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ORIGINAL RESEARCH

Retrospective analysis of medication-related osteonecrosis of the jaw at a maxillofacial prosthetics clinic

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ABSTRACT

Purpose: Medication-related osteonecrosis of the jaw (MRONJ) poses significant challenges in patient care because of its complex etiology, clinical manifestations, and management. This study aims to provide an overview of patients with MRONJ treated at our clinic over the past 12 years, highlighting incidence, clinical characteristics, and prosthetic treatment outcomes.

Materials and Methods: The study included patients with MRONJ who visited our clinic between January 2012 and April 2024. Data on demographic characteristics, lesion location, clinical presentation, primary diseases, prosthetic management and medications were collected from health records.

Results: This retrospective analysis of cases of MRONJ over 12 years at a maxillofacial prosthetics clinic reveals a rising prevalence of the condition, particularly in the elderly, with treatments for breast and prostate cancer emerging as prominent risk factors. Distinct medication-specific effects on distribution of lesions suggest variation in pathogenic mechanisms, which require tailored treatment strategies. Management strategies encompass a spectrum of interventions from conservative measures to prosthetic rehabilitation, highlighting the importance of interdisciplinary collaboration and personalized care.

Conclusion: The rising incidence of MRONJ, especially among elderly patients, indicates the need for enhanced preventive measures and interdisciplinary care. Breast and prostate cancer treatments are significant risk factors, necessitating tailored monitoring. Effective prosthetic management is crucial for improving oral function and quality of life in MRONJ patients. (*Int J Maxillofac Prosthetics 2024;7:8-15*)

Keywords

Bisphosphonates, denosumab, antiresorptive agents, medication-related osteonecrosis of the jaw, maxillofacial prosthetics.

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AUDIO ABSTRACT

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) has garnered increasing attention in recent years because of its severe impact on patient quality of life and the challenges associated with its treatment.[1] Antiresorptive agents, including bisphosphonates and denosumab, along with various other medications, have been implicated as potential triggers for MRONJ.[2] Antiresorptive medications are widely used in the treatment of osteoporosis and for the complications of cancer that metastasizes to bone.[3] These agents reduce bone loss and the risk of morbidity and mortality resulting from bone fracture by interrupting osteoclastic bone resorption through various mechanisms of action.[4] However, these medications have been identified to be risk factors for development of osteonecrosis of the jaw, the major lesions of which are fistulas in the gingiva or oral mucosa and exposure of sequestra in areas of ulceration.[5]

Multiple risk factors contribute to the development of MRONJ.[6,7] These include the patient's underlying medical condition, the duration of anti-osteoporosis drug therapy, decisions regarding tooth extraction, anatomical

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considerations, use of dentures, and concurrent oral disease.[8,9] Although basic and clinical studies have been undertaken to clarify the pathophysiology of MRONJ, they have been inconclusive,[10] and a definitive treatment strategy has not yet been developed. The prosthetic approach to treatment of MRONJ varies according to the extent of the defect and whether there is an oronasal connection following exfoliation of necrotic bone or surgical removal. Precautions are necessary during each prosthetic procedure,[11] and multidisciplinary management is recommended for optimal patient care.[12]

The phenomenon of "super-aging" societies, characterized by a substantial proportion of individuals aged 65 years or older, is becoming increasingly common in many countries.[13] Therefore, the numbers of patients with osteoporosis and cancer are likely to increase worldwide, further increasing the use of antiresorptive agents and the risk of MRONJ.[10] Japan has become one such country in which the incidence of MRONJ is continuing to increase.[14] Lack of communication and interaction between physicians and dentists may also be contributing to the continuing increased incidence of MRONJ in Japan.[3] Moreover, neither physicians nor dentists receive timely updates regarding advances in the diagnosis and treatment of MRONJ.[15]

Surgery has been found to be very effective for MRONJ regardless of disease stage.[16] However, this approach occasionally results in a surgical defect that is too large for predictable primary closure, and a maxillofacial prosthodontist needs to be consulted to restore oral function. Our clinic has been providing maxillofacial prosthetic treatment for patients with and without cancer for more than 35 years.[17] The aim of this study was to provide an overview of the patients with MRONJ who have visited our clinic over the last 12 years and shed light on the incidence and clinical characteristics of this condition in the context of prosthetic treatment.

MATERIALS AND METHODS

Study approval

The study was approved by the ethics committee at Institute of Science Tokyo (Approval #D2016-085). Informed consent was secured via the optout route, whereby information about research activities involving patient data at our institution are presented in poster format at treatment locations as well as in digital format on the university website.

Data Collection

Patients were selected through review of the health records and photographic data for patients who visited the Clinic for Maxillofacial Prosthetics at Institute of Science Tokyo between January 2012 and April 2024.

Patients were included regardless of age and sex if they had a history of MRONJ affecting either one or both jaws. Data regarding lesion location and distribution, clinical presentation, and prosthetic management were recorded. Information concerning the primary disease for which the treatment that induced MRONJ was prescribed, and the medication used was collected. No exclusion criteria were applied.

Statistical methods

Data are summarized as frequency or percentage. All statistical analyses were performed using JMP version 16 (JMP Statistical Discovery LLC, Cary, NC).

RESULTS

A total of 42 cases of MRONJ were identified between 2012 and 2024. There was a notable increase in cases in the last 5 years of the study period, representing 62.6% of the total number of cases (Fig 1). The demographic and clinical characteristics of these cases are summarized in the following sections.

Demographic characteristics

Age

The mean patient age was 70 years (range 43–97), with 69% of cases of MRONJ occurring in patients aged older than 65 years.

Sex

MRONJ was more common in women than in men (59.5% vs 40.5%; Fig 2). Treatment for breast cancer was the primary cause of MRONJ in women, accounting for 88% of cases (Fig 2). The majority of men with MRONJ had a history of treatment for prostate cancer (Fig 2), with 82% of cases attributed to this primary disease.

Clinical characteristics

Primary disease

MRONJ was associated with various primary diseases, including breast cancer, prostate cancer, lymphoma, rheumatoid arthritis, osteoporosis, multiple myeloma, oropharyngeal cancer, and others. Notably, 52.4% of cases were associated with treatment for breast cancer and 33.3% with treatment for prostate cancer (Fig 2).

Oral manifestations

The oral manifestations of MRONJ were variable and included unilateral or bilateral involvement of the maxilla, mandible, or both (Fig 3). Seventy-four percent of MRONJ lesions occurred in the maxilla, indicating a predilection for this anatomical site. In contrast, only 19% of lesions were in the mandible, with both jaws affected concurrently in 7% of cases. Unilateral MRONJ lesions

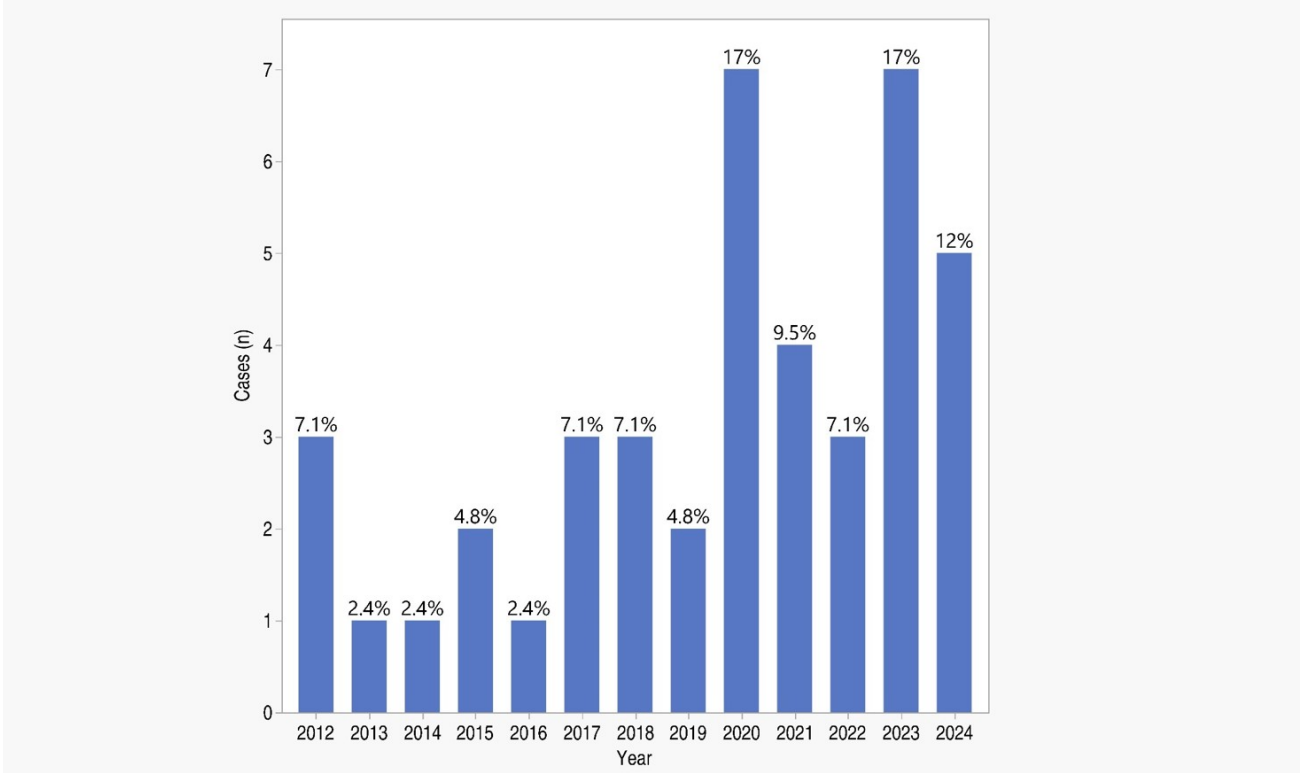


Fig 1. A histogram showing the annual distribution of cases with MRONJ.

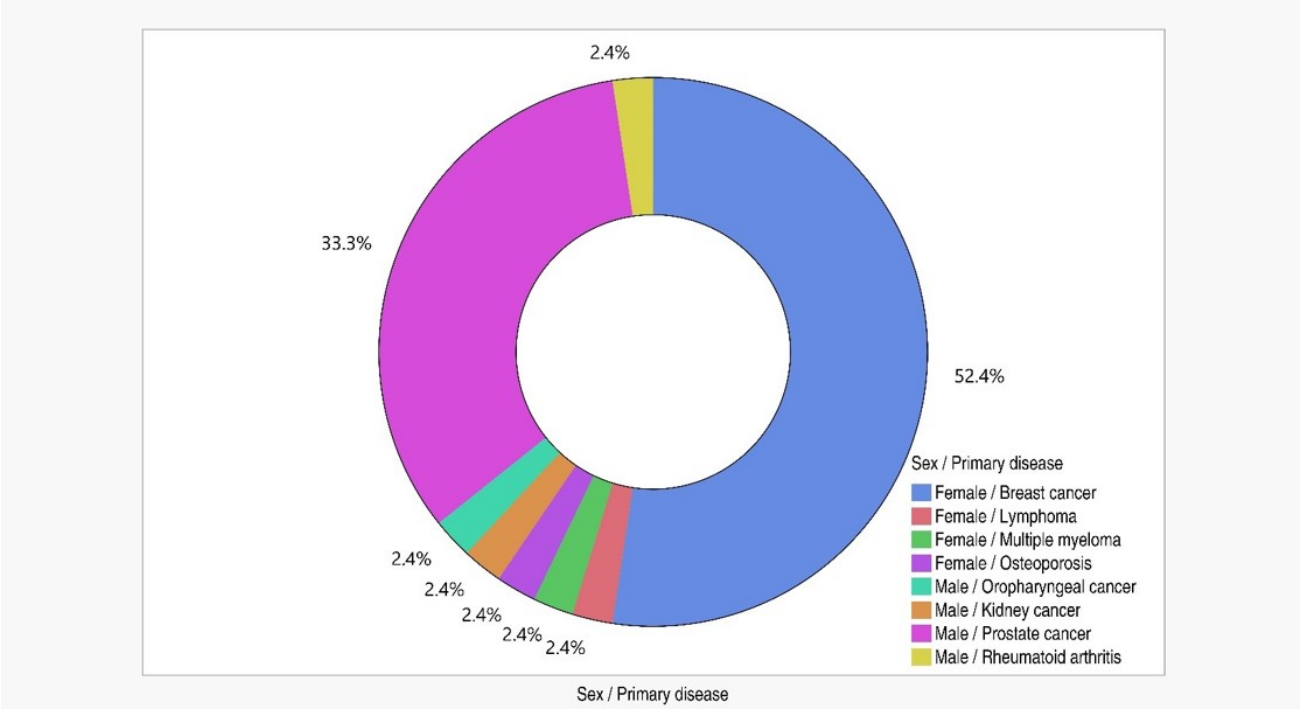


Fig 2. Pie chart showing the sex distribution of the primary diseases causing MRONJ during treatment.

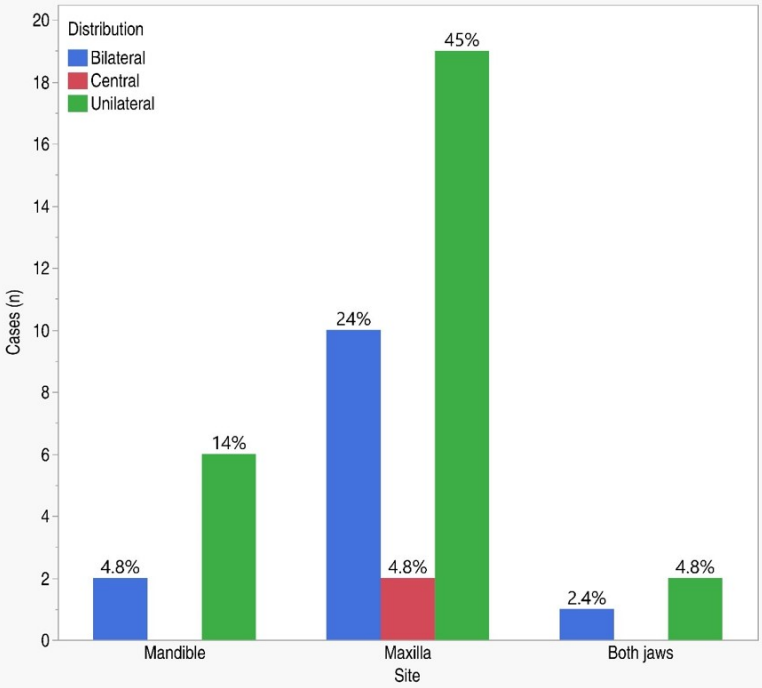


Fig 3. Pie chart showing the sex distribution of the primary diseases causing MRONJ during treatment.

were more common than bilateral lesions across all anatomical sites. Specifically, unilateral lesions accounted for 64% of cases overall. In contrast, bilateral lesions represented 31% of cases across all anatomical sites.

Nonspecific symptoms suggestive of MRONJ, such as pain, swelling, or altered sensation without obvious oral lesions, were present in 23.8% of cases. Furthermore, 47.6% were found to have localized areas of exposed necrotic bone, typically adjacent to extraction sites, indicative of early-stage MRONJ (Figs 4, 5). Extensive areas of exposed necrotic bone as a result of bone perforation after surgery or spontaneous exfoliation were observed in some of the more advanced cases (28.6%). An obturator prosthesis was provided in 21.4% of patients and complete or partial dentures in 30.95% (Fig 6).

Medication

The medications associated with MRONJ included denosumab (administered via subcutaneous injection) and zoledronic acid (a bisphosphonate administered intravenously). These medications accounted for 60% and 25% of MRONJ cases, respectively, with 15% attributed to combined use of these two medications. Most of the MRONJ lesions associated with denosumab had a bilateral distribution, whereas those induced by zoledronic acid predominantly affected one side of the jaw (Fig 7).

DISCUSSION

This study investigated the prevalence and clinical manifestations of MRONJ and the therapeutic modalities associated with the disease in a cohort of patients who attended our clinic over a 12-year period.The increase in the number of MRONJ cases during the last 5 years of the study period raises important questions regarding changing patterns in use of medications, patient demographics, and dental management practices. The rising incidence of MRONJ in Japan is thought to be linked to the increased long-term utilization of bisphosphonates.[2] Previous research has indicated that inadequate preventive measures might be contributing to the increased incidence of MRONJ and that Japanese physicians may lack sufficient understanding or engagement in dental treatment, which could further exacerbate the situation.[3]

Most cases occurred in individuals aged more than 65 years, with 69% of cases falling within this age group. This finding highlights advanced age as an important risk factor for development of MRONJ, which is consistent with the existing literature[18] and has implications within the context of Japan's status as a super-aging society. Japan faces unique demographic challenges, including a rapidly aging population and a declining birth rate, which have resulted in a disproportionate burden on health care systems.[19] As life expectancy continues to increase and the proportion of elderly individuals in the population

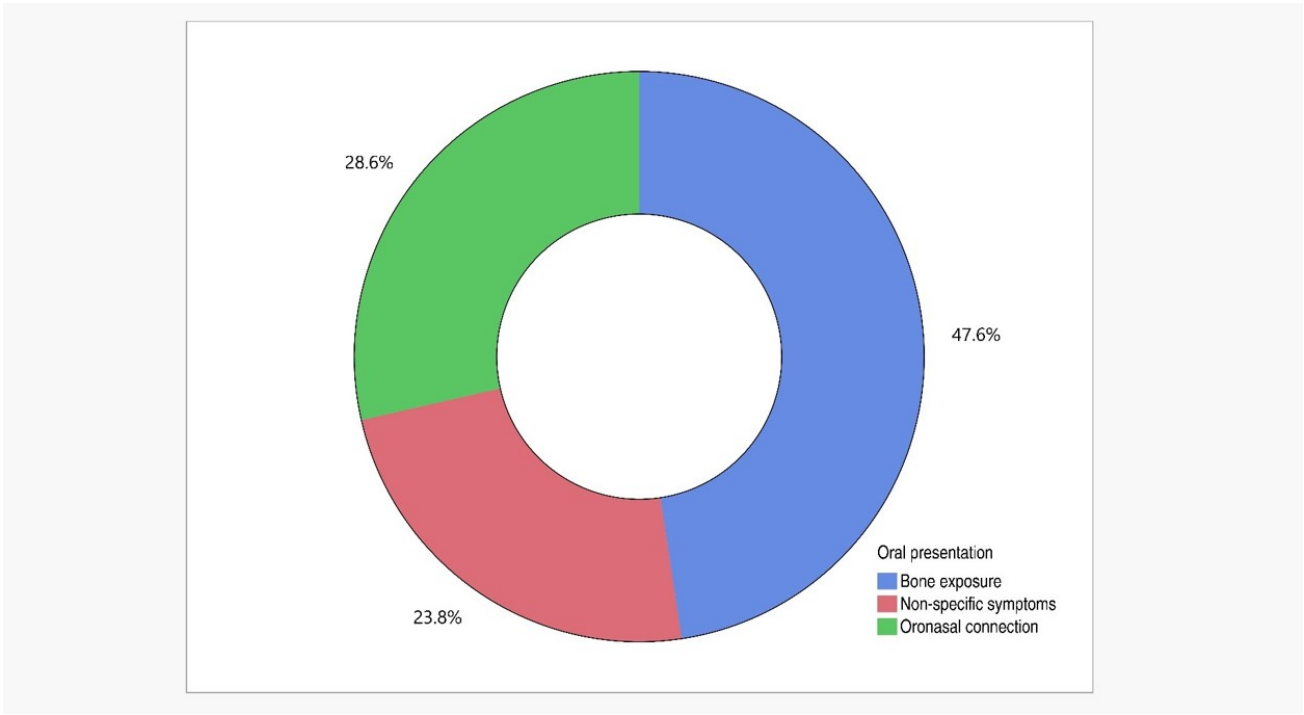


Fig 4. Pie chart analysis of clinical presentations in cases of MRONJ.

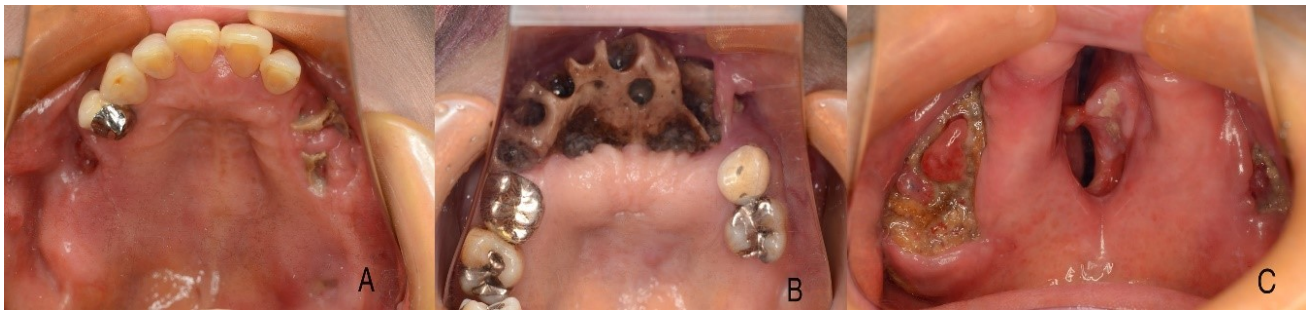


Fig 5. Clinical presentations of MRONJ. A) Early-stage MRONJ with localized bone exposure related to extraction site. B) Bilateral extensive MRONJ with exposed necrotic bone. C) A severe case of MRONJ involving multiple sites bilaterally and causing palatal perforation.

grows, the prevalence of age-related conditions such as MRONJ is expected to increase in parallel.

The observed difference in distribution of lesions associated with denosumab and of those associated with zoledronic acid suggests potential medication-specific effects on the pathogenesis of MRONJ. The bilateral jaw involvement in patients with denosumab-induced MRONJ may indicate a more widespread and systemic impact compared with the localized effects seen with zoledronic acid. Further research is needed to explain the underlying mechanisms driving these differences and to optimize management strategies for MRONJ associated with various medications.

Treatments for breast cancer and prostate cancer, in particular, are significant risk factors for development of MRONJ, and close monitoring and preventive measures are needed in these patient populations. The increased risk of MRONJ in patients with breast cancer may be attributable to improved survival rates as a result of introduction of novel therapeutics, such as trastuzumab.[20] Consequently, patients with breast cancer often experience prolonged exposure to bisphosphonates, potentially contributing to the heightened incidence of MRONJ in this population. Earlier studies have noted that a prolonged duration of bisphosphonate exposure is a significant risk factor for development of MRONJ.[6,21] Dentists should inquire about any history of treatment for cancer, including use of antiresorptive or antiangiogenic medications, which are known risk factors for MRONJ. By identifying susceptible patients early on, dentists can adopt a more cautious and conservative approach to dental procedures, minimizing the risk of complications such

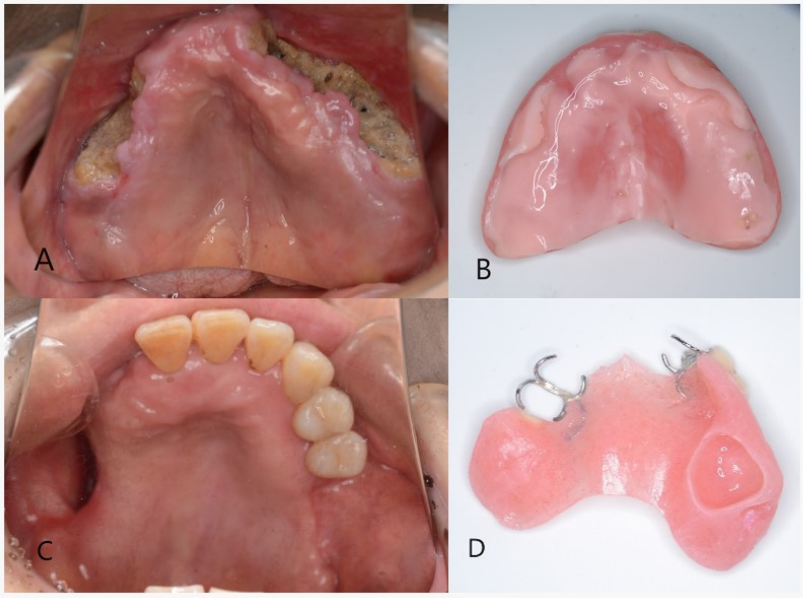


Fig 6. Prosthetic management of MRONJ. **A**) A severe case of active MRONJ that was managed with a complete denture. **B**) The fitting surface of the denture was modified using a tissue conditioning material to enhance adaptation and promote healing. **C**) A MRONJ defect that has completely healed, leaving an oronasal connection. **D**) An obturator prosthesis was fitted to close the oronasal connection.

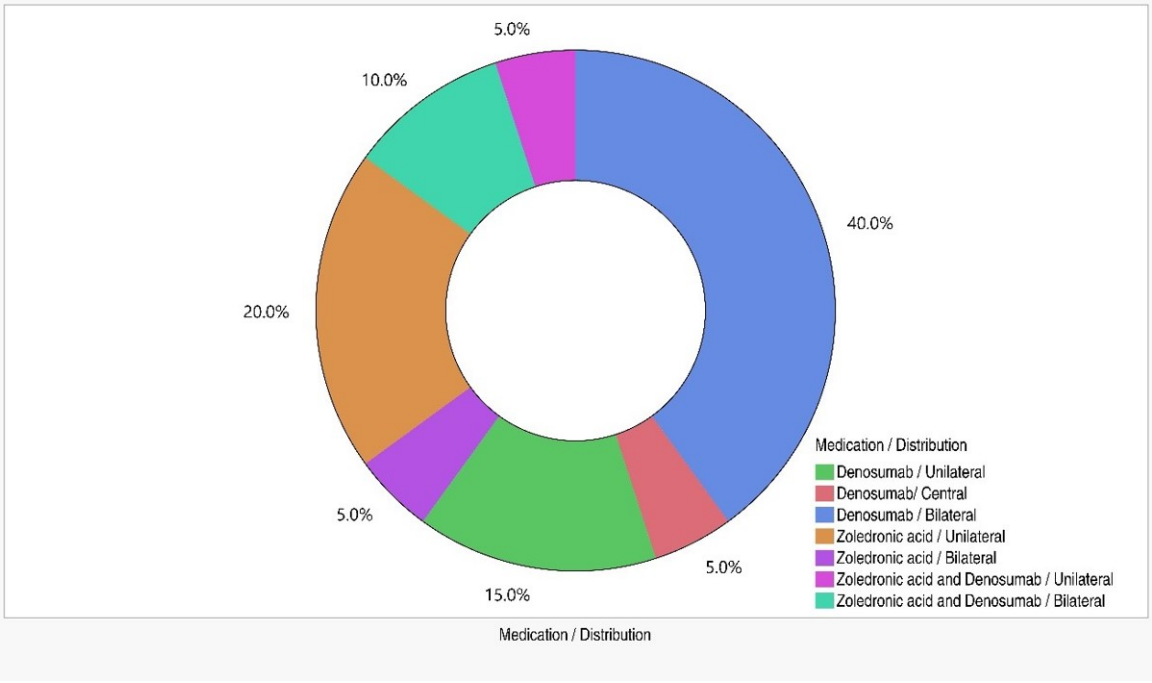


Fig 7. Pie chart showing distribution of MRONJ as unilateral, bilateral, or central according to type of medication.

as MRONJ. This may involve avoiding invasive dental procedures whenever possible and using alternative treatment modalities with close monitoring of oral health to detect any signs of MRONJ or other oral complications in a timely manner. Additionally, educating patients, dentists, and medical professionals about the real risks associated with antiresorptive therapy and adopting a multidisciplinary approach to the treatment of patients receiving these therapies are important.[22] Implementing these proactive measures could decrease the number of patients who develop MRONJ and reduce the need for extensive maxillofacial prosthetic treatment.

Our findings are in contrast with previous literature suggesting a predilection of MRONJ for the mandible owing to its limited blood supply and higher cortical to cancellous bone ratio.[7] The observed predominance of MRONJ in the maxilla in our study suggests a need to re-evaluate the previously proposed anatomical and physiological differences between the maxilla and mandible.

Management of MRONJ varied widely in our cohort, reflecting the complexity of the condition and individual patient needs (Fig 6). Conservative measures, including careful observation and oral hygiene instructions, antimicrobial mouthwash, rinsing and cleaning of a fistula, and periodontal treatment were implemented in cases with early-stage MRONJ and those with asymptomatic lesions.[2] For patients with advanced disease, interventions such as denture construction were used to improve oral function and quality of life. When an oronasal communication was evident, an obturator prosthesis was delivered to facilitate speech and mastication. In cases where surgical intervention was deemed high-risk or impractical, oral surgeons sometimes recommended observation until the necrotic bone naturally exfoliated or the patient's condition was sufficiently stable for surgery. During this time, dentures were delivered to restore oral function and facial esthetics. The fitting surface of the denture was modified using a soft liner or tissue conditioning material to accommodate the irregularities caused by the underlying MRONJ lesion.[11] Collaboration between oral and maxillofacial surgeons, general dentists, maxillofacial prosthodontists, and other health care professionals is essential for developing a treatment plan tailored to the needs of the individual patient and the severity of the disease.[12] Close monitoring and timely intervention are also important to prevent disease progression and minimize complications.

This study has some limitations. First, we could not obtain detailed medication histories, including information on drug holidays, doses, and potential risk factors. Second, maxillofacial prosthodontists are not typically the first health care professionals to encounter patients with early-stage MRONJ. Therefore, there may be delays in diagnosis and referral for prosthetic treatment, such that MRONJ is not diagnosed until it is well established. Continued research and collaboration are important for improvement of our understanding of the pathogenesis of MRONJ and optimizing treatment strategies to minimize its impact on patient quality of life.

CONCLUSIONS

Within the limitations of this study, several conclusions can be drawn.

First, there has been a notable rise in cases of MRONJ, particularly in the last 5 years, underscoring the urgent need to address this condition. Second, medications used in the treatment of breast cancer and prostate cancer are significant risk factors for development of MRONJ, indicating a need for better monitoring and preventive measures in these patient populations. Third, the medication-specific effects on the distribution of lesions highlight the complex pathogenesis of MRONJ and emphasize the need for tailored treatment approaches. Fourth, effective prosthetic management plays an important role in restoring oral function and quality of life in individuals with MRONJ. Finally, the diverse range of management strategies for MRONJ emphasizes the importance of interdisciplinary collaboration and individualized patient care.

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