis of the Jaws (University of Messina, Italy) 15 patients fulfill the above mentioned inclusion criteria.

Conventional risk factors

The characteristics of patients together with the conventional risk factors for MRONJ recurrence are reported in **Table 1**.

Table 1: Study population features and conventional risk factors for MRONJ recurrence after surgical treatment divided according to clinical outcome

	Healed (n° 9)	**Not Healed (n° 6)**	**p-value***
Age years (average)	68,22 ± 8,45	69,17 ± 6,05	0.8166
Sex (%)			
Female	7 (77.8)	1 (16.7)	**0.0406**
Male	2 (22.2)	5 (83.3)	
Primary disease (%)			
Cancer	6 (66.7)	6	0.2286
Osteoporotic	3 (33.3)	/	
Antiresorptive medications (%)			
Zoledronic acid	3	5 (83.33)	0.1189
Denosumab	3	1	0.6044
Oral bisphosphonate	3	/	

Duration of antiresorptive therapy in months (SD)			
Cancer patients	35,33 ± 18.79	40,33 ± 20.71	0.6356
Osteoporotic patients	72,33 ± 51.73	/	
MRONJ Location (%)			
Lower jaw	7	3	0.3287
Upper jaw	2	1	1.0000
Both jaws	/	2	
MRONJ Stage (%)			
I a	1	/	
I b	/	/	
II a	4 (44.4)	1	0.5804
II b	3 (33.3)	2	1.0000
III a	/	/	
III b	1	3	0.2352

Nine patients were enrolled in the “healed” group and 6 patients in the “not healed” group.

No statistically significant difference between the “healed” (68.22 ± 8.45) vs the “not healed” (69.17 ± 6.05) group was registered in relation to mean age of the patients (p-value = 0.8166).

The majority of the patients in the “healed” group were women (n = 7; 77.8 %) with the remaining (n =2; 22.2%) male patients. In the “not healed” group 1 (16.7%) subject was a female patient and 5 (83.3%) were male patients.

The sex of the subjects represented a variable that significantly influenced post-surgical healing (p = 0.0406).

In relation to primary disease in the “healed” group there were 6 cancer patients (66.7%) and 3 patients affected by osteoporosis (33.3%) while in the “not healed” group all the patients had cancer.

The underlying pathology had not a statistical significant impact on healing(p=0.2286).

Among patients enrolled in the “healed” group 3 patients were treated with zoledronic acid, 3 patients received denosumab and 3 patients were exposed to oral bisphosphonates while in the “not healed” group almost all the patients received zoledronic acid (n=5; 83.33%) with denosumab being administered to the remaing patient (n=1).

The type of antiresorptive medication was not significanty related to healing since no difference in the use of zoledronic acid (p=0.1189) or denosumab (p = 0.6044) has been observed.

In relation to the duration of therapy this information has been stratified on the basis of the clinical indication of the administered medication (cancer vs osteoporosis) and expressed in months.

Cancer patients in the “healed” group received anti-resorptive treatment (35.33 ± 18.79) for a shorter period of time than cancer patients in the “not healed” group (40.33 ± 20.71).

Median duration of anti-resorptive treatment in patients affected by osteoporosis was calculated only for the “healed” group (72.22 ± 51.73 months) as all the patients healed.

Duration of antiresorptive therapy was not statistically related to a better outcome of surgical treatment (p= 0.6356).

The most common location of MRONJ was the mandible in both “healed” (n= 7) and “not healed” (n=3) groups with the upper jaw being affected in n=2 patients in the “healed” and 1 patient in the “not healed” group. In 2 cases of the “not healed” group both jaws were affected. MRONJ location was not significantly related to post-surgical healing in lower (p=0.3287) nor in upper jaw (p=1.0000).

According to the SIPMO classification, the most frequent stage of MRONJ in the “healed” group was stage IIa (n = 4; 44.4 %) followed by stage IIb (n = 3; 33.3%). The remaining 2 patients were stage Ia (n=1) and IIIb (n=1).

In the “not healed” group there was a higher proportion of stage IIIb (n= 3; 50 %) patients followed by stage IIb (n= 2;33.3%) and IIa (n= 1; 16.67%).

In this case series MRONJ stage did not affect surgical treatment outcome.

CD34 and CD105 expression

Fiftheen MRONJ tissue samples were evaluated.

Table 2 shows the immunohistochemical expression of the angiogenetic factors evaluated.

Table 2: Immunohistochemical parameters in patients with MRONJ divided according to treatment outcome

	Healed (n° 9)	Not Healed (n° 6)	t-value	p-value

CD34 MVD (v/ mm2) - median rate	66.57	3.94	-2.33203	**.015756**
CD105 MVD (v/ mm2) - median rate	19.33	0	-3.59139	**.000973**

Abbreviations: MVD= microvessel density

Vascularization as expressed by the median CD34 rate was higher in the "healed" group (MVD =66.57) compared with "not healed" patients (MVD =3.94).

This difference in vascularization was significant between the two groups (p=.015756).

Newly formed angiogenesis-related capillaries, which stained positively for CD105, were detected only in the specimen of "healed" patients (MDV= 19.33).

The inhibition of neoangiogenesis was strongly significantly related to surgical treatment outcome (p=.000973).

Correlation between CD34 and CD105 expression and conventional risk factors

The possible relationship between patient's characteristics and angiogenesis is examined in **Table 3.**

Table 3: Correlation between angiogenetic biomarkers and conventional risk factors

	CD34		**p-value***	**CD105**		**p-value***
	Present N = 11	**Absent N = 4**		**Present N = 8**	**Absent N = 7**	
Sex (%)						

Female	8	/	**0.0256**	6	2	0.1319
Male	3	4		2	5	
Primary disease (%)						
Cancer	8	4	0.5165	6	6	1.0000
Osteoporotic	3	/		2	1	
Antiresorptive medications (%)						
Zoledronic acid	5	3	0.5692	3	5	0.3147
Denosumab	3	1	1.0000	3	1	0.5692
Oral bisphosphonate	3	/		2	1	1.0000
Duration of antiresorptive therapy in months						
<= 24 months	5	1	0.6044	4	2	0.6084
>24 months	6	3		4	5	
MRONJ Location (%)						
Lower jaw	2	1	1.0000	1	2	0.5692
Upper jaw	9	1	**0.0769**	7	3	0.1189
Both jaws	/	2		/	2	
MRONJ Stage (%)						
I a	1	/		1	/	
I b	/	/		/	/	
II a	5	/		3	2	1.0000
II b	3	2	0.5604	3	2	1.0000
III a	/	/		/	/	
III b	2	2	0.5165	1	3	0.2821

Pertaining the correlation between angiogenetic biomarkers and conventional risk factors in the observed sample **s**ex was significantly related to the presence CD34 stained capillaries (p=0.0256) although it showed to be uninfluent to the expression of CD105 (p= 0.1319).

Primary disease didn't affect vascolarization (p=0.5165) nor neoangiogenesis (p=1.0000).

The different administration of zoledronic acid in the "healed" (p=0.5692) vs the "not healed" (p= 0.3147) as well as the assumption of denosumab in the "healed" (p=1.0000) vs the "not healed" (p= 0.5692) groups was not statistically significant.

The duration of the anti-resorptive therapy itself appeared to be unrelated to the vascolarization of the jaw bone and the neovessels formation (p= 0.6084).

In relation to MRONJ location the upper jaws was significantly related to a greater vascularization (p=0.0769).

In this analysis the MRONJ lesions divided in the three SIPMO stages didn't show a statistical difference in the local expression of the investigated angiogenetic biomarkers.

Table 4 summarizes the anti-cancer therapies undertaken in order to explore the concomitant use of antiangiogenic agents that can affect the investigated parameters.

Table 4 : Summary of anti-cancer treatments of the 15 MRONJ cancer patients

Patient Number	Age/gender	Site of carcinoma	Cancer medications
1	70/male	Prostate	Degarelix
2	68/male	Myeloma	Bortezomib + Melphalan; Daratumumab; Lenalidomide + Dexamethasone
3	79/male	Prostate	Enantone+22RaCl

4	72/male	Myeloma	Lenalidomide
5	63/female	Breast	Fulvestrant Palbociclib Letrozolo
6	63/male	Renal cell	Sunitinib; Everolimus; Sorafenib
7	60/male	Prostate	Bicalutamide; Abiraterone acetate
8	59/female	Breast	Tamoxifen, Letrozole, Lapatinib, Fulvestrant, Exemestane, Docetaxel, Capecitabine, Vinorelbine, Cyclophosphamide, Methotrexate, Eribulin, Doxorubicin, Palbociclib + Fulvestrant, Fluorouracil (5-FU)
9	67/female	Breast	Everolimus; Paclitaxel; Exemestane; Doxorubicin; Anastrozole; Eribulin
10	72/male	Breast	Cyclophosphamide + Methotrexate
11	80/female	Breast	Everolimus + Exemestane
12	79/female	Myeloma	Lenalidomide + Dexamethasone; Bortezomib + Melphalan + Prednisolone

DISCUSSION

Aim of the present study was to investigate the role of altered angiogenesis and its relationship with wound healing in MRONJ surgery starting from the consideration that angiogenesis is a critical component of MRONJ development [31].

