MEDICATION RELATED OSTEONECROSIS OF THE JAWS (MRONJ)

Diagnosis & treatment

SARINA PICHARDO

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Colofon

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Cover front: artistic impression of 3D CT scan of stage III MRONJ with severe necrotic mandibular corps and excessive subperiosteal bone formation.
Cover back: artistic impression of the same patient 1 year post-operative after removal of entire necrotic mandibular corps. The continuity of the mandible was saved with the remaining sub-periosteal bone.

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Medication Related Osteonecrosis of the Jaws (MRONJ)

Diagnosis and treatment

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"All things are possible until they are proved impossible
and even the impossible may only be so, as of now."
Pearl S. Buck, schrijfster en Nobelprijswinnaar Literatuur 1938

To my mother

CONTENTS

1

General Introduction and Aim of this thesis

GENERAL INTRODUCTION

After its first description in 2003, Bisphosphonate related osteonecrosis of the jaws (BRONJ) became one of the most debated side-effects of an anti-resorptive drug[1]: a serious complication that still plagues several clinicians. It had serious consequences for the patients, who could suffer years of pain and sequestration and even loss of parts of the jaws. In 2008 the first cases of denosumab osteonecrosis of the jaw were reported[2, 3], another anti-resorptive drug, as well as anti-angiogenic inhibitors, such as sunitimib or bevacizumab, related osteonecrosis of the jaws (ONJ) and it became apparent that more drugs could induce this clinical picture[4]. Therefore, since 2014 the term medication related osteonecrosis of the jaws (MRONJ) was adopted[4]. The proper treatment is still discussed throughout the literature.

But is MRONJ a new disease? Its clinical features strongly resemble the so-called "phossy jaw" which was already described in nineteenth century[5-9]. During that age a clinical picture of (severe) inflammation with sequestration and lyses of jaw bone with (sometimes excessive) subperiosteal bone formation was reported; the "phossy jaw". This clinical picture strongly resembles the current clinical presentation in all forms of MRONJ.

Historical overview

Phossy Jaw

In the nineteenth century the phossy jaw as seen in figures 1 and 2 was a major problem, leading to the loss of jaw bone and sometimes even leading to death[8]. It was noticed that patients had been exposed to phosphorus fumes. These phosphorus fumes were inhaled in the matches or fireworks industry. In these industries yellow phosphorus was frequently used for ignition.

Figure 1 Phossy Jaw - Left mandible of 19th century male aged 26-35 years at death with bone changes suggesting possible phossy jaw. London Museum

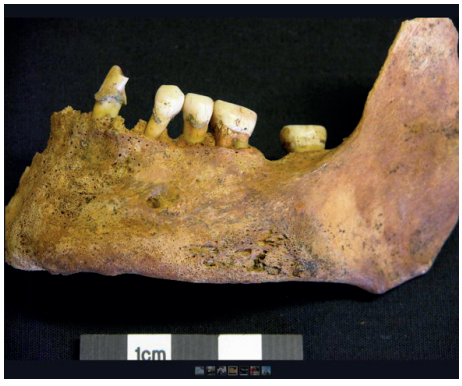


Figure 2 Phossy Jaw – Huntarian Museum - Odontologic Museum, Royal College of Surgeons, in London, England.

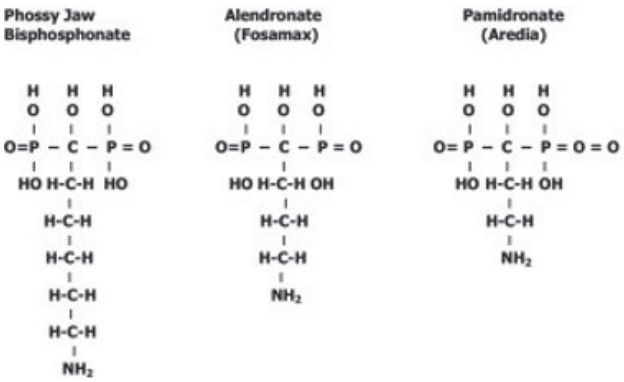
Therefore strike-anywhere-matches became very popular and the industry was flourishing. Employees inhaled phosphorus fumes (P_4O_{10}) and this lead to a chemical reaction in the body although the precise mechanism has not been fully elucidated. One hypothesis was that inhaled phosphorus has a chemical reaction with water, carbon dioxide (CO2) and lysine, a common amino acid in the body, which leads to the formation of a diphosphonate (fig 3) which chemical structure is almost identical to that of bisphosphonates[5].

The combination of phosphorus exposure and poor dental hygiene caused a clinical picture with striking resemblance to the disease currently known as MRONJ. After the association with yellow phosphorus became clear, its use was forbidden in 1906. However, reports of this so-called "phossy jaw" were published until the early sixties[7].

Bisphosphonates

Bisphosphonates were already developed in the 19th century. Originally, they were developed for non-human use in the textile, fertilizer and oil industries. In irrigation systems they were also used to soften water. In 1968 their potential use in disorders of bone metabolism was reported[10]. It was observed that the bisphosphonate prevented the dissolution of hydroxy apatite, and thus was capable of arresting bone resorption. The non-nitrogen containing bisphosphonates Etidronate and Clodronate were developed. These showed evident decrease in osteoclastic resorption in vitro as well as in vivo[11-13]. After these reports bisphophonates have been widely investigated as a potential treatment for osteoporosis, bone metastases and metabolic bone disease[14].

Figure 3 Chemical formula phossy jaw BP compared to alendronate and pamidronate (Marx[5])



Current use of anti-resorptive therapy

Bisphosphonates (BP) and denosumab (Dmab) are anti-resorptive agents that are being used in the treatment of various conditions such as osteoporosis (OP), bone metastases, multiple myeloma (MM) and Paget's disease. They inhibit osteoclast activity and thus bone resorption. In this thesis the use of anti-resorptive treatment in osteoporosis, metastatic bone disease and MM will be predominantly discussed.

Osteoporosis (OP)

Osteoporosis is a condition where there is a decrease in bone mass and bone structure leading to increased bone fragility. In the treatment of OP BP's are often described as weekly oral formulations or yearly zoledronic acid. Dmab is given in a dose of 60mg every 6 months.

Metastatic bone disease

In the case of to the bone metastasized solid malignancies, some of these metastases may cause local pain and hypercalcemia with accompanied complaints such as nausea, vomiting, fatigue. Inhibition of bone resorption will correct the hypercalcemia and will reduce pain. Strengthening of the bone with anti-resorptive medication may also prevent pathological fractures. Both bisphosphonates and denosumab can be used as treatment for these indications. Although dosages will be higher and more frequent then in OP, for instance oral formulations are hardly used and Dmab 120mg or Zoledronic acid is given monthly.

Anti-resorptive therapy might also be used as neoadjuvant therapy in e.g. breast cancer.

Multiple myeloma (MM)

In the case of MM, a malignancy of the plasma cells in the bone marrow, anti-resorptive treatment consisting of predominantly iv BP's, are part of the standard treatment since MM often presents with lytic bone lesions, hypercalcemia and pain. MM cells also produce osteoclast activating and osteoblast inhibiting factors.

Dosages anti-resorptive therapy

Due to the high turnover of bone in malignancies the dosage for this indication is higher than for osteoporosis, despite the medication.

Mechanism of action

Bisphosphonates

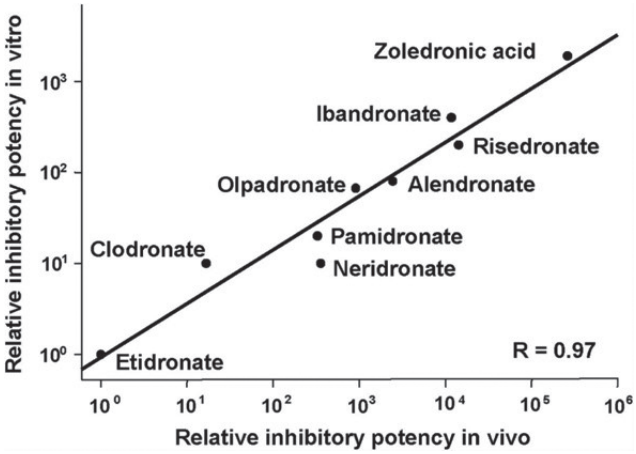
Pyrophosphates are a by-product of cell metabolism (hydrolysis of ATP) and inhibit bone mineralization. When an oxygen-atom of pyrophosphate is replaced by a carbon-atom, pyrophosphate, a diphosphate, changes to a bisphosphonate (BP). BP's have a higher affinity for bone than diphosphonates and the BP is bound to the hydroxy apatite with a larger affinity. Due to this competitive binding, BP's inhibit bone resorption. The addition of nitrogen-chains to the bisphosphonate will provide a covalent binding with the bone mineral. This defines the potency of the bisphosphonate to bind to bone. The potency is expressed in numbers compared to the "weakest" non-nitrogen BP etidronate, which has a potency of 1. Nitrogen containing BPs start with a potency of 100 (pamidronate) to >10.000 zoledronic acid (fig 4).

Nowadays, only nitrogen containing bisphosphonates are used. Because of their attachment to bone, they have a long half-life of several years and will stay active for years after administration of the medication.

The osteoclast is responsible for the resorption of bone. Bisphosphonates inhibit formation and the activity of osteoclasts[15, 16]. Bisphosphonates cause dysfunction by preventing adhesion of osteoclasts to bone matrix and by inducing early apoptosis with inhibition of bone resorption as a result[17, 18].

During the years more potent BP's have been developed, starting from the non-nitrogen containing BP etidronate, which has the lowest affinity to bone, to the zoledronic acid which has the highest affinity and is the most powerfull nitrogen containing BP.

Figure 4 Potency N-BP Adapted from Aapro M et al 2007[19]



Denosumab

Denosumab is an RANK-L inhibitor and therefore interacts on a different level with osteoclasts compared to bisphosphonates. RANK-L is necessary for activation of osteoclasts and maturation of preosteoclasts to osteoclasts. Denosumab binds RANK-L causing immediate cessation of the osteoclast and preosteoclast function and therefore inhibition of bone resorption. Unlike BP's, the effect of denosumab is temporary, and after several months osteoclast activity will re-start. Recent literature shows this could even result in a rebound in bone metabolism with bone markers increasing above baseline markers and subsequent increased fracture[20-22].

Osteonecrosis of the jaws (ONJ)

In 2003 a serious side effect of bisphosphonates was reported by Robert E. Marx[1]. He reported 36 patients presenting with osteonecrosis of the jaw(s) (ONJ) combined with pain, dental ab-

scesses, denuded bone (also in edentulous patients) and osteomyelitis. Removal of teeth often initiates exposed non-healing extraction sockets, although he also reported spontaneous occurrence of necrosis. Since then various cases have been described (ref) but the exact aetiology remains unknown. Some authors suggest a spontaneous "inside-out" origin, where they claim spontaneous disease starting in the jaw bone and then extending into the oral cavity[23-34]. Other authors report dental "outside-in" origins in which the disease starts after a dental extraction or treatment, from dental pathology, placement of implants or pressure sores with edentulous patients[35-38]. Osteonecrosis has also been reported after the use of Denosumab[2-4, 39, 40].

ONJ has an incidence of only 0,04-0,186%[40], which is relatively low, although the incidence may vary in patient groups.

Clinical features

Because of the variety of anti-resorptive agents causing ONJ, the American Association of Oral & Maxillofacial Surgeons decided to change the term: Bisphosphonate related osteonecrosis of the jaws[41, 42] to Medication related osteonecrosis of the jaws[4]. This disease was described as:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Patients may present with a variety of symptoms (fig 5-9). Most patients experience complaints of pain, swelling, foetor, exposed bone, pus discharge intra- or extraorally and/or neurosensory disturbances. They may even lose teeth or have undergone extraction of teeth or other dental surgical procedures such as implants. Sometimes symptoms have started with periodontal diseases or pressure sores in edentulous patients.

Figure 5 Extraoral submental fistula with pus discharge

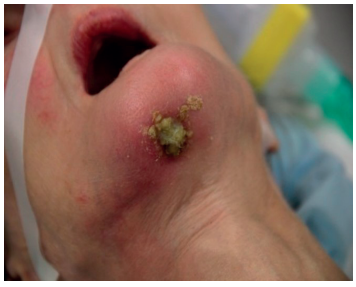
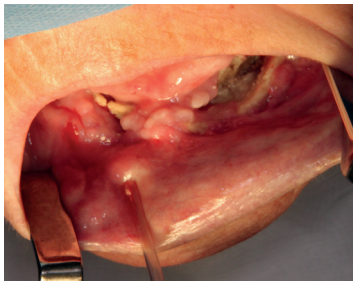
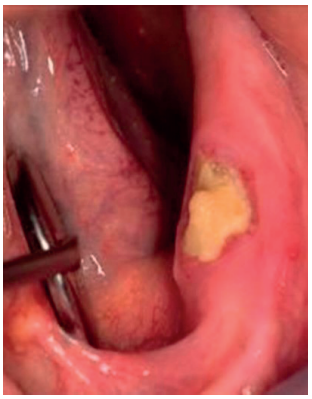


Figure 6 Intraoral view with denuded bone and fistula of the mandible



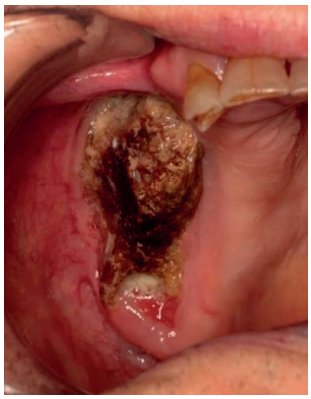
In addition stages (0-III) are defined based on the severity of the disease.

Figure 7 Stage 2 MRONJ in the lower left quadrant



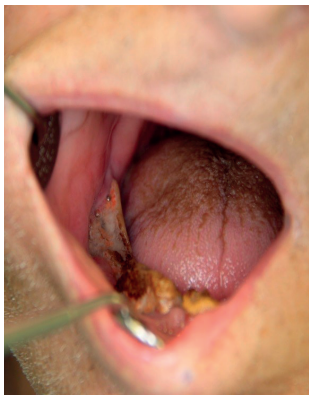
Stage 2

Figure 8 Stage 3 MRONJ in the upper right quadrant



stage 3

Figure 9 Stage 3 MRONJ in the lower right quadrant



stage 3

Table I: Rugierro SL et al Position paper AAOMS update 2014[4]

Stage	Clinical symptoms*	Treatment recommendations#
At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates	No treatment indicated patient education
0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms	Systemic management, including use of pain medication and antibiotics
1	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse clinical follow-up on a quarterly basis patient education and review of indications for continued bisphosphonate therapy
2	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics oral antibacterial mouth rinse pain control debridement to relieve soft tissue irritation and infection control
3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor	Antibacterial mouth rinse antibiotic therapy and pain control surgical debridement or resection for longer-term palliation of infection and pain

* Exposed or probable bone in the maxillofacial region without resolution for longer than 8 weeks in patients treated with an antiresorptive or an antiangiogenic agent who have not received radiation therapy to the jaws.

Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should be considered because it is unlikely that extraction will exacerbate the established necrotic process.

Radiographic findings

Imaging in ONJ patients starts with the usual panoramic radiograph (PR)[43, 44]. The PR gives an impression of a lesion and its extent in 2D. Chronic use of anti-resorptive drugs may show the findings as mentioned in the updated Position Paper from 2014, as shown in table II.