Indeed the hypothesis that the impairment/inhibition of angiogenesis has an important role in the development and maintenance of MRONJ seems to be the most relevant pathogenetic theory explaining the pathway in which necrosis occur [40,41].

It involves avascular necrosis through VEGF and PECAM-1 suppression confirming the interplay between angiogenesis and osteogenesis in bone integrity maintenance [42,43].

The few studies published on the topic have mostly been restricted to the comparison between MRONJ vs health subjects [44].

According to Gao et al the suppression of angiogenesis and osteogenesis (identified by a reduction in CD31 in MRONJ models) could be significant in the potential mechanism of MRONJ itself [45].

The results by Wehrhan et al. showed that the capillary area related to CD31-associated vascularity was slightly reduced in the MRONJ-related specimens compared to normal mucoperiosteal tissue, likewise the newly formed angiogenesis-related capillaries which were positively stained for CD105, were detected o a lesser extent in MRONJ-related specimens than in mucoperiosteal tissue not exposed to bisphosphonates [31].

Compromised angiogenesis would most likely be involved in post-intervention healing, although other aspects of the vasculature (eg, blood flow) could contribute to MRONJ [46,47].

The results of the present study showed a greater number of newly formed angiogenesis-related capillaries detected by CD105 staining in tissue belonging to healed MRONJ patients (p=.000973) and a higher

expression of CD34 (p=.015756) indicating that inhibition of angiogenesis is strongly implicated in MRONJ healing.

The present study also address these conventional factors affecting MRONJ recurrence and their correlation with the immunohistochemical parameters expression.

There are several variables that have a statistically significant impact on MRONJ post-surgical healing: gender, patient's underlying pathologies, anti-resorptive drugs used, time to treatment, MRONJ stage and others [11,12,23].

Almost none of the conventional factors taken into consideration (age, type of medication, duration of antiresorptive therapy, underlying pathology, MRONJ location and MRONJ stage) was significantly related to MRONJ surgical treatment outcome with the exception of sex.

This data is considered to be due to the prevalence of women in the examined cohort (68%) reflecting the fact that MRONJ related medications are mostly prescribed for post-menopausal osteoporosis and breast cancer.

Although in this analysis the underlying pathology and the type of antiresorptive medication had not a statistical significance it is noteworthy that all patients with osteoporosis assuming oral bisphosphonates completely healed after surgery.

This consistent with is Martins et al. that observed significant differences in outcomes and time to healing according to primary disease ($p < 0.05$) [48].

Data from the literature confirm its importance on the outcome of the therapy indeed cancer patients treated with high potency bisphosphonates may experience a poor treatment outcome in comparison to denosumab-related MRONJ, likewise patients with prolonged bone anti-resorptive therapy may show a worse outcome [13,14].

In relation to MRONJ location the upper jaws was significantly related to a greater vascularization (p=0.0769) but this didn't translate in a better surgical outcome.

This may be due to the anatomical differences between the maxillary and mandibular bones and owing to the intimate anatomical relationship with the sinus [49-51].

Patients attributable to the three stages of the disease were treated, with a higher frequency of cases attributable to stage II.

It has been reported that early stage treated with radical surgery showed a better treatment outcome [52]. Nevertheless the MRONJ stage neither played a significant role in the incidence of surgical failure (p= 0.2352) in this case series.

Analysis of the correlation between neoangiogenetic biomarkers and conventional risk factors showed that the presence of CD34 stained capillaries was significantly correlated with sex and MRONJ location.

MVD as assessed by CD34 and CD105 expression were significant predictive factors for surgical treatment outcome.

Comparison was very difficult to perform because of the limited size of the study samples. Nevertheless within this group of selected patients

we found that some markers of angiogenesis were useful tools to characterize patient's surgical healing and were significant prognosticator of disease outcome.

However, consideration should be given to concomitant anti-cancer therapies (**Table 4)** since the use of antiangiogenic agents can affect the investigated parameters contributing to angiogenesis inhibition, microenviroment alterations and immune response [53-56].

Our results highlight the need for a wider and more a reliable investigation on neoangiogenesis biomarkers in MRONJ

Strenght and Limitations

The main limitations of our study is the small sample size. As far as the size of the study group is concerned we chose only patients treated with radical intent to avoid bias resulting from different prognoses of palliative treatment.

Furthermore it must be recognized that single-center studies related to the surgical treatment of MRONJ always present limited data and the examined cohorts varied from a few subjects to a maximum of thirty.

Nevertheless, despite the limited sample, we were able to demonstrate a significant impact of the expression of CD34 and CD105 on MRONJ outcome.

CONCLUSIONS

The first study correlating MVD with prognosis in MRONJ surgically treated patients.

In the examined cohort the MDV as assessed by CD34 and the presence of neovessels by CD105 was highly predictive of better treatment outcome after radical surgery of MRONJ.

Exploring CD34 and CD105 expression in MRONJ surgically treated patient's specimens revealed that the healing potential of patients could be also influenced by the presence of neovessels in the MRONJ lesion.

To identify diagnostic markers of drug-induced vascular injury would add value in MRONJ risk management and prognosis [57-58].

The implication on clinical practice of having such information available would be important to schedule surgery, post-operative wound management and follow-up examinations on the basis of the success/failure risk.

Furthermore since tooth extraction is the major precipitating event in MRONJ tis tooth extraction investigating the role of altered angiogenesis in wound healing ay have future implications in MRONJ prevention as well as in the surgical treatment.

Finally we believe that the understanding of angiogenesis dependent factors deserves further attention as a future target for MRONJ therapies.

Indeed on the basis of these results a potential protection of the jaw from the negative influence of zoledronic acid and/or denosumab by

locally enhancing angiogenesis could be imagined for MRONJ prevention and treatment.

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Chapter 6: Future development

Our research group is presently investigating the expression of several angiogenetic markers on a wider sample of MRONJ patients and controls to provide a better definition of their potential prognostic value.

In the field of the biotechnologies we aim at the development of new treatment strategies adjuvants or alternatives to surgical treatment for all non-eligible patients for whom nowadays only palliative therapies are available.

The purpose of our future investigations is to test the efficacy of innovative molecules in reversing the anti-angiogenic effect of MRONJ-related drugs that cause avascular necrosis.

Our belief is that local treatment with anti-angiogenic inhibitors can lead to new therapeutic strategies for MRONJ.

Assuming that the inhibition of bone remodeling and the reduced ability of soft tissues to cover bone, which are the main characteristics of MRONJ, are caused by the antiangiogenic properties of the drugs that have been related to the manifestation of the disease, to limit this effect could represent a new therapeutic strategy.

We are trying to answer the following questions:

Could avascular necrosis be partially reversed through the administration of an anti-angiogenic inhibitor?

-Could we imagine a loco-regional delivery with this targeted drug?

It has been shown in vitro that geranylgeraniol (GGOH), a metabolite of the mevalonate pathway, is able to reverse the negative biological effect of bisphosphonates [1].

Local administration of a recombinant teriparatide-containing composition attenuated osteonecrotic manifestation in a rat-induced MRONJ model [2].

Recombinant platelet-derived growth factor-BB (PDGF-BB) preserved the proliferative, pro-angiogenic and osteogenic functions of rat mandible-derived bone marrow mesenchymal stem cells in a combined in vivo / in vitro induced MRONJ model [3] .

The involvement of microRNA-210 (miR-210) in steroid-induced osteonecrosis of the femoral head has been demonstrated and the results obtained from a study conducted on mice have shown that its use in this setting determines an increase in neovascularization through up- regulation of VEGF, allowing to advance the hypothesis that the demethylation of miR-210 could serve as a potential therapeutic target for the treatment of necrosis through the stimulation of angiogenesis [4].

The up-regulation of microRNA-210 regulates renal angiogenesis mediated by the activation of the VEGF signaling pathway in case of ischemia in vivo and in vitro [5].

In an animal model of meniscal injury on a rat, the intra-articular injection of synthetic microRNA-210 accelerated the healing of the avascular meniscus [6].

Similarly, local injection of synthetic miR-210 into the injured Achilles tendon in a rat model accelerated tendon healing [7].

These assumptions underline the hypothesis that local treatment with anti-angiogenic inhibitors could represent a new therapeutic option for MRONJ patients.

This study would help to confirm the feasibility of a rat-induced MRONJ model and to validate its reliability, testing the efficacy of administering microRNA-210 to stimulate jaw bone perfusion would represent a therapeutic chance to promote MRONJ healing.

If it were confirmed in vitro synthetic microRNA-210 as an inhibitor of the anti-angiogenic effect of drugs related to the development of MRONJ can influence the healing of osteonecrotic lesions this would represent a non-surgical therapeutic opportunity for the pathology alternative to surgery able to improve the clinical course of those affected by MRONJ not eligible for surgery for which there is currently no curative treatment but only symptomatic relief.

The request for approval of the research project entitled “Use of microRNA210 for the treatment of medication-related osteonecrosis of the jaws” is set to be presented to the Body for the Protection of Animals (OPBA).

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