Table II Radiological findings adapted from Ruggiero 2014 position paper update[4]

Radiological findings*
Alveolar bone loss or resorption not attributable to chronic periodontal disease
Changes to trabecular pattern—dense bone and no new bone in extraction sockets
Regions of osteosclerosis involving the alveolar bone or surrounding basilar bone
Thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased periodontal ligament space)

Panoramic radiographs (fig 10-13)

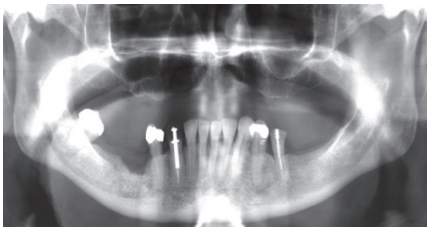


Figure 10 Panoramic radiograph: Stage 2 MRONJ: lysis in the right alveolar process in the region of the 45. Sclerosis is visible in the right mandibular body (the alveolar nerve canal is more lucent and the bone marrow is more opaque in comparison to the left side).

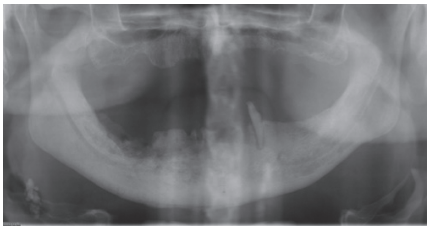


Figure 11 Panoramic radiograph Stage 2 MRONJ: severe lysis in 4th quadrant with sequesters. Subperiosteal bone is visible at the inferior border. There is substantial sclerosis with a lucent alveolar nerve canal and the wall of the contralateral canal is thickened.

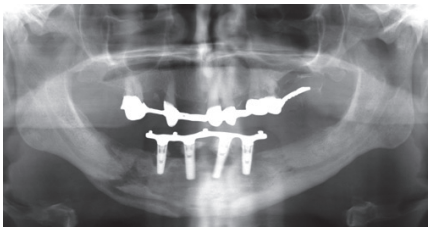


Figure 12 Panoramic radiograph Stage 3 MRONJ: Severe peri-implantitis around the 4 implants with horizontal and vertical bone loss, osteolysis and sequestra throughout the mandibular body extending to the inferior border. Subperiosteal bone formation is visible.

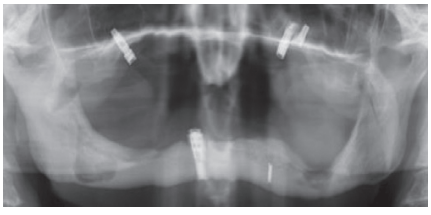


Figure 13 Panoramic radiograph Stage 3 MRONJ: Severe lysis and sequestra bilateral in the mandible with involvement of the inferior border.

For a more detailed examination (CB)CT is necessary. (CB)CT provides more information on the extent of the disease, involvement of nerves, sinuses, inferior border of the mandible and pathological fractures in advanced cases. Furthermore a scan is important in the planning of possible surgery.

Radiological findings on (CB)CT for bisphosphonate related osteonecrosis of the jaws have been well defined. These include thickened lamina dura, sclerosis, subperiosteal bone formation, sequestra, a pronounced inferior alveolar canal and discontinuation of the cortical border of the jaw(s)[43, 45-52].

Figure 14 Sequestrum

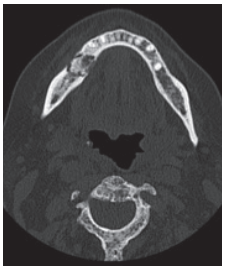


Figure 15 Subperiosteal bone

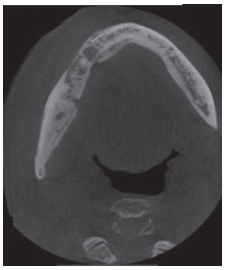


Figure 16 Lysis cortical border

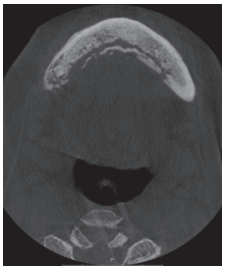
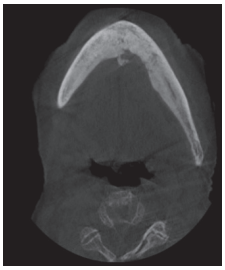


Figure 17 Sclerosis



Treatment

The optimal treatment strategy for ONJ has been debated extensively since the first report in 2003[1]. In the beginning a conservative approach was promoted[23, 24, 41, 42]. This meant treatment with antibiotics and mouth rinses. In severe cases, when there was a fracture or involvement of sinus or inferior border, a resection was performed with or without (free flap) reconstruction. However, in time a more predominantly European approach reported success with a relatively simple surgical technique in combination with the use of antibiotics[53-55]. This procedure consisted of a thorough sequestrectomy, often with saucerization and rounding off of sharp edges, and had success rates of 80-100%. Nevertheless controversies remained and international guidelines based on the AAOMS still promote conservative treatment with antibiotics and mouth rinses in the first 2 stages of MRONJ. Intervention in these stages would in their opinion lead to deterioration of the disease or development of further necrosis. From stage III surgical intervention with resection of the mandible with a microvascular flap reconstruction, an extensive procedure, is advised.

In conclusion etiology and treatment of MRONJ remain topics of discussion. But just as widely discussed are the surgical techniques stated above. These controversies have large effects on the treatment outcome of patients. Should or can a surgeon perform extensive surgery in an often vulnerable and fragile population? Or is successful treatment also possible while using a less

aggressive approach? Further evaluation of the differences in outcome will help to reach more consensus on treatment of this disease. Therefore further studies into cause, treatment and prevention of this disease are needed.

The aim of this thesis is to provide more insight in the diagnosis of MRONJ and the optimal treatment and intends to provide guidance for (dental) practitioners.

Outline of the thesis

PART I of this thesis will focus on the diagnosis of MRONJ, the origin(s) of MRONJ and possible risk factors.

CHAPTER 2 is a retrospective analysis on the precipitating factors for development of MRONJ in 45 patients. All possible (dental) events leading to complaints were studied.

CHAPTER 3 addresses the risks for MRONJ when there are implants involved in the necrosis. We retrospectively analysed our cohort for the relation between the implant and the development of MRONJ.

CHAPTER 4 is an observational pilot study on the findings on (cone beam) computed tomography ((CB)CT) regarding denosumab or bisphosphonate necrosis in 34 patients. The differences on several known characteristics of osteomyelitis are compared in order to assess possible differences in radiological presentation of both entities.

CHAPTER 5 illustrates the first case of denosumab necrosis of the jaws in the LUMC.

PART II focuses on treatment with a special emphasis on surgical treatment of MRONJ-patients.

CHAPTER 6 addresses the outcome of our surgical technique in 74 stage II/III-patients with bisphosphonate necrosis at the LUMC.

CHAPTER 7 is a retrospective analysis on the surgical results of a series of 11 patients with denosumab necrosis.

CHAPTER 8 shows the retrospective analysis of the treatment results of pathologic fractures of the mandible in 15 stage III MRONJ patients.

CHAPTER 9 assesses the surgical technique of the LUMC treatment protocol.

CHAPTER 10 shows a patient with severe stage III MRONJ in the mandible, in whom, due to excessive reactive subperiosteal bone formation around the jaw, the continuity was preserved after removal of all diseased bone.

In CHAPTER 11 a general discussion on this thesis is presented. CHAPTER 12 and 13 are summaries of the thesis in English and Dutch.

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Part I

DIAGNOSIS

2

Bisphosphonate related osteonecrosis of the jaws: spontaneous or dental origin?

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ABSTRACT

INTRODUCTION

Bisphosphonates are frequently used worldwide mostly in osteoporosis and skeletal bone metastases. However, a serious side-effect is bisphosphonate related osteonecrosis of the jaws (BRONJ). The mechanism behind BRONJ remains unclear. In literature several origins are suggested. Presence of the teeth in the jaws may play an important role. Therefore in this study 45 patients were analyzed retrospectively.

METHODS

Files of 45 patients with a diagnosis of BRONJ were analyzed, meaning clinical features, bisphosphonate use, dental history including luxating moment and (previous) treatment.

RESULTS

In 97.5% (n = 44) a certain or presumable dental focus, such as extractions, a previous dental treatment or prosthesis complaints were found as initiating factor of BRONJ.

CONCLUSION

In contrast to findings in literature, in our group of patients a dental focus was found in 44 of 45 cases. This implies a dentoalveolar start of BRONJ with subsequent spreading into the jaws in nearly all cases.

INTRODUCTION

Bisphosphonates are frequently used worldwide. There are several indications to prescribe bisphosphonates. The most important indications are osteoporosis and skeletal bone metastases in malignancies. Bisphosphonates decrease the function of osteoclasts and hence bone resorption. They stabilize the osteoporotic process, further growth and metastasizing in bone and improve complaints such as pain.

However, the use of bisphosphonates may have side effects. Most frequently described are gastrointestinal effects. In 2003 the first case of osteonecrosis of the jaw was reported[1]. According to the definition of BRONJ given by the American Association of Oral and Maxillofacial Surgeons (AAOMS) patients may be considered to have BRONJ if 3 characteristics are present: current or previous treatment with a bisphosphonate, exposed, necrotic bone in the maxillofacial region that persisted for more than 8 weeks, no history of radiation therapy to the jaws[2]. In addition, different stages of the disease according to signs of inflammation were developed (Table I).

Table I. Staging of bisphosphonate-related osteonecrosis of the jaw[2]

Stage	Clinical symptoms
At risk category	No apparent exposed or necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed or necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed or necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed or necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border or sinus floor

The precise mechanism of BRONJ still remains unclear. In the literature BRONJ is said to be resistant to therapy and may lead to serious loss of bone. Many authors including large dental associations as the AAOMS[3], the American Dental Association[4,5], and the American Society of Bone and Mineral Research[6] advise a conservative treatment, based on the fact that bisphosphonate use causes systemic changes in bone and may start spontaneously. However, since no bisphosphonate related osteonecrosis of other bones has been reported in the literature, it seems that the presence of teeth in the jaw plays an important role.

In literature there is no definition of the minimum duration of the use of oral bisphosphonates for developing BRONJ. According to the AAOMS[3] the risk for developing BRONJ increases when the duration of oral bisphosphonate therapy exceeds 36 months. Marx[7] and other authors[8,9] include patients with a duration of oral use of at least 24 and even 128 months.

For the oral use of bisphosphonates in our group a minimum of 24 months was taken. For the use of intravenous bisphosphonates a minimum use of 12 months was taken.

In this study a distinction was made between spontaneous and dental causes of BRONJ. If the latter is the case, then treatment results could possibly be improved by using treatment used for chronic suppurative osteomyelitis (CSO), which nearly always has a dental cause. In CSO a thorough surgical intervention with primary closure in layers and an antibiotic protocol leads to good results and healing of the defect[10]. In the treatment of BRONJ, recent literature using this type of treatment shows also acceptable results.

METHODS

The files of 51 patients using bisphosphonates and with exposed bone of the jaws were reviewed. All patients were treated and followed in the Department of Oral and Maxillofacial Surgery of the Leiden University Medical Center. All patients were diagnosed with BRONJ according to the AAOMS definition. To be included into this study patients a minimum use of bisphosphonate for at least 12 months intravenously or 24 months orally. Considering these criteria 45 patients were included in this study.

Patient characteristics, bisphosphonate use, clinical features, dental history, and (previous) treatment were studied. Patients with a combination of oral and intravenous bisphosphonates were counted into the intravenous group.

In order to analyze the luxating moments of BRONJ, all initiating factors were categorized into 4 groups: a certain dental focus, a presumable dental focus, spontaneous and unknown.

A certain dental focus was defined as a recent dental procedure as an extraction, removal of retained roots, placing of implants, an apical inflammation or clear pre-existent periodontal problems in the region of the BRONJ.

A presumable dental focus was defined as an elevated mylohyoid ridge, a clear knife-edge ridge and (gingival) trauma caused by non-fitting dentures.

Spontaneous exposed bone was defined as no previous dental history, no previous therapy, no previous trauma, or no previous existing complaints related to dentures.

Patients were categorized as unknown dental focus when the previous history was unclear or not traceable.

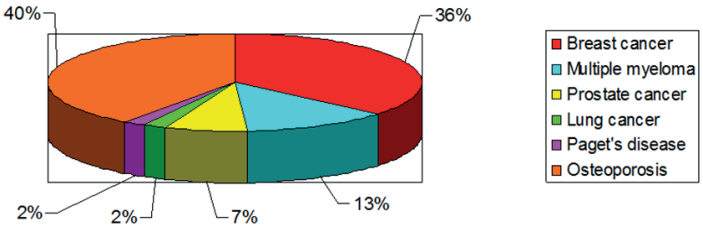
RESULTS

Patient characteristics

Most patients suffered from malignancies 57.8% (n = 26). From this group 61.6% (n = 16) had (metastasized) breast cancer, 23.1% (n = 6) had multiple myeloma, 11.5% (n = 3) had prostate

cancer and 3.8% (n = 1) had lung cancer. One patient (2.2%) had Paget's disease. Osteoporosis counted for 40.0% (n = 18) of the indications for bisphosphonate treatment (Figure 1).

Figure 1. Indications of bisphosphonate use in percentages.



The clinical characteristics of the 45 patients are listed in Table III. A total of 80.0% (n = 36) was female, 20.0% (n = 9) was male. Age varied from 45 to 84 with a mean of 66.1 years.

From 45 patients 77.8% (n = 35) had BRONJ of the mandible, 15.5% (n = 7) of the maxilla and 6.7% (n = 3) of both jaws.

Oral bisphoshonates were used in 16 cases (35.6%) with a minimum of 24 months and a maximum of 132 months and a mean of 57.3 months. Intravenous bisphosphonates were used in 29 cases (64.4%) with a minimum of 12 months and a maximum of 108 months and a mean of 30.8 months.

Table II. Features patients, indication and bisphosphonate use

Nr	Age	Sex	Indication	Bisphosphonate	Duration use	Administer manner	Location	Luxating moment	Category
1	83	F	OP	Pam	84	O	Mandible	Preprosthetic surgery	Presumable
2	84	F	Paget's disease	Pam	24	O	Both	Extraction	Certain
3	46	M	OP	Pam, Al	132; 12	O	Mandible	Extraction	Certain
4	84	F	OP	Pam	48	O	Maxilla	Extraction	Certain
5	88	F	OP	Pam, Al	24	O	Mandible	Extraction	Certain
6	77	F	OP	Pam, Al	72; 60	B	Both	Extraction	Certain
7	67	F	OP	Et, Al	9; 30	O	Mandible	Implants	Certain
8	84	F	Mult Myel	Pam	12	Iv	Mandible	Implants	Certain
9	45	F	Breast ca	Clo	29	O	Mandible	Periodontal disease	Certain
10	59	F	Breast ca	Pam	36	Iv	Mandible	Extraction	Certain
11	54	F	OP	Pam	108	Iv	Mandible	Pressure sore	Presumable
12	65	F	Breast ca	Pam	53	Iv	Mandible	Extraction	Certain
13	82	F	Mult Myel	Et, Pam	1; 72	B	Both	Extraction	Certain
14	83	F	OP	Pam	96	Iv	Mandible	Extraction	Certain

Table II. Features patients, indication and bisphosphonate use (*continued*)

Nr	Age	Sex	Indication	Bisphosphonate	Duration use	Administer manner	Location	Luxating moment	Category
15	67	M	Mult Myel	Zol, Pam, Al	12; 10; 22	B	Mandible	Extraction	Certain
16	73	F	OP	Al	46	O	Mandible	Extraction	Unclear
17	75	F	OP	Pam, Al	84; 36	O	Mandible	Presumable extr	Presumable
18	53	F	Breast ca	Pam	24	Iv	Mandible	Extraction	Certain
19	72	F	OP	Pam	24	Iv	Mandible	Extraction	Certain
20	76	M	OP	Al	52	O	Mandible	Mylohyoid ridge	Presumable
21	80	F	Breast ca	Pam	54	Iv	Mandible	Unknown	Unclear
22	57	F	Mult Myel	Pam	83	Iv	Mandible	Knife-edge ridge	Presumable
23	66	F	Breast ca	Pam	24	Iv	Mandible	Extraction	Certain
24	52	F	Breast ca	Pam	48	Iv	Mandible	Extraction	Certain
25	60	F	Breast ca	Pam	24	Iv	Maxilla	Extraction	Certain
26	51	F	Breast ca	Pam	45	Iv	Mandible	Pressure sore	Presumable
27	59	M	Prostate ca	Pam, Zol	24; 26	Iv	Mandible	Dental treatment	Presumable
28	84	M	Mult Myel	Pam	24	Iv	Maxilla	Extraction	Certain
29	47	F	OP	Al	24	O	Mandible	Apical granuloma	Certain
30	68	M	Lung ca	Al	31	O	Mandible	Pressure sore	Presumable
31	61	F	Breast ca	Pam	24	Iv	Maxilla	Implants	Certain
32	55	F	Breast ca	Pam	24	Iv	Mandible	Extraction	Certain
33	70	F	OP	Ris	24	O	Mandible	Extraction	Certain
34	65	M	Prostate ca	Zol	36	Iv	Mandible	Extraction	Certain
35	70	F	OP	Al	120	O	Mandible	Extraction	Certain
36	67	F	OP	Al	84	O	Mandible	Implants	Certain
37	60	M	Prostate ca	Zol	12	Iv	Mandible	Extraction	Certain
38	54	F	Breast ca	Pam	38	Iv	Mandible	Extraction	Certain
39	52	F	Breast ca	Pam, Iban	12;44	B	Maxilla	Implants	Certain
40	75	F	Breast ca	Pam	12	Iv	Mandible	Extraction	Certain
41	71	F	OP	Pam	12	Iv	Mandible	Extraction	Certain
42	71	F	Breast ca	Iban, Zol	48, 12	B	Maxilla	Extraction	Certain
43	56	F	Breast ca	Pam	38	Iv	Mandible	Extraction	Certain
44	75	F	OP	Al	36	O	Maxilla	Implants	Certain
45	76	M	Mult Myel	Pam	18	Iv	Mandible	Extraction	Certain

F, female; M, male; OP, osteoporosis; Mult Meyl, multiple myeloma; ca, cancer; Al, Alendronic acid (Fosamax); Pam, Pamidronic acid; Ris, risedronate (Actonel; Procter & Gamble, Cincinnati, OH, USA); Et, etidronate (Didronel; Procter & Gamble); Zol, Zolendronic Acid (Zometa; Novartis); Iban, Ibandronate (Boniva; Roche, Basel, Switzerland); OR, orally; IV, intravenously; B, both orally and intravenously.

Table III. Overview literature origin BRONJ

Author		Number patients	Admin manner	Spontaneous(%)	Dental Focus (%)
Badros[20]	2008	97	iv	53	47
Bagan[21]	2006	20	iv	55	45
Bamias[11]	2005	17	iv	11,8	88,2
Bedogni[12]	2008	11	iv	18,1	81,9
Boonyapakorn[22]	2007	22	iv	23	77
Dimopoulos[13]	2006	15	iv	13,3	86,7
Durie[23]	2005	152	iv	19-31	69-81
Estilo[24]	2008	35	iv	40	51,4
Ficarra[14]	2005	9	iv	0	100
Filleul[25]	2010	2400	b	26	74
Kos[15]	2009	34	iv	0	91,2
Lugassy[26]	2004	3	iv	66,7	33,3
Maerevoet[27]	2005	9	iv	1	0
Manfredi[10]	2011	25	b	28	72
Marx[8]	2005	119	b	25,2	74,8
Marx [28]	2007	30	or	50	50
Mavrokokki[16]	2007	112	b	21	79
Melo[17]	2005	11	iv	9,1	91,85
Merigo[9]	2006	29	b	48,3	51,7
Migliorati[29]	2005	17	iv	60	40
O'Ryan[30]	2012	30	or	33,3	66,7
Otto[18]	2011	66	b	0	100
Pichardo	2013	45	b	0	97,8
Pires[31]	2005	12	iv	33	67
Purcell&Boyd[32]	2005	13	b	62	38
Rugierro[33]	2004	63	b	14,1	86
Saad[34]	2011	89	iv	35,1	64,9
Then[35]	2012	29	b	34,5	65,5
Thumbigere-Math[36]	2012	576	iv	41	59
Vescovi[37]	2010	567	b	31,7	68,3
Vescovi[38]	2012	151	b	29,1	70,9
Wang[39]	2003	3	iv	33,3	66,7
Watters[40]	2012	109	iv	33,9	59,7
Woo[41]	2007	368	b	40	60
Zarychanski[19]	2006	12	iv	17	83

IV, intravenously; OR, orally; B, both orally and intravenously.

Pamidronate (Aredia; Novartis, East Hanover, NJ, USA) was the bisphosphonate most frequently used intravenously. In the oral group Alendronate (Fosamax; Merck & Co., Whitehouse Station, NJ, USA) was most frequently used. There were 9 patients who had used both oral and intravenous bisphosphonates (Table II). These patients were counted in the intravenous group, for intravenous bisphosphonates are far more potent than bisphosphonates taken orally and therefore more at risk for BRONJ.

Initiating factors

In Table II the luxating moments are listed. In 97.8% (n = 44) of the patients a dental focus was found. In 80.0% (n = 36) of the cases this was a certain dental focus. In 20.0% (n = 9) of the cases the dental focus was presumable according to the definitions listed earlier. In one case (2.2%) we were not able to trace a luxating moment, despite retracing the dental history. Case number 16 presented with a fistulating swelling underneath an ill-fitting denture. No patients were found with a history of spontaneous exposed bone.

DISCUSSION

In literature many authors show a high percentage of spontaneous causes of BRONJ. Recently there is a rising percentage of dental causes of BRONJ. Since the cause of BRONJ may influence the treatment choices we studied all possible initiating factors of BRONJ. They were categorized in: “a certain dental focus,” “a presumable dental focus,” “spontaneous,” and “an unknown dental focus” in order to give us more insight in the mechanisms of the etiology of BRONJ. In none of the patients we found a convincing spontaneous origin. In 97.8% of the patients a certain or presumable dental focus was found. In our series as well as in the literature, there seems to be no difference between the causes in the intravenous and the oral bisphosphonate group.

Our findings correspond with those of a few authors in the literature[11-19]. Most of the authors report a higher percentages of spontaneous cases (Table III), varying from 14.1% to 60%[2,20-40]. This may be due to the fact that it is difficult to establish the initiating factor in some patients. For example, in our series 1 patient (2.1% classified as ‘unknown dental focus’) presented with a fistulating swelling underneath an ill-fitting denture, making gingival trauma due to trauma likely. The question remains whether the swelling caused the denture not to fit, or the ill-fitting denture caused gingival trauma and hence an inflammation and swelling. In this case the information to make it ‘certain or presumable’ could not be traced.

In the category ‘certain dental origin’ patients had procedures, which created a direct port d’entree for microorganisms to enter the jaw. This is in line with the pathogenesis of osteomyelitis of the jaw with a common dentoalveolar start of the disease and subsequent spreading throughout the jaw. In these cases early treatment gives good results[41-44]. When the pathogenesis of BRONJ resembles the pathogenesis of chronic osteomyelitis, early treatment according to

the principles of the treatment of osteomyelitis should give better results than those reported in the literature of BRONJ so far. In fact several authors as Alons[41], Williamson[42], Wilde[43], and Voss[44] already have shown to be able to cure a high percentages BRONJ, thus strongly suggesting a pathogenesis of the disease similar to the "ordinary" osteomyelitis. All patients of this series were treated according to the protocol reported by Alons[40].

In the category 'presumable dental origin' several patients were found with prosthetic problems leading to trauma to the overlying soft tissues thus presumably leading to a BRONJ. Possibly many of the 'spontaneous' cases found in the literature belong to this category[2,20-40].

In conclusion a spontaneous origin of BRONJ has not been found in this series of patients. In 44 patients (97.8%) a dental origin was found. This may lead to a treatment approach as in chronic osteomyelitis with more aggressive surgical intervention with better treatment results, which has already been suggested in the literature.

However, this conclusion is based on a relatively small, retrospective study. Further research is mandatory.

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3

Dental implants as a Risk Factor for Medication Related Osteonecrosis of the Jaws (MRONJ)

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ABSTRACT

INTRODUCTION

Recently, an increasing number of cases of medication related osteonecrosis of the jaws (MRONJ) have been reported. It is still debated whether the presence or placement of dental implants can lead to MRONJ. The aim of this study is to investigate whether dental implants are a risk factor for MRONJ.

METHODS

From January 2003-January 2019 180 patients with MRONJ were seen at the Leiden University Medical Center. Retrospectively, luxating moments for the onset of MRONJ were determined. Clinical data and details of anti-resorptive medication use were collected; 22 patients with dental implants and MRONJ were found. In 18 patients the implants were located in the region of the MRONJ.

RESULTS

18 patients were included in this study. 77.8% received dental implants prior to anti-resorptive drug use and 22.2% had anti-resorptive drug use before or at the time of implant placement. The median time between the placement of implants and the diagnosis of MRONJ in these two groups was 24 months and 6 months respectively. Among 47 implants present in these patients, 30 were located in the necrotic region. All these 30 implants were either lost spontaneously or had to be removed during treatment of MRONJ.

DISCUSSION

This cohort study shows an increased risk for developing MRONJ in patients with dental implants. Both peri-implantitis around previously placed implants and insertion of dental implants can be seen as risk factors. Therefore, prevention of peri-implantitis and caution when indicating dental implants in patients that use anti-resorptive medication are important.

INTRODUCTION

Bisphosphonates and denosumab have become very common in the oncologic field, both as anti-resorptive medication and as neoadjuvant therapy. They are also still the drugs of choice in the treatment of osteoporosis. Although the exact mechanism of action differs, bisphosphonates as well as denosumab are responsible for a direct and strong decrease in osteoclast activity and thus in bone resorption. One of the most debated side-effects of this type of anti-resorptive medication is medication related osteonecrosis of the jaws (MRONJ). MRONJ can be difficult to treat and further insight in its cause and approach to treatment are needed. Ever since the first publication on MRONJ there has been discussion on its origin[1-4], especially whether it is spontaneous or related to dental procedures and/or pathology. There have been reports showing that the presence or the placement of dental implants can initiate MRONJ, especially in patients with intravenous bisphosphonate use[4-10]. Studies have been published that describe MRONJ in patients who use oral bisphosphonates[6, 7, 10]. Several authors[9, 11-16] however found no increased risk for implant failure in patients with oral bisphosphonate use.

The association between MRONJ and dental implants is still unknown. It is not yet clear whether the use of anti-resorptive medication is a contra-indication for the placement of dental implants. The aim of this study was to investigate implants as a possible risk factor for MRONJ in patients seen in our center. All MRONJ patients in this study were surgically treated according to our previously reported protocol[17-19].

METHODS

180 consecutive patients presenting with MRONJ at the department of Oral and Maxillofacial Surgery of the Leiden University Medical Center between January 2003 and January 2019 were studied.

For inclusion in this study a diagnosis of MRONJ according to the criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS) was a required. MRONJ was diagnosed when there was exposed bone present for more than 8 weeks, current or previous anti-resorptive drug use and no history of radiation therapy in the head and neck region[20].

Patients

All patients with dental implants and MRONJ from our cohort were collected. Only patients with one or more dental implants in the necrotic region were included. Their implant history was studied and protocolled clinical and radiographic analysis was performed. Possible peri-implantitis was studied. This was described as local gingivitis, an infrabony pocket and an angular bony defect around the implant.

The following patients characteristics were analyzed as well: sex, age, medication use, co-morbidity, type and duration of anti-resorptive medication and the type of treatment of MRONJ prior to referral of the patient to our department.

Treatment

The patients were treated following our previously reported[17-19] protocol with a combination of surgery and antibiotics. The surgical outcomes were studied. Healing was defined as a closed mucosa without a fistula or pain.

Statistics

For continuous variables median and range were recorded. Statistical analyses were performed in SPSS (Version 25; SPSS Inc., Chicago, IL, USA). Data are reported in median unless reported otherwise.

RESULTS

Among the 180 MRONJ patients, 22 patients had dental implants and 18 (10%) had implants in the necrotic area and were included in our study. The clinical characteristics for the 18 patients are listed in table I-III.

Clinical features

There were 15 female patients and 3 male. Age varied from 52-86 with a mean of 68,5±9 years.

Eleven patients (57,8%) used anti-resorptive drugs for osteoporosis and the remaining for cancer (42,2%). Five patients used anti-resorptive drugs for metastasized breast cancer, 2 for multiple myeloma and 2 for metastasized prostate cancer.

Stage II was seen in 50% (n=9) of the patients and no statistical difference was found between stage and indication (p=0.629), (see table I).

The median duration of use of anti-resorptive medication in the oral bisphosphonate group was 60 months (range 18-120). The intravenous bisphosphonate users and the denosumab users respectively had a median duration of 18 and 24 months. Oncologic patients seem to have a shorter time of anti-resorptive medication use until development of MRONJ. However, the data was not normally distributed, therefore further statistical analysis was not conducted. The specific durations can be seen in table III.

Duration of symptoms had a median of 6 months (3-48) for cancer patients and a median of 8 months (2-84) with osteoporosis patients.

Preservation of implants was found in 28,6% (n=2) in cancer patients and in 71,4% (n=5) in osteoporosis patients. The location of preserved implants was mostly seen in the mandible in

Table I Clinical features

	Cancer	Osteoporosis	Total	p-value
Gender				0.280[C]
Female	5	10	15	
Male	2	1	3	
	7	11	18	
Indication			18	
Osteoporosis		11	11	
Cancer	7		7	
Breast cancer	5			
Prostate cancer	2			
Anti-resorptive medication			18	
Bisphosphonates		15		
Intravenous use		5		
Zolendronic acid monthly		1		
Zolendronic acid yearly	1			
Pamidronic acid monthly		3		
Oral use		10		
Alendronic acid 70mg weekly		8		
Risedronic acid 35 mg weekly		2		
Denosumab-subcutaneous use			3	
Xgeva 120mg monthly	3			
Prolia 60mg every 6 months				
Stage[1]				0.629[C]
II	3	6	9	
III	4	5	9	
	7	11	18	
Duration of medication (months)	18 (7-24)	60 (18-168)		
Duration of symptoms (months)	6 (3-48)	8 (2-84)		
Preservation of implants				0.513[C]
Loss	5	6	11	
Survival	2	5	7	
	7	11	18	
Location of preserved implant				0.468[C]
Mandible	2	4	6	
Maxilla		1	1	
			7	
	2	5		

[C]=Chi-square-test, not statistically significant

[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)

Table II Patient characteristics

Nr	Indication	Location implants/MRONJ	Cause MRONJ	Lost implants (placed implants)
1	OP	Mand ant	P	4 (4)
2	MM	Mand ant	P	2 (2)
3	BC	Max post	P	2 (2)
4	OP	Mand ant	T	1 (2)
5	BC	Max ant	P	1 (1)
6	OP	Max post	T	1 (6)
7	OP	Max post	P	2 (2)
8	OP	Max ant	T	1 (1)
9	OP	Mand ant	P	2 (2)
10	PC	Mand post	P	1 (3)
11	OP	Mand ant	T	1 (4)
12	BC	Max post	P	1 (1)
13	OP	Mand ant	P	2 (2)
14	PC	Mand ant	P	1 (1)
15	OP	Mand ant	P	1 (4)
16	OP	Mand ant	P	2 (2)
17	OP	Mand ant	P	1 (4)
18	BC	Mand ant	P	4 (4)

Nr= Patient number,
Indication of anti-resorptive medication: OP= osteoporosis, MM= multiple pyeloma, BC= breastcancer, PC= prostate cancer
Location of implants/MRONJ, mand= mandible, max=maxilla, ant=anterior, post=posterior
Cause of MRONJ: P= peri-implantitis; T=traumatic with insertion of implants
Number of Lost and placed implants

85,7% (n=6), but also in osteoporosis patients in 71,4% (n=5). No statistical difference was found between the groups (see table I).

Implant features

Fourteen patients (77,8%) were implanted before the use of anti-resorptive drugs. These patients had osseointegrated and functioning dental implants before the onset of MRONJ. However, they developed peri-implantitis around the implants which evolved into MRONJ after some time of anti-resorptive drug use. The median time of onset of MRONJ in this group was 24 months (range 7-120) after the start of anti-resorptive medication. In some patients implants had already fallen out at presentation due to the extensive peri-implantitis and bone loss. Other patients had typical peri-implantitis with bleeding on probing, deep pockets and mobile implants.

Four patients (22.2%) received dental implants during anti-resorptive medication use. They developed MRONJ shortly after insertion of the implants. The median time of onset of MRONJ in this group was 6 months (range 3-6). The median use of anti-resorptive medication in this

Table III Characteristics risk factors MRONJ

Cause MRONJ	Administration manner	Duration of complaints	Duration of AR therapy
Peri-implantitis (n=14)	PO (n=6)	10 (2-84)	56 (18-120)
	IV (n=5)	20 (5-48)	18 (12-60)
	SC (n=3)	6 (3-6)	24 (7-24)
Total P	(n=14)	9 (2-84)	24 (7-120)
Trauma (n=4)	PO (n=4)	5 (3-13)	72 (36-168)
Total T	(n=4)	5 (3-13)	72 (36-168)

Risk factors MRONJ: P= peri-implantitis, T=Trauma due to insertion of implants
Administration manner: po=oral bisphosphonates, iv= intravenous bisphosphonates, sc=subcutaneous denosumab
Duration of complaints in months: median (range)
Duration of AR therapy until MRONJ in months: AR= anti-resorptive, median (range)

group was 72 months (range 36-168). The 18 patients in our study group initially had a total of 47 implants. 30 (64%) of the implants were lost. Most of the implants were already lost before referral. The remaining implants involved in the necrosis were removed during surgery.

Treatment outcome

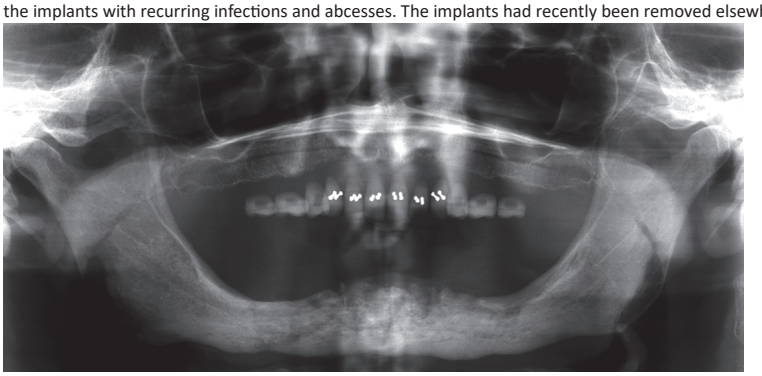
Fifteen patients were admitted to our hospital, underwent sequestrectomy and remained hospitalized for one week for intravenous antibiotic therapy followed by two weeks of oral antibiotics. Three patients were treated in the outpatient clinic. The period of follow-up was at least 3 months postoperatively. One case is shown in figures 1-3.

Seventeen patients had a closed and healed mucosa and were free of complaints after a minimum follow-up of 3 months. The follow-up had a median duration of 12,5 months (range 3-36). One patient died during follow-up after three months due to metastasized disease.

In seven patients a total of 17 implants, close to but not involved in the necrosis, could be preserved. There was a stage III MRONJ patient who developed a pathologic fracture after surgery where fixation was carried out and a pseudarthrosis could be achieved without further complaints.

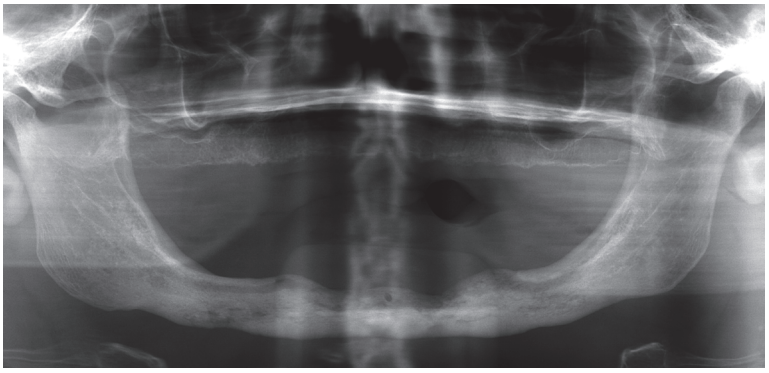
Figure 1 Patient with BRONJ of the mandible

Case Female 65 years old with osteoporosis and dental implants inserted in the region of the lower cuspids 8 years before and anti-resorptive medication use since 48 months. At presentation in our hospital she had a history of 4 years of complaints of the implants with recurring infections and abcesses. The implants had recently been removed elsewhere.



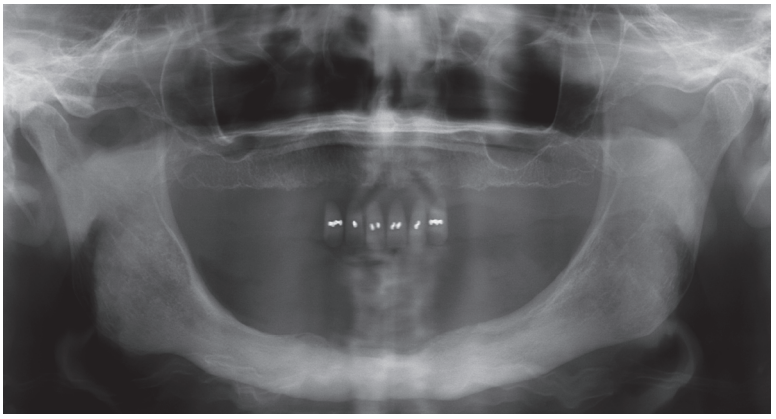
Pre-op panoramic radiograph shows osteolysis and sequestration in the mandibular symphysis

Figure 2 Panoramic radiographs of immediately postoperative from patient fig 1



Panoramic radiographs immediately postoperative after saucerization with visible smooth contours of the bone

Figure 3 Panoramic radiographs 2 years postoperative from patient fig 1



Panoramic radiograph shows smooth edges and healing of bone. There is a suggestion for regeneration of the bone in the mandible.

DISCUSSION

The purpose of this study was to establish whether dental implants could be a cause for MRONJ. The hypothesis is that dental implants can be related to MRONJ. Further clinical & implant features were studied and the treatment outcomes were analyzed.

The results of this study confirm the hypothesis that dental implants can be related to the development of MRONJ. We found 2 major risk factors: peri-implantitis (77.8%) and insertion of dental implants (as a surgical trauma) (22.2%). Peri-implantitis leading to MRONJ was observed with the anti-resorptive drug use after insertion of implants. With placement of implants MRONJ was seen during or after anti-resorptive therapy.

This study shows that osseointegrated and functioning dental implants, present at the start of anti-resorptive medication use may initiate the development of MRONJ when there is peri-implantitis. The insertion of dental implants during anti-resorptive medication use led even faster to the development of MRONJ.

More than sixty percent of the implants were lost. All lost implants were located in regions of MRONJ. In cases where not all implants were located in the region of osteonecrosis, early intervention seemed to save close implants. Based on these results, caution with placement of dental implants and a strict dental hygienic regiment and follow-up seems necessary, to prevent development of MRONJ.

In literature there are several possible risk factors for implant failure. Implant loss is reported to be more often seen in the mandible[21-23], but our results could not confirm this. On the contrary, our results shows survival of implants in osteoporosis and the mandible. This suggests that when there is no peri-implantitis MRONJ will not develop spontaneously.

The time elapsing between implant insertion and the onset of MRONJ seemed more than 3 times longer in the osteoporosis patients than in the cancer patients. High doses of anti-resorptive medication is usually intravenously administered to oncologic patients. Together with the often compromised general medical condition of cancer patients it may explain the higher risk of MRONJ when dental implants are present or inserted.

The median time of anti-resorptive medication use in the peri-implantitis group reflects the time necessary for the bone to become susceptible or prone to MRONJ. This time is similar to the reported duration of medication use before development of MRONJ as stated by other authors[1, 3]. Patients with a shorter period of medication use may not have developed MRONJ yet and were therefore not seen with MRONJ. The period of time from insertion of the implant(s) to the initiation of the anti-resorptive drug therapy in the peri-implantitis group seems irrelevant, because implants were sometimes already functioning for more than 5 years in our patients before anti-resorptive medication was started.

Considering the increasing number of reports on implant related MRONJ an association between implants and the development of MRONJ becomes more evident[7, 8, 10, 21, 22, 24]. There is a tendency in the literature to focus on two main causes for MRONJ in relation to dental implants.

Firstly, MRONJ seems to be related to peri-implantitis around dental implants that were placed before anti-resorptive medication was started. Secondly, MRONJ seems related to the insertion of implants in patients with anti-resorptive medication use. These risk factors are confirmed in this study and in other reports[7, 8, 10, 12, 22]. It is still unclear which of these two factors are more associated to the risk of MRONJ. Further longitudinal research it is required to investigate whether peri-implantitis in patients that use anti-resorptive medication can be stabilized and so prevent development of MRONJ.

There is no consensus on placement of implants during bisphosphonate therapy. However, literature shows no hard contra-indications for placement of dental implants in combination with oral bisphosphonate use[10]. Several authors show good results of dental implants in combination with anti-resorptive therapy with even reports of large series of patients with oral bisphosphonate use and implant placement without or with just a few failed implants[5, 11-16, 25-27]. No increased risk was found for MRONJ in relation to dental implants. Madrid & Sanz (2009) report that it is safe to undergo dental procedures such as the insertion of dental implants with oral bisphosphonate use for a duration of less than 5 years[5]. In a few reports development of MRONJ in patients with implants after bisphosphonate use was not observed[28]. Due to the heterogeneity of the studies, however there is not enough evidence in literature to draw conclusions regarding implant insertion in patients with anti-resorptive medication or in relation to MRONJ[16]. This may suggest a possibly smaller risk for the development of MRONJ with oral bisphosphonate use than assumed earlier. The insertion of dental implants under the right circumstances and precaution measures seems justified.

This study among others[5, 6, 10, 24, 29, 30] also reports extensive failure of implants and development of MRONJ and possible loss of parts of the jaw(s) when anti-resorptive medication are used including users of oral bisphosphonates. In these “high risk” patients with anti-resorptive therapy reserve should be taken when planning dental implants and good dental hygiene and follow-up of dental implants is recommended. Early surgical intervention of MRONJ may save adjacent dental implants. Considering all the risks treatment in a specialised centre is advised.

CONCLUSION

There is an increased risk for development of MRONJ due to the insertion of dental implants and due to peri-implantitis. These two risk factors seem to contribute to the overall risk of MRONJ. Overall, the use of intravenous anti-resorptive medication is more likely to lead to implant failure and MRONJ than the use of oral anti-resorptive medication. MRONJ due to these two risk factors can lead to considerable morbidity including loss of parts of the jaw. Therefore prevention is important. Further research regarding dental implants as a risk factor for the development of MRONJ is recommended.

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4

A comparison of the CBCT findings in MRONJ related to denosumab versus bisphosphonates: an observational pilot study.

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ABSTRACT

INTRODUCTION

The aim of this study was to compare the radiographic abnormalities on cone beam computed tomography (CBCT) in patients with medication-related osteonecrosis of the jaws (MRONJ) related to denosumab use versus bisphosphonate use.

METHODS

The study included 34 consecutive patients with MRONJ who had a history of exclusive use of denosumab (n = 17) or bisphosphonates (n = 17) and had undergone CBCT for determination of extent of disease. Demographic data of the patients were collected. Differences in radiologic characteristics between patients with denosumab-related osteonecrosis of the jaws (DRONJ) and those with bisphosphonate-related osteonecrosis of the jaws (BRONJ) were scored and studied on CBCT.

RESULTS

In patients with DRONJ, sequestra (P = .015) and lysis of the cortical border of the jaw (P = .033) were significantly less common than in patients with BRONJ. Subperiosteal bone formation did not differ between the groups (P = .545). There was no association between stage of disease and duration of drug therapy or duration of symptoms for either medication group.

CONCLUSIONS

The radiologic features of DRONJ may be different from those of BRONJ with regard to the presence of sequestra and cortical lysis and might, therefore, be improperly diagnosed. Underestimation and undertreatment of DRONJ may potentially lead to progression of disease and, thus, make treatment more difficult.

INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is a serious condition that causes severe morbidity. MRONJ is the collective term that includes necrosis of the jaws related to all forms of anti-resorptive medications including bisphosphonates (BRONJ)[1, 2] and Denosumab (DRONJ),[3-5] as well as anti-angiogenic medications such as Sunitimib and Bevacuzimab[6].

There is an ongoing debate on the etiology and best treatment for MRONJ[2, 7-9]. When diagnosing[2, 6] MRONJ, the first diagnostic procedure performed in daily clinical practice is usually a panoramic radiograph (PR). This provides an immediate view of the lesion, its location, and its size. A disadvantage of PR is that minor lytic lesions in bone can be undetected[10, 11]. Cone beam computed tomography (CBCT) is frequently used to determine the extent of the disease. It provides more detailed information regarding the size of the lesion and exposes the patient to less radiation than multidetector CT. Radiological features on CBCT for BRONJ have been well described and include thickened lamina dura, sclerosis, subperiosteal bone formation, sequestra, a visible inferior alveolar canal, and lysis of the cortical border of the jaw(s)[12-21]. Some of these findings, in particular sequestra, subperiosteal bone formation, and lysis of the cortical border, are decisive for the diagnosis of MRONJ. The remaining features such as thickened lamina dura or visibility of the inferior alveolar canal provide information regarding the effect of the anti-resorptive medication on the bone in general[6, 9].

Denosumab is another anti-resorptive agent used to treat osteoporosis (e.g., Prolia 60 mg every 6 months) or to treat or prevent skeletal complications in malignancies (e.g., Xgeva 120 mg up to every month). Denosumab has been shown to lead to clinical features comparable to BRONJ.

The specific radiological findings in DRONJ are less well described than in BRONJ. There is only one study reporting on differences between these 2 medications. A significant difference was reported in the presence of subperiosteal bone and the size of sequestra in DRONJ[22]. However, there was no significant presence of sequestra in DRONJ. A difference in mechanism of action between both drugs may cause a different radiographic presentation. Both anti-resorptive drugs have effect on osteoclasts, but on different levels.

Bisphosphonates inhibit bone resorption. The nitrogen-chain will form a covalent bond with bone mineral. Due to the attachment to bone, bisphosphonates have a long half-life and will stay active for years after administration. When an osteoclast, which is responsible for resorption of bone, ingests a bisphosphonate, the osteoclast will malfunction and eventually go into apoptosis. Bisphosphonates lead to a decrease in osteoclast number and function and will thus inhibit bone resorption[23].

Denosumab is a RANK-L inhibitor. RANK-L, when binding to the osteoclast cell membrane, activates osteoclasts and leads to maturation of preosteoclasts to osteoclasts. Denosumab binds

RANK-L, causing immediate cessation of the osteoclast function and preosteoclast differentiation and thereby inhibits of bone resorption[24, 25]. Unlike bisphosphonates, the effect is temporary[6]; after six months osteoclast activity will start over.

This underlying difference in mechanism of action may cause a difference in radiological features. Therefore the objective of this pilot study was to compare the frequency and/or severity of the most relevant radiological features detected on CBCT examinations in patients with osteonecrosis of the jaws who had taken denosumab versus those who had taken bisphosphonates. The null hypothesis stated that there are no differences in frequency or severity between the two groups of patients for any of the radiological features.

METHODS

Patients

MRONJ patients, classified according to the criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS)[6] into 4 stages of the disease as listed in Table I, who presented between January 2012 and January 2018 at the outpatient clinic of Oral & Maxillofacial Surgery

Table I: Criteria and Classification Stages MRONJ and recommendations adapted from Ruggiero et al., 2014 (AAOMS)[6]

Criteria MRONJ
-Current or previous treatment with antiresorptive or antiangiogenic agents
-Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
-No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

MRONJ stage	Description	Treatment strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
Stage I	No symptomatic lesions or bone exposure in the absence of signs of infection	Topical antiseptic therapy Follow-up
Stage II	Bone exposure with pain, infection, and swelling in the area of the lesion	Oral antibiotics, antibacterial mouth rinse, pain control Superficial debridement to relieve soft tissue irritation
Stage III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

were included in the present study. Only patients exclusively using bisphosphonates (BRONJ-group) or denosumab (DRONJ-group) were included. Patients with a recent or previous combination of anti-resorptive drugs were excluded.

Demographic data and clinical features including sex, age, indication for drug therapy, anti-resorptive medication regimen, duration of drug therapy, duration of symptoms, and stage of the disease, were collected for patient characterization.

CBCT

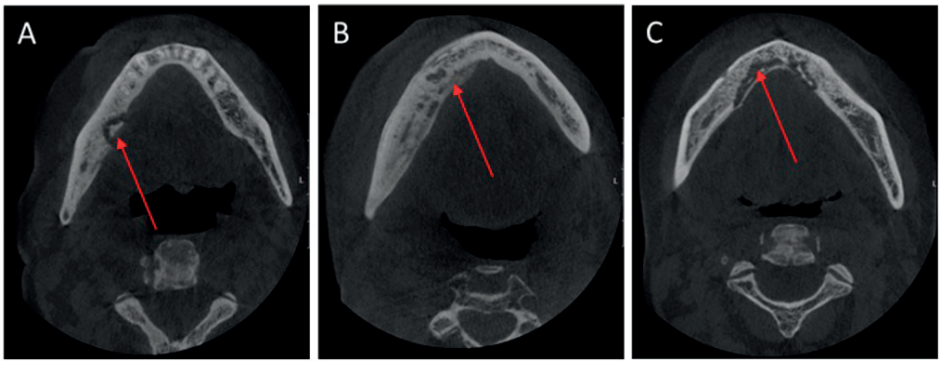
In our center all newly presenting MRONJ patients undergo PR and CBCT. For all patients, the Promax 3D Planmeca cone beam CT scanner was used (Promax® 3D Max, Planmeca USA, Roselle, IL), with exposure parameters of 96 kV, 5.6 mA, 12 s exposure time, FOV 13 x 5.5 cm, voxel size 200µm. The scan volumes were exported in Digital Imaging and Communications in Medicine (DICOM) format and imported into Planmeca Romexis 5.1.1.1dental imaging software (Planmeca, Helsinki, Finland).

Radiological features

CBCT scans were examined for osseous abnormalities previously reported in BRONJ: sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaw(s).

These variables were classified as “present” or “absent” with a 2-point-scale: 0= not present, 1= present (Figure 1).

Figure 1 MRONJ changes on axial view CBCT



A=sequestrum
B=subperiosteal bone formation
C=lysis of the cortical border

All CBCT scans were examined and scored according to this classification by 2 experienced oral and maxillofacial surgeons together, who were blinded to the patients’ clinical status and anti-resorptive medication use. Differences were resolved by consensus, so the Kappa statistic for interexaminer agreement could not be calculated.

Statistics

For continuous variables (duration of drug therapy and duration of symptoms), median and range were calculated. Statistical analysis to evaluate categorical data for group differences was performed with the chi-squared test for sex, indication for drug therapy, stage of the disease, and scores for the presence of sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaws. A logistic regression model was used to assess the effect of the duration of the drug therapy on the duration of symptoms, stage of the disease, and the radiological features; and to assess the relation between the duration of drug therapy and stage. Statistical analysis was performed in SPSS software for Windows (Version 23; SPSS Inc., Chicago, IL). A p-value <0.05 was considered significant.

RESULTS

Patient characteristics (Table II)

From 2012 to 2018, 50 new patients with MRONJ presented to our outpatient clinic, of whom 34 fulfilled the inclusion criteria. The median age was 69 (range 49-86) years. Of the included patients, there were 21 females and 13 males. Denosumab and bisphosphonates were each exclusively used by 17 patients.

Thirteen patients were treated for osteoporosis, and the rest was treated for malignancies: ten for breast cancer, ten for prostate cancer and one for lung cancer. In the Denosumab group only 1 out of 17 patients used the drug for osteoporosis versus 11 in the bisphosphonate group, ($p<0.001$), meaning more widespread anti-osteoporotic drug use in the bisphosphonate group. Five patients had intravenous use of bisphosphonates for malignancies. The remaining twelve patients had osteoporosis and used either oral bisphosphonates (n=10) or received a yearly intravenous dose (n=2). The regimens for Denosumab and bisphosphonates are summarized in the table.

Median duration of therapy before developing MRONJ was shorter in the Denosumab group (18 months, with a range from 8-48) then in the bisphosphonate group (42 months, with a range of 18-240). Because the data were not normally distributed, statistics were not performed. The median duration of symptoms was 6 months with Denosumab and 8 with Bisphosphonates. The duration of symptoms were also not normally distributed, therefore further statistical analysis was not performed either. Disease severity as indicated by stage was equally distributed between the groups ($p=0.169$) with 16 patients and 18 patients classified in stage II and III, respectively.

Table II Clinical features

	Denosumab	Bisphosphonates	Total	p-value
Age	69 (52-83)	69 (49-86)		
Gender				0.078[C]
Female	8	13	21	
Male	9	4	13	
Indication				<0.001*[C]
Osteoporosis	1	12	13	
Cancer	16	5	21	
Breast cancer	7	3		
Prostate cancer	8	2		
Lung cancer	1			
Duration of medication (months)	18 (8-48)	42 (18-240)		
Anti-resorptive medication				
Bisphosphonates			17	
Intravenous use		7		
Zolendronic acid monthly		4		
Zolendronic acid yearly		2		
Pamidronic acid monthly		1		
Oral use		10		
Alendronic acid 70mg weekly		9		
Risedronic acid 35 mg weekly		1		
Denosumab			17	
Xgeva 120mg monthly	16			
Prolia 60mg every 6 months	1			
Stage[1]				0.169[C]
II	10	6	16	
III	7	11	18	
Duration of symptoms (months)	6 (2-16)	8 (2-39)		

[C]=Chi-square-test
[I]=Independent T-sample test
*p<0.05 was considered statistical significant
[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)

Radiologic characteristics (Tables III and IV)

The CBCT scans of 17 consecutive DRONJ patients were compared to 17 consecutive BRONJ-patients.The DRONJ group had a significantly lower frequency of sequestra (70.6%) than the BRONJ patients, all of whom exhibited sequestra (p=0.015). Subperiosteal bone formation was present in 94.1% in the DRONJ-group. This was not significantly different from the incidence in of 93.3% in the patients taking bisphosphonates (p=0.545). Lysis of the cortical border was present in 76.5% of the patients treated with denosumab compared to 100% of patients treated with bisphosphonates, which was significantly different (p=0.033).

Table III Group results for radiological features

Medication	Sequestra scores (Cumulative percentage)	Subperiosteal bone formation scores (Cumulative percentage	Lysis of the cortical border of the jaw(s) (Cumulative percentage)
Denosumab	0=29.4% 1=70.6%	0=5.9% 1=94.1%	0=23.5% 1=76.5%
Bisphosphonate	0=0% 1=100%	0=6.7% 1=93.3%	0=0% 1=100%
Chi-square test	p=0.015*	p=0.545	p=0.033*

*p<0.05 was considered statistically significant

Statistics

Logistic regression showed no association between stage of the disease and duration of drug therapy for denosumab (p=0.813) or bisphosphonates (p=0.867). Nor for duration of symptoms and stage of the disease an association was found for denosumab (p=0.824) or bisphosphonates (p=0.501)

Additional analyses for the separate radiological characteristics of MRONJ (sequestra, subperiosteal bone formation, lysis of the cortical border) were not possible due to the small number of patients in the groups.

Table IV Logistic regression models

	Denosumab			Bisphosphonates		
Stage of disease	p-value*	OR	CI	p-value*	OR	CI
Duration of drug therapy	0.813	1.012	(0.919;1.114)	0.867	1.001	(0.985;1.018)
Duration of symptoms	0.824	1.028	(0.805;1.314)	0.501	1.041	(0.927;1.169)

*p<0.05 was considered statistical significant
OR=Odds Ratio
CI=confidence interval (95%)

DISCUSSION

The aim of this study was to analyse the most relevant radiologic abnormalities detected on CBCT between DRONJ and BRONJ. We observed that 2 characteristics of BRONJ, sequestra and cortical lysis, were significantly less prevalent in DRONJ patients. Another radiological characteristic often identified in BRONJ, subperiosteal bone formation, did not differ in prevalence between groups. Based on these results DRONJ may be unintentionally underdiagnosed, thereby leading to an unnecessary delay in treatment.

Radiologic features of BRONJ are clearly described in literature[6, 12, 14-21]. As mentioned, these include bone sclerosis, thickening of the lamina dura, lysis of the cortical border, prominence of the inferior alveolar nerve canals, and pathological fracture, in addition to the features of

sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaw(s) that were examined in this research. In the clinical setting of MRONJ, these 3 radiological features are considered pathognomic for the diagnosis of osteonecrosis of the jaws. Some differences between the specific medications have been reported by Baba et al, who reported CT imaging findings of 64 BRONJ patients compared to 10 DRONJ patients[22]. The results revealed that the presence of sequestra in the DRONJ group was not significantly different in frequency between the 2 groups but the sequestra were significantly larger. However, the small patient group of DRONJ was a limitation that made it difficult to interpret and generalize the results. Furthermore, the study showed absence of subperiosteal bone formation in BRONJ patients. This is in contrast to other reports in the literature in which subperiosteal bone formation is considered a relevant clinical and radiological feature for BRONJ[6, 9, 10].

The study, however, revealed that sequestra and cortical bone lysis were up to 30% less frequent in DRONJ patients than BRONJ patients. This may lead to underdiagnosis of DRONJ. If there are no visible sequestra or subperiosteal bone formation, a surgeon might inappropriately decide to delay treatment.

The different mechanism of action between Denosumab and bisphosphonates could be a possible explanation for these findings. Since osteoclasts are responsible for sequestra formation and lysis of the cortical border, the observed difference may lie in the fact that Denosumab is a more powerful inhibitor of osteoclast formation and activation then bisphosphonates[24, 25]. Therefore, the radiological features between BRONJ and DRONJ patients may differ. This is also extremely relevant for the treatment of DRONJ patients since in BRONJ the evident sequestration of bone demarcates the healthy bone margins. Without evident sequestration it is sometimes difficult to find the margins of viable bone, possibly leading to insufficient treatment in DRONJ cases.

As a small observational study in an academic referral center, this investigation has several limitations. In the DRONJ-group nearly all patients had an oncological indication for anti-resorptive use. Due to the absolute difference in dosing, monthly administration of Xgeva (120mg) compared to a half yearly dose of Prolia (60mg) for osteoporosis, one could argue that this is the cause of the observed differences. However, correction for treatment indications in the analyses' observed radiological differences is not possible due to the sample size. In addition, stage did not differ between groups, as were their total duration of anti-resorptive treatment. There was no association between stage and the duration of symptoms, but the present study did not have sufficient power to generalize this outcome. Since MRONJ is a condition of progressive nature, early detection in symptomatic patients remains of upmost importance. Despite these limitations, we believe the differences are clinically relevant and may hold implications for clinical daily practice. Whenever possible, a CBCT scan should be routinely done. Considering our observations, this would be of additional value, especially for stage 2 and stage 3 DRONJ patients, in diagnosing and treating DRONJ. CBCT is readily available and should be added to panoramic radiography to get more insight into the different clinical aspects of the disease in 3 dimensions[17,21,22].

The absence of sequestra and/or cortical bone lysis may unintentionally imply that there is no necrosis. This could potentially lead to the choice of a conservative treatment, which could lead to serious deterioration of the DRONJ[23-26] and then to a more difficult treatment.

CONCLUSION

This study indicated that Denosumab-related necrosis may present clinical and radiological features that differ from bisphosphonate necrosis. Sequestra and cortical bone destruction seems to be significantly less common in the Denosumab group versus the bisphosphonate group. This is an important finding, since underestimation and undertreatment of DRONJ potentially leads to deterioration of the disease and thus a more complicated clinical outcome.

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5

Denosumab osteonecrosis of the mandible: a new entity? A case report.

J Craniomaxillofac Surg. 2013 Jun;41(4):e65-9.

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ABSTRACT

In the treatment of osteoporosis, M. Kahler and bone metastases from prostate and breast cancer bisphosphonates play a major role. Not all patients respond well to bisphosphonate treatment. Since a few years adverse effects of these drugs have been reported. A new drug, denosumab, a fully human monoclonal antibody to RANKL, has recently been developed. This case reports a 74-year-old male patient with a medical history of diabetes mellitus, angina pectoris, coronary bypasses, hypertension, and prostate cancer with multiple metastases to lymph nodes, bone and lungs. The prostate cancer was treated according to the protocol. But he was never treated with bisphosphonates. Instead he was included in a phase III randomized double blind multicenter trial, testing the efficacy of denosumab compared to zoledronic acid in the treatment of bone metastases of hormone resistant prostate cancer. Only 7 months after start of denosumab infectious symptoms developed, followed by infestation of the mandible. Despite surgical treatment fistula and exposed bone remained. This case illustrates that use of denosumab can lead to a type of osteonecrosis resembling bisphosphonate related osteonecrosis of the jaws.

INTRODUCTION

In the treatment of osteoporosis multiple myeloma and bone metastases from prostate and breast cancer bisphosphonates play a major role. Bisphosphonates, particularly the use of intravenous bisphosphonates, reduce bone resorption by inhibiting osteoclast function, thereby reducing pain[1,2] and correcting hypercalcemia[3,4]. However, not all patients respond well to bisphosphonate treatment and even in those who do respond well, there is increasing awareness and reporting of the adverse effects of these drugs in the literature[5]. Many of these reports relate to concerns regarding gastrointestinal complaints, but more frequently 0,01%-9,1% osteonecrosis of the jaw is being recognised and reported[6]. This is a serious condition which can lead to loss of part if not all of the jaw even in the face of best known treatment. Intravenous use of bisphosphonates are limited in dosage because of their renal toxicity[7]. In addition bisphosphonates have a long half-life and once incorporated into the bone, remains effective for several years after intake. In the search for a better solution a new drug, Denosumab (Prolia, Xgeva: Amgen Europe), a fully human monoclonal antibody targeted to Receptor Activator of Nuclear Factor kB Ligand (RANKL), has recently been developed. RANKL has been found to act as the primary signal for bone removal[8-16]. Denosumab is more effective in inhibiting osteoclasts in comparison to bisphosphonates. Because there is no binding to bone, it potentially will reduce the long term effects associated with bone incorporation. Denosumab's binding to RANKL theoretically will produce a more physiologic action with hence fewer side effects. Its main indications for use are stated to be osteoporosis and bone metastases with the drug having recently been granted approval by the FDA for these indications.

There have been several publications on Denosumab, most reports investigate the effect of denosumab when compared to the effect of bisphosphonates. To our knowledge adverse effects of denosumab on the mandible or maxilla have received relatively little attention[12,17,18]. Osteonecrosis of the jaw may still be one of these adverse effects of denosumab, with the incidence of osteonecrosis of the jaw ranging from 0.9% to 5%[12,14,16].

We present a case of osteonecrosis of the jaw following denosumab treatment.

CASE REPORT

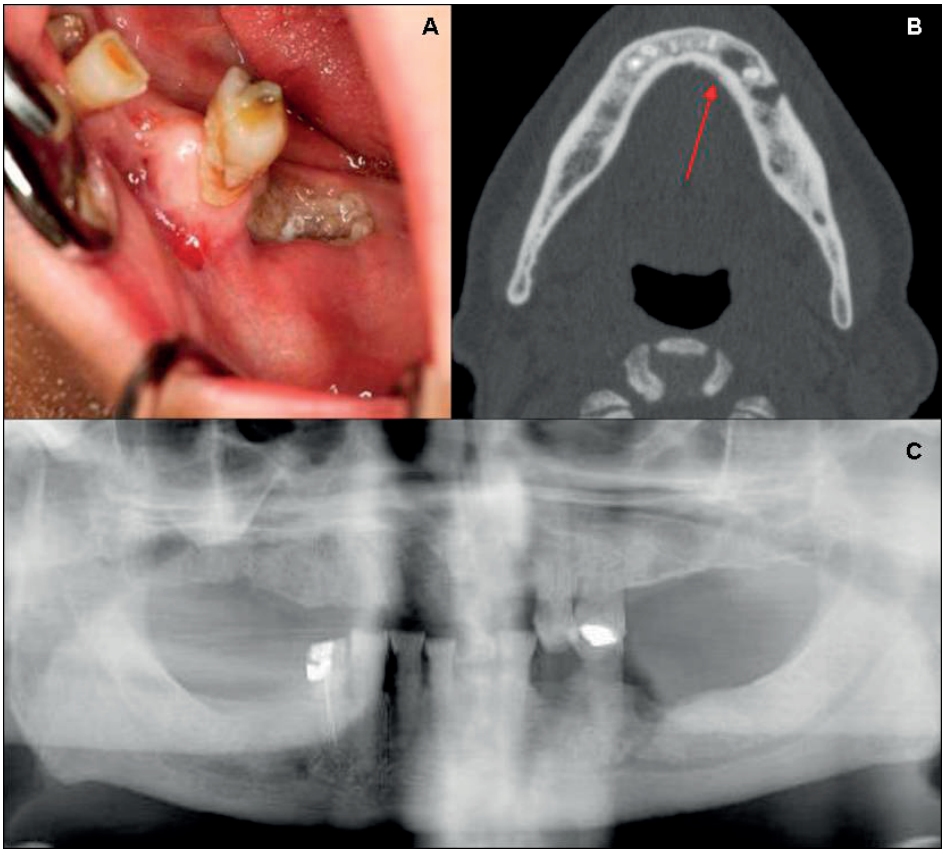
The patient was a 74 year old male, non-smoker who did not drink alcohol. The medical history included diabetes mellitus, hypertension, angina and subsequent coronary bypass in 1996, and prostate cancer in 1994. This was treated with a TURP and chemo-radiotherapy ending in 1995. Lung and skeletal metastasis were identified in 2007.Due to increasing PSA-values in 2000 the patient was treated with bicalutamide and gosereline; dutasteride and calcichew were also given. Bisphosphonates did not feature in his treatment.

In October 2007 he was enrolled into a phase III randomized double blind multicentre trial, testing the efficacy of denosumab with zoledronic acid in the treatment of bone metastases of hormone resistant prostate cancer.

In May 2008 a dehiscence of the oral mucosa developed in the lower left quadrant without sequestration of the underlying bone. In February 2009 he was admitted with swelling of the floor of mouth and tongue of infectious origin, this was treated with surgical drainage and antimicrobials amoxicillin and clavulanic acid (Augmentin). Because of ongoing symptoms he was referred to the Leiden University Medical Center in May 2009.

At presentation intra and extra-oral swelling and an area of brown-colored exposed bone was present in region 34 to 36 (figure 1A), The submandibular swelling later developed into an abscess with fistula. A panoramic radiograph and CT-scan showed sclerosis and lysis in the left mandible (region 33-35) and subperiosteal bone formation (figure 1B+C). Cultures showed

Figure 1 Intra-oral and radiological situation at first presentation in LUMC May 2009



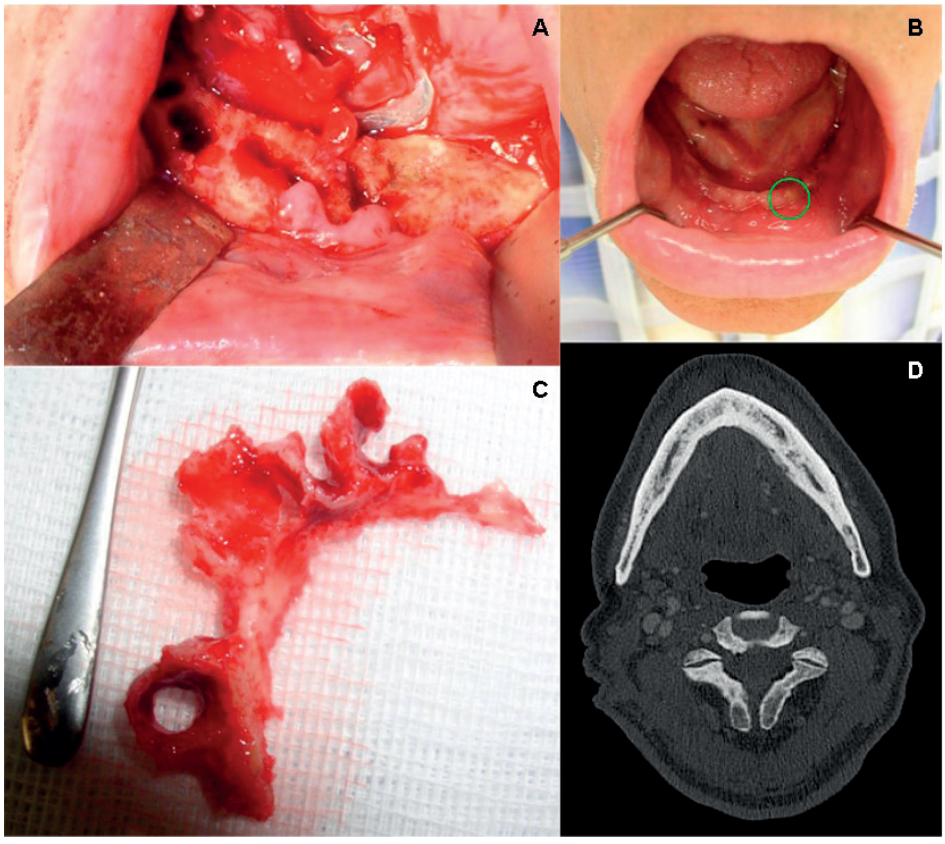
A. Intra-oral view: exposed bone.
B. CT scan: lysis regions 33/35, red arrow: subperiosteal bone formation.
C. Panoramic radiograph: lysis region 33/35.

mixed flora although Actinomyces was not found. The patient was treated by drainage of the abscess and antibiotics for four weeks.

Because of persisting symptoms a sequestrectomy was performed under general anaesthesia with removal of the remaining dentition from the clinically sclerotic bone. The lingual cortex and alveolar process particularly in region 34 to 36 appeared non-vital; bone was lowered and removed (figure 2A+C) until bleeding, relatively viable bone remained. The wounds were primarily closed in a multi-layer technique[5].

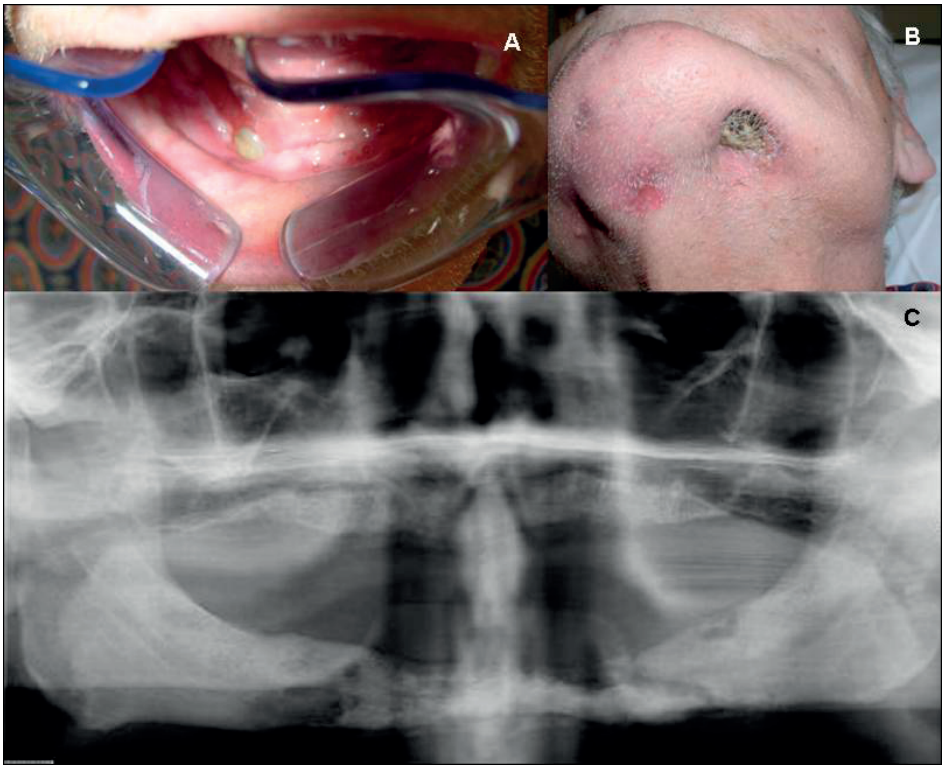
One fistula produced yellow grains, and new cultures at the time of surgery grew Actinomycosis. Penicillin and metronidazole were administered for five days intravenously followed by an eight week oral regime. Histologic examination of the bone showed necrotic bone and areas of extensive remodelling. A mixed-cell infiltrate and Actinomycosis were seen; there were no signs of metastases of the prostate cancer.

Figure 2 First surgery: intra-operative view of third quadrant



A. Intra-oral view in surgery. B. Intra-oral view 3 weeks after surgery with exposed bone, remaining fistula (circle). C. Removed non-vital bone from the alveolar process of the mandible at surgery. D. CT scan 6 weeks after surgery: subperiosteal bone formation at the lingual lower aspect of the left lower jaw.

Figure 3 Six weeks after second surgery



A. Intra-oral view with multiple fistulas and exposed bone. B. Extra-oral view with submental/submandibular fistula, with exposed bone. C. Panoramic radiograph with osteolysis, subperiosteal bone and pathologic fracture in the left lower mandible.

The research group organizing the phase III trial was asked to code break and reveal the drug given to the patient; it was Denosumab. Twice a year he received a subcutaneous injection with a dose of 60 mg Denosumab.

Three weeks after surgery there were again two small areas of exposed bone in the 35 and 44 region (figure 2B), with a discharging extra-oral fistula. Pain had however slowly diminished.

Six weeks after surgery a CT scan showed no large abnormalities besides subperiosteal bone formation (figure 2D).

Sixteen weeks after the first surgery the extra-oral fistula had not disappeared and bone could be probed through it; with new abscess formation a second surgery was performed. During exploration from area 36 to 46 a significant amount of subperiosteal bone formation was seen on both buccal and lingual surfaces. The entire region showed barely bleeding bone and greyish marrow. As much affected bone as possible was removed, up to the point of risking loss of continuity. Again, the wounds were primarily closed in layers. Histologic findings were similar to the first surgery. Cultures showed Streptococcus constellatus, Fusobacterium and Actinomyces, all sensitive to Penicillin, which was given intravenously for five days combined with metronidazole. Amoxicillin was prescribed orally for a further three months.

On the first postoperative day the patient developed neurologic symptoms, found to be as the result of cerebral metastasis of the original prostate cancer (confirmed histologically). He underwent craniotomy to decompress the lesion, the patient recovered and was discharged for rehabilitation.

He was followed up in the out-patient clinic. Complaints of pain had diminished, but the extra-oral fistula and intra-oral dehiscence remained and were slowly progressive (figure 3A+B). The panoramic radiographs showed a slowly deteriorating mandible as shown in figures 3C. Eleven months after the first surgery the patient died of brain metastases from prostate cancer.

DISCUSSION

Bisphosphonates are currently the first drugs of choice when treating bone metastases from e.g. prostate or breast cancer, multiple myeloma and osteoporosis[10]. Prostate cancer is the most common newly diagnosed cancer in men worldwide. Approximately 30 % of postmenopausal women in the US and Europe have osteoporosis[19], and yearly nearly 2 million hip fractures occur in the US as a result of this[20]. These numbers illustrate the large cohort of patients that are potentially eligible for these drugs. A recently highlighted, and well-reported side-effect of this treatment is bisphosphonate osteonecrosis[5].

A new drug in this field is Denosumab, a fully human monoclonal antibody to receptor activator of NF-κB ligand (RANKL), a cytokine member of the TNF family, and the principal mediator of osteoclastic bone resorption[10]. By binding to RANKL, Denosumab prevents the activation of RANK. This results in the inhibition of the maturation of osteoclasts and hence a decrease in their function and subsequent inhibition of osteoclast-mediated bone resorption. In trials it is delivered to the patient by subcutaneous injection several times a year with a dose varying from 60-120 mg[8,9,12-14,16].

Phase I, II and III trials in both patient categories have been published demonstrating that Denosumab has resulted in decreased levels of bone turnover markers[9,15] and significant increases in bone mineral density compared with placebo[9,21]. This has led to a decrease in occurrence of non-vertebral and hip fractures[8,9,15]. Further studies have shown that osteoporotic patients that have used alendronate and have switched to Denosumab have a significantly greater increase in Bone Mineral Density (BMD)[11].

A potential hazard of Denosumab might be that several non-skeletal cells, including activated T and B cells, also express RANK and RANKL; therefore Denosumab could have a negative effect on the immune system. Several Denosumab trials have monitored the side effects[8,9,12,14,16]. A higher incidence of serious adverse effects were found in the Denosumab group compared to the placebo group (34,6 % vs. 30,6 %)[9], this was not significant, although the former group did have a higher rate of infections requiring hospitalization and a higher occurrence of several skin-related conditions. Fizazi et al. showed serious adverse events of 63% vs. 60% of respec-

tively Denosumab vs. zoledronic acid, this was not significant either[12]. They also showed 2% (n=943) of osteonecrosis in the Denosumab group compared to 1% (n=945) in the zoledronic acid group, but with no significant difference. Smith et al. reported 5% (n=720) development of osteonecrosis of the jaws in patients who used Denosumab compared to zero osteonecrosis in patients receiving a placebo[14]. Saad et al. found a low incidence of osteonecrosis of the jaw with Denosumab of 0,9% (n=5723 patients)[16]. One study reported an increased incidence of cataract in the Denosumab group[9].

In this case, there was evidence of infectious symptoms only seven months after start of Denosumab followed by invasion of the mandible and established osteomyelitis not withstanding repeated antibiotic and surgical treatment. Our expectation was that the mandible would ultimately loose its continuity by sequestration.

Although there is an increasing body of literature about bisphosphonate related osteonecrosis, the exact mechanism by which it is caused and develops is still unclear and debated[22].

In this case report about the detrimental effects of Denosumab on the jaw bone a definite model of the working mechanism cannot be given either. However, the patient has not used any other medication aimed at influencing the bone metabolism by suppressing bone resorption. It is for this reason in our opinion there is a clear link between the drug and the disease. We feel reporting this serious, previously unknown side-effect has clinical relevance in the on-going debate on Denosumab.

CONCLUSION

The use of Denosumab may lead to a type of osteonecrosis resembling bisphosphonate related osteonecrosis of the jaws. This is a report of the upcoming serious side-effect of Denosumab.

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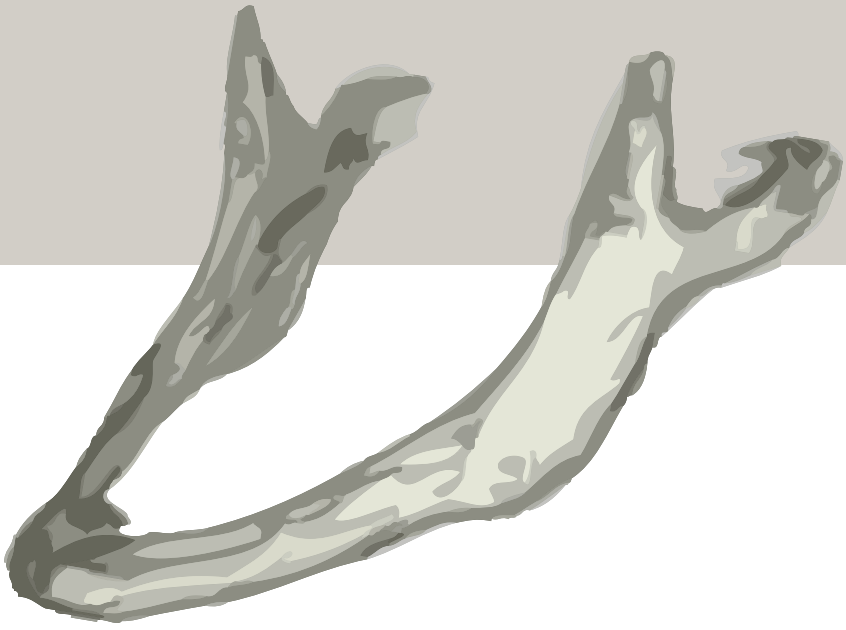

Part II

TREATMENT

6

Bisphosphonate-related osteonecrosis of the jaws: Cohort study of surgical treatment results in seventy-four stage II/III patients.

J Craniomaxillofac Surg. 2016 Sep;44(9):1216-20

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ABSTRACT

INTRODUCTION

Bisphosphonates are used in the treatment of osteoporosis and bone metastases. They inhibit osteoclast function, thereby decreasing bone resorption. A side effect of these drugs is bisphosphonate-related osteonecrosis of the jaw (BRONJ), which can be difficult to treat. The purpose of this study was to evaluate the surgical treatment protocol used in our hospital for BRONJ patients. The patients were retrospectively analyzed and followed-up at the Leiden University Medical Center.

METHODS

All patients who were referred to our hospital with therapy-resistant BRONJ between 2003 and 2014 were seen. At first presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were recorded. Patients underwent surgical intervention, performed by senior surgeons, following the principles of our previously published protocol.

RESULTS

Seventy-four patients were followed-up for 6-96 months. Curation was successful with this surgical approach in 93.2% of the patients.

DISCUSSION

All the patients were cured with our surgical protocol, for up to 5 years after surgery. We conclude that this treatment protocol has a high success rate in treating all stages of BRONJ.

INTRODUCTION

Bisphosphonates are medications used to treat osteoporosis and bone metastases. They decrease bone resorption by inhibiting the resorption function of the osteoclasts, and by causing apoptosis of the osteoblasts. In addition, they reduce pain, and resolve hypercalcemia in bone-metastasized cancer. Bisphosphonates are reported to have side effects, mainly gastrointestinal complaints. However, a rare but more severe side effect is the risk of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ). Many authors have claimed BRONJ to be difficult to treat. The first cases were reported in 2003[1]. Although several reports have since been published, the exact pathogenesis remains unclear. While some authors state that it has a spontaneous origin[2-4], others claim that it has a dental or a traumatic etiology[5-8]. Despite the difference in opinions on the etiology of BRONJ, the treatment recommendations are either, 1) non-invasive approaches[9,10], which involve treatment with antibiotics, or a chlorhexidine mouth rinse, or removal of loosened sequestra, or 2) invasive approaches with sometimes aggressive surgical methods that often involve resection of large parts of the jaw with free-flap osseous reconstructions. BRONJ, if untreated at an early stage, involves worsening of the symptoms with possibly serious consequences such as pathological fractures[9,11,12]. Recently more authors have promoted early surgical intervention[13-17].

The initial BRONJ patients in our institution were treated with a simple surgical intervention based on the treatment of chronic suppurative osteomyelitis (CSO) of the jaws. These patients seemed to respond very well to this treatment[18,19]. This treatment was based on the treatment of chronic suppurative osteomyelitis, which has a dental cause[19]. As mentioned earlier, BRONJ seems to show a dental cause, thereby strongly suggesting a similar pathogenesis of BRONJ and CSO. We believe that early surgical intervention produces the best treatment results in BRONJ. Therefore, the purpose of this study was to evaluate our combined surgical and antimicrobial method of BRONJ patients. Secondary outcomes were to characterize the patients by investigating clinical features, medication use, (dental) history and (previous) treatment.

METHODS

In this cohort study, consecutive patients referred from other clinics, presenting with therapy-resistant BRONJ, were treated and retrospectively analyzed. The study population consisted of all patients presenting for evaluation of BRONJ between January 2003 and December 2014 in the department of Oral & Maxillofacial Surgery of the Leiden University Medical Center. At presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were noted.

The inclusion criterion for this study was a BRONJ diagnosis according to the criteria stated by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[2]. This implies a recent use of bisphosphonates, the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, and no history of radiation therapy to the jaws. Further, a minimum bisphosphonate use of at least 12 months intravenously or 24 months orally was necessary for inclusion. The patients who used both oral and intravenous (IV) bisphosphonates were considered as IV users, for the purpose of this study.

The first aim of this study was to observe the result of our combined surgical and antimicrobial treatment.

Curation was classified as present or absent and defined as a situation with no complaints, and the presentation of a healed, closed mucosa. Additionally healing was classified as ideal if there was a closed mucosa within 2 weeks of surgery and non-ideal if a closed mucosa was reached after this amount of time or if needed an extra intervention (antibiotics or surgery). The patients were followed-up for at least 6 months: weekly in the first postoperative month; monthly, a month after; every 3 months, after 3 months post-surgery, up to a maximum of 5 years. During the follow-up the main focus was on the mucosa, and whether dehiscence or recurrence of the exposed bone had developed.

Secondary aims were to characterize the patients with BRONJ. Variables studied consisted of sex, age, bisphosphonate indication, duration of bisphosphonate use and administration manner. The duration of complaints and other medication (immunosuppressants, steroids, cytostatics) were studied. Clinical features (location and stage), dental history (luxating moment) and (previous) treatment were investigated. The collected data were statistically analyzed with SPSS.

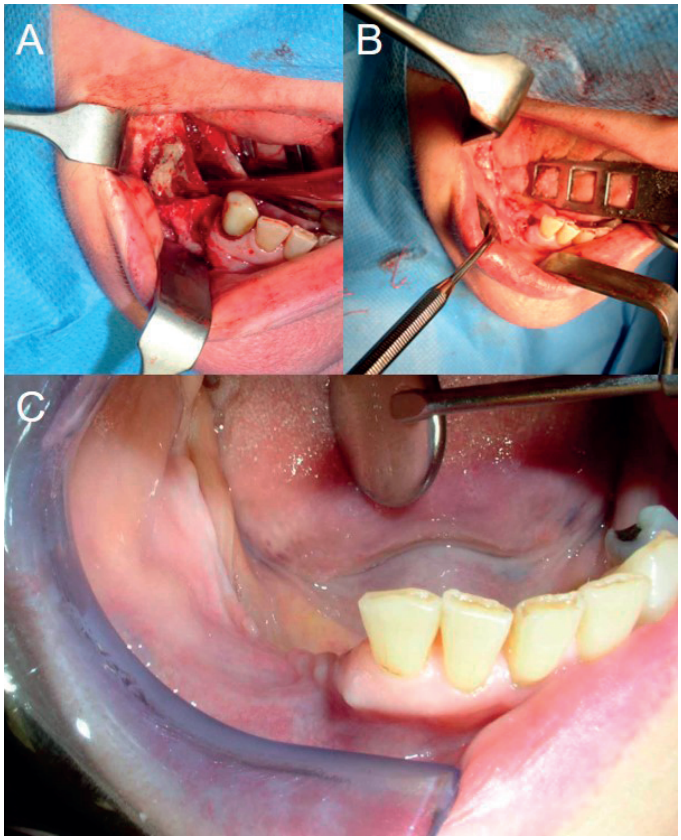
At presentation, panoramic radiographs were taken of all the patients to localize the lesion, and to gain a first impression of the lesion. Then, a computed tomography (CT) scan was used to determine the extent of the defect. The clinical features and the radiological findings, together, defined the stage of BRONJ, based on the AAOMS classification[10] (Table I). The patients with an absence of any radiological findings on the X-ray or CT scan, but with clinical bone exposure, were categorized as stage I. Radiological findings on the CT scans such as osteolysis and sequestra in the alveolar process were categorized as stage II. Osteolysis in large parts of the jaws or pathologic fractures was categorized as stage III.

The patients underwent surgical intervention as reported before[18,19]. Surgery was performed by senior surgeons. The surgical approach consisted of the removal of the sequestra, thorough surgical removal and saucerization of the non-vital bone until reaching the bleeding bone margins, and closing the defect primarily in layers (Fig. 1). This meant closing the periosteum as close to the bone as possible with mattress sutures, leaving no or as little dead-space as possible when

Table I Classification Stages BRONJ and recommendations by Ruggiero et al., 2009 (AAOMS)[2].

BRONJ stage	Description	Treatment strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
Stage I	No symptomatic lesions or bone exposure in the absence of signs of infection	Topical antiseptic therapy Follow-up
Stage II	Bone exposure with pain, infection, and swelling in the area of the lesion	Oral antibiotics, antibacterial mouth rinse, pain control Superficial debridement to relieve soft tissue irritation
Stage III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

Figure 1 Surgery



A: Preoperative sequestra and persistent extraction socket, B: Defect closed primarily in layers, C: Six months post-operation.

closing the overlying mucosa in layers. During the surgery, no gastric tube was placed, culture samples were collected, and the resected bone was submitted for histopathological analysis.

The surgical treatment was supplemented by the administration of the antibiotics, penicillin G and metronidazole, intravenously for 1 week, and amoxicillin and metronidazole, orally for 3 weeks.

Panoramic radiographs were taken immediately after surgery, and every 3–6 months, for up to 1-year after the surgery, in order to monitor the condition of the bone margins and the healing of the bone. After 1-year, an annual radiographic follow-up was considered sufficient.

Overlying dentures were not allowed during the first 12 weeks in order to avoid pressure and damage to the mucosa, which could lead to dehiscence of the wound. The patients were instructed to maintain a liquid diet postoperatively for 2 weeks, and were permitted a soft diet after that period.

RESULTS

Seventy-four patients were included in this retrospective cohort study. These patients were surgically treated and followed-up for 6–96 months.

Patient characteristics (Table II)

Most patients (56.7%; n = 42) had osteoporosis as an indication for bisphosphonate use. In this group, 26 patients used bisphosphonates because of the use of steroids such as prednisolone (in cases of rheumatoid arthritis). The most common malignancies (n = 30) were breast cancer (60.0%; n = 18), prostate cancer (16.7%; n = 5), and multiple myeloma (20.2%; n = 6).

The clinical features are listed in Table 1. The ages of the female (83.8%; n = 62) and the male (16.2%; n = 12) patients varied from 26 to 91 years, with a mean of 67.9 years.

BRONJ was located in the maxilla in 11 patients, in the mandible in 58 patients, and in both the jaws in 5 patients. Fifty-two patients were found to have stage III disease, and 22, stage II.

Oral bisphosphonates had been used in 40 cases, with a minimum of 24 months and a maximum of 120 months (mean = 68.0). Intravenous bisphosphonates had been used in 34 cases, including both oral and intravenous use (n = 6), with a minimum of 12 months and a maximum of 96 months (mean = 31.2 months). In 45 patients, steroids, such as prednisone, or methotrexate were used as co-medication.

Table II Clinical features

Gender			74
	Male	62	
	Female	12	
Indication			74
	Osteoporosis	42	
	Multiple Myeloma	6	
	Prostate Cancer	5	
	Breast cancer	18	
	Other	3	
Intravenous use			34
	Zoledronic acid	10	
	Pamidronic acid	24	
Oral use			40
	Alendronic acid	30	
	Risedronic acid	9	
	Ibandronic acid	1	
Co-medication			45
	None	29	
	Steroids	19	
	Immunosuppressants	5	
	Cytostatics	11	
	Combination	10	
Location			74
	Mandible	58	
	Maxilla	11	
	Both	5	
Luxating moment			74
	Extraction	54	
	Implants	10	
	Pressure soar	4	
	Other dental cause (periodontitis, apical pathology)	6	

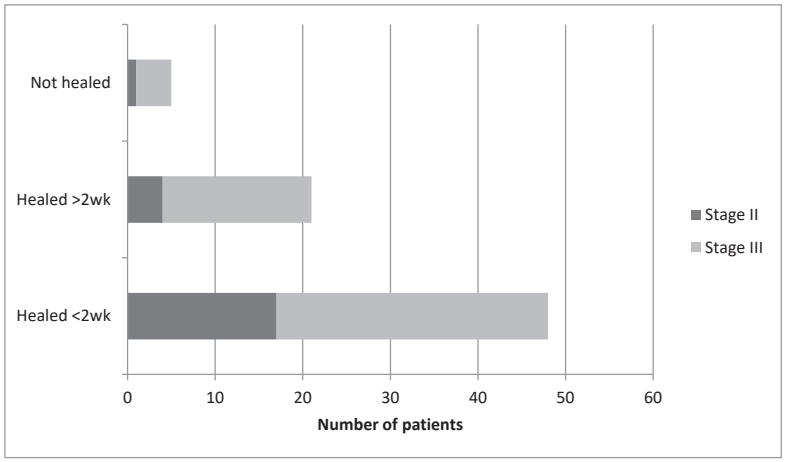
The luxating moments of the BRONJ were mainly extractions (73.0%; n = 54), implants (13.5%; n = 10), and pressure sores due to ill-fitting dentures (5.4%; n = 4). All BRONJ were retraceable to a dental surgery/origin.

Surgical outcome

The majority of patients (n = 72) were treated under general anesthesia. After the surgery, all patients were followed-up for at least 6 months. In 69 patients (93.2%), curation was achieved by the senior surgeons using our previously established surgical approach (Table III). Of these, curation was achieved within 2 weeks (ideal healing) in 48 patients (31 cases of stage III). They presented a healed and closed mucosa with no pain or complaints.

During the follow-up, these patients had no extraordinary pain or recurrences. All panoramic radiographs taken during the follow-up showed an ingrowth of bone, without further osteolysis.

Table III Treatment results.



Healing:
ideal <2wks (n=48);
not ideal >2wks (n=21);
not healed (n=5)

Of these patients, 28 were using co-medications such as prednisolone, immunosuppressants, and cytostatics.

There were 21 patients (17 cases of stage III) who were not cured within 2 weeks. They all presented with small dehiscences or fistulae that were initially treated with antibiotics. Six patients were cured within a few weeks with an extended use of antibiotics. Thirteen patients still needed a minor second surgery. This involved a small curettage, and sequestrectomy under local anesthesia. Treatment under general anesthesia in this group was necessary in only a few cases. Of the patients with non-ideal healing, 53.9% (n = 14) were using co-medication.

Five patients were not cured. In one patient, a reconstruction plate had been placed, and the plate was visible intraorally. This patient died before another surgery. The other patients had small non-producing fistulas or dehiscences with no other complaints, despite antibiotics or a second surgery.

Four patients died of metastases. The remainder of the patients reported an acceptable quality of life following the first surgery, and therefore, refused any more surgery during the follow-up.

DISCUSSION

In this study consecutive patients, referred from other clinics, presenting with therapy-resistant BRONJ, were treated and retrospectively analyzed. Secondary aims were to characterize the patients by investigating sex, age, medication use, medical and dental history, (previous) treatment and the duration of complaints.

This study demonstrates that our surgical method, reported earlier[18,19], leads to curation in a high number (93.2%) of BRONJ patients without serious adverse events in the affected area. Our results are consistent with those of other recent reports[13-17]. These authors seem to have achieved, more or less, the same rate of healing with comparable surgical intervention. Removing the infected and non-vital bone thoroughly, closing the defect with vital periosteum, leaving as little dead-space as possible, and then closing in layers, allows the bone to be fully covered, and gives it the opportunity to heal under the most optimal conditions, thus increasing the chances for curation. The wound is more prone to dehiscences and delayed healing if the mucosa is not closed in layers.

Of the 74 patients, 45 used co-medication. Although it was expected that the use of co-medication such as steroids, immunosuppressants, and cytostatics could have a negative influence on bone healing[20-23], we did not find any significant difference in bone healing (P = 0.366) between the co-medication users and the non-users. We did see a tendency towards worse outcomes since four of the five patients with dehiscences were on co-medication, but of the 26 patients who did not have ideal healing, only 14 used co-medication. There is a tendency in co-medication cases to exhibit less than ideal outcomes. However, in contrast to previous reports[20,22], we have not found a significant difference to establish that as a fact.

Another reason for dehiscences and the necessity for secondary procedures could be the advanced stage (stage III) of the BRONJ disease. In the non-ideal healing group, 16 of the 21 patients had stage III, and only five had Stage II BRONJ. Previous reports, and even the AAOMS, recommend large resections for stage III disease. However, we were able to cure most of our patients by a conservative surgical treatment with thorough saucerization of the bone. Despite the conservative surgery, no significant difference in healing was found between the stage III and stage II cases (P = 0.146).

We noticed more mandibular cases than maxillary or bimaxillary cases. This is probably because the maxilla contains less cortical bone, and has a better vascularization than the mandible. However, its ability to heal was not significantly better, since the non-ideal group was even in the number of maxillae and mandibles.

The duration of bisphosphonate use and the duration of complaints were both not significant factors in the outcome. These values were comparable not only in both the closed and open groups, but also in the ideal and non-ideal group.

In contrast to some reports[24], an association between the healing and the type of bisphosphonates, or the mode of administration (P = 0.157) could not be found. The results of the comparison between the two variables were the same. Even zoledronic acid seemed to have a comparable outcome, as did alendronic acid or pamidronic acid. This could be, because once the bone is saturated with bisphosphonates, the result is similar.

There is still a lot of discussion on the treatment of BRONJ. However, a majority of the reports express reservations about surgical treatment. Some authors report worsening of symptoms, pathological fractures or even loss of parts of the jaw upon surgical treatment[9-11]. Although, treating the patients with only mouth-rinses or antibiotics might reduce the symptoms, and provide temporary relief, it will not resolve the problem. Instead, this may lead to a larger, therapy-resistant osteonecrosis, which will be difficult to treat. There are several examples in the literature, of the worsening of BRONJ in inadequately-treated patients[12,17,25]. Treatment under local anesthesia showed a tendency to lead to a second surgery under general anesthesia. This may be due to the fact that, under local anesthesia, thorough treatment with adequate saucerization could be more difficult.

Given these results and the ongoing debate on the treatment of BRONJ, our focus should change towards a better prevention of dental problems before starting with bisphosphonate treatment. In addition since the exact pathogenesis of BRONJ is still unknown, further research is mandatory.

CONCLUSION

The high success rate of the combined surgical and antimicrobial treatment in this study, the relative long follow-up, and the fact that our findings are consistent with literature suggests that this combined surgical and antibiotic protocol is the treatment of choice at all stages of BRONJ. Hence, our results are of clinical relevance in the ongoing debate about the treatment of BRONJ.

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Evaluation of a surgical treatment of denosumab-related osteonecrosis of the jaws.

Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Sep;122(3):272-8

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ABSTRACT

INTRODUCTION

Denosumab, a monoclonal antibody, is a relatively new antiresorptive agent that has recently shown a serious adverse effect: denosumab-related osteonecrosis of the jaws (DRONJ). The purpose of this study was to retrospectively observe the efficacy of the combined surgical and antimicrobial treatment of DRONJ.

METHODS

In this case series, all patients with osteonecrosis that occurred after starting treatment with denosumab, were treated with surgery and antimicrobial treatment and followed up. The primary outcome was healing of the jaw. For patient characterization, secondary variables, such as clinical features, denosumab use, dental history (including luxation), and duration of complaints, were studied.

RESULTS

Eleven patients met the criteria to be included in this study. Nine patients experienced healing within 4 weeks after surgery. Two patients were not cured and died as a result of their underlying disease. In all patients, a dental focus was found. Six patients had been treated only with denosumab, and five had also been treated with bisphosphonates.

CONCLUSION

We were able to achieve healing in 9 of the 11 patients with DRONJ. Our treatment protocol showed promising results; however, further research is needed.

INTRODUCTION

Denosumab (Xgeva, Prolia®) is a relatively new antiresorptive medication. So far, bisphosphonates have been the commonly used medications, mainly prescribed in osteoporosis and skeletal bone metastases in malignancies. They inhibit bone resorption by decreasing osteoblast function, thereby stabilizing the osteoporotic process, preventing further growth and metastasis of malignant bone lesions, and alleviating pain. However, the use of bisphosphonates may have side effects, of which gastrointestinal or nephrotoxic effects are the most frequently reported[1,2]. Another serious side effect of biphosphonates was reported in 2003—osteonecrosis of the jaws[3].

Because of the nephrotoxicity of zoledronic acid[1,2], denosumab was developed and introduced as an alternative. Denosumab is a relatively new anti-resorptive agent, which is being used more frequently in the treatment of osteoporosis, bone metastases, and giant cell tumors[4,5,6,7]. It is a monoclonal IgG2 antibody against Receptor Activator of Nuclear Factor kB Ligand (RANKL), which belongs to the tumor necrosis factor (TNF) family, and is the main mediator of osteoclastic bone resorption[8]. Denosumab mimics the effect of osteoprotegerin on RANKL[9,10,11]. Osteoprotegerin has a potent antiresorptive effect, and together with RANKL, it regulates osteogenesis[12,13].

Tumor cells produce factors that stimulate osteoblasts to express RANKL. RANKL normally activates osteoclasts by binding to their RANK receptor, and stimulates differentiation of preosteoclasts into osteoclasts. Denosumab acts by binding to RANKL. This inhibits the activation of osteoclasts and the maturation of preosteoclasts, resulting in decreased bone resorption.

According to the literature, denosumab is effective in increasing bone mineral density and thereby preventing skeletal-related events (SRE)[4,7,14,15]. It is not cleared by the kidneys so there is no nephrotoxicity[16]. This is a great advantage over the use of zoledronic acid, which is a very potent and effective bisphosphonate, but limited in its use due to the associated nephrotoxiciy. Another advantage of denosumab is that it does not bind to bone, which makes its effect only temporary and not as longlasting as that of bisphosphonates, which bind covalently to the hydroxyapatite in bone[17,18]. Denosumab takes 10 days after administration to reach the mean maximum concentration (Cmax) in serum. Its half-life is approximately 25.4 days for Prolia[20] and 28 days for Xgeva[21].

A serious side effect of denosumab is denosumab-related osteonecrosis of the jaws (DRONJ). A few cases have been reported in literature[22,23,24,25,26]. The clinical features of this necrosis seem to resemble those of the therapy-resistant and very difficult to treat bisphosphonate-related osteonecrosis of the jaw (BRONJ). Therefore, diagnostic criteria similar to those for BRONJ can be used for DRONJ[27]: a current or previous treatment with denosumab; exposed, necrotic bone in the maxillofacial region for more than 8 weeks; and no history of radiation therapy in the head and neck area. Like BRONJ, DRONJ can also be classified into stages 0–3 (Table 1).

Table I Classification Stages of Medication-Related Osteonecrosis of the Jaws (MRONJ) and recommendations by Ruggiero et al. 2014 (AAOMS)

MRONJ stage	Description
At risk category	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates
Stage 0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms
Stage I	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection
Stage II	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage III	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor

In our clinic, we have encountered 11 patients with osteonecrosis of the jaws who had been using denosumab. Our treatment approach was similar to that used for BRONJ[28,29,30,31]. We treated our patients surgically according to our previously reported protocol[26,28,32]. The purpose of this study was to observe the efficacy of this treatment retrospectively. Secondary aims were characterization of the patients by mapping age, medication use, medical and dental history and (previous) treatment.

METHODS

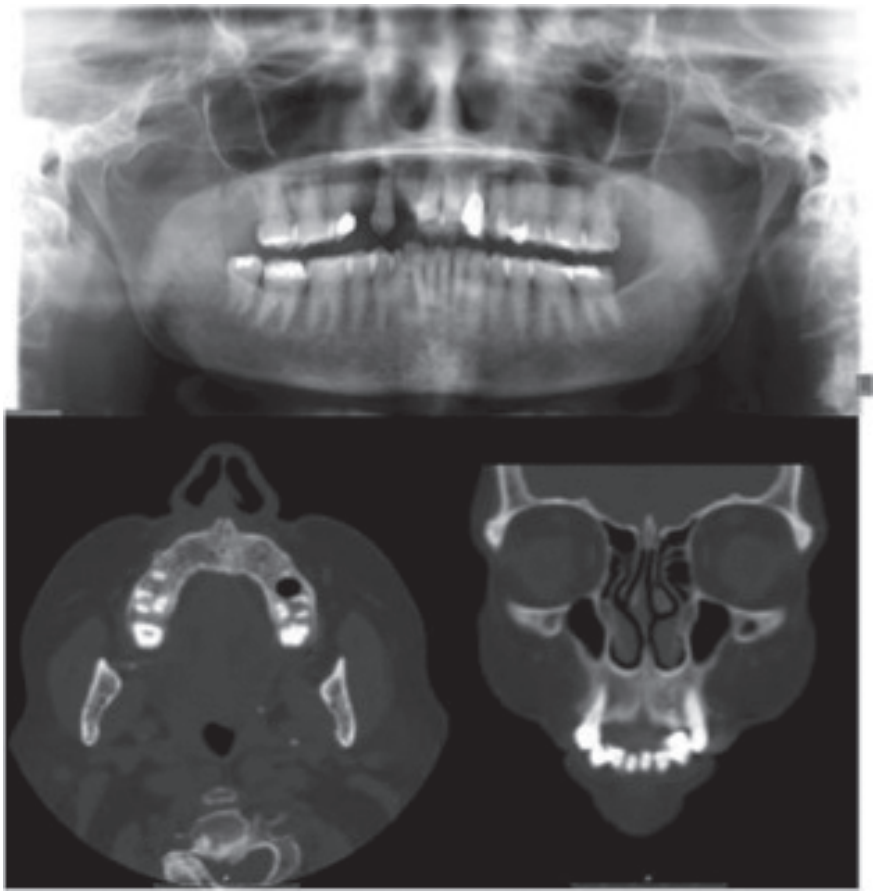
In this case series, consecutive patients presenting with osteonecrosis of the jaw due to denosumab treatment were retrospectively investigated. The study population was composed of all patients presenting for evaluation of osteonecrosis with the use of denosumab between January 2007 and May 2015 in the department of Oral & Maxillofacial Surgery of the Leiden Medical University Center. In order to be included in the study sample, patients needed to have exposed bone in the oral cavity for at least 8 weeks, previous use of denosumab and no previous radiation in the head and neck area (according to the criteria of medication related osteonecrosis of the jaws[27]). Only patients with at least eighteen years of age and with a minimal follow-up of 6 months were included.

The first aim of this study was to evaluate the outcome after our previously reported combined surgical and antimicrobial treatment. Therefore, the primary outcome variable was healing. Healing was classified as present or absent within 4 weeks post-operatively and defined as a healed and closed mucosa without complaints. Follow-up visits were scheduled at 1, 2, and 4 weeks, 2, 3, and 6 months, and 1 year post-surgery. Patients were followed for at least 6 months.

Secondary aims were to characterize the patients with DRONJ. Secondary outcome variables that were studied consisted of sex, age, anti-resorptive indication and duration of denosumab use. The duration of complaints, and the time between the last denosumab dose and onset of complaints were also studied. Other medication (bisphosphonates, steroids, immunosuppressants, cytostatics), clinical features (location and stage), dental history, and (previous) treatment were recorded.

Panoramic radiography and (cone beam) computed tomography ((CB)CT) were performed to determine the extent of the disease (figure 1). Since clinical symptoms of DRONJ are comparable to those of BRONJ, the staging classification used in BRONJ[27] (table 1) was used for these patients as well. The patients were treated according to our (previously reported) BRONJ treatment protocol[28], which is based on the treatment of chronic suppurative osteomyelitis.

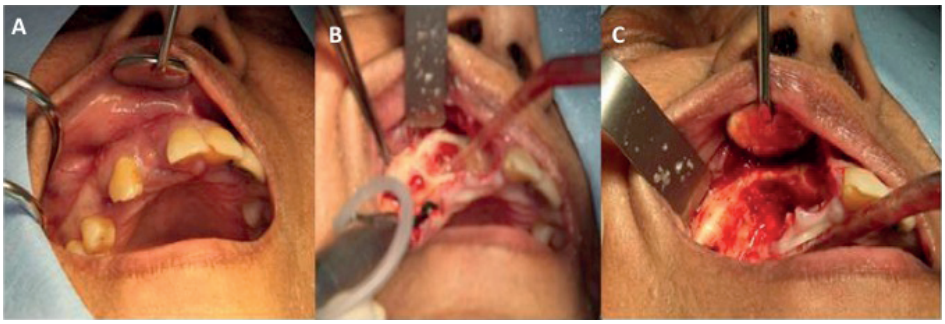
Figure 1. Case DRONJ right maxilla



Preoperative panoramic radiograph: osteolysis region 13, relatively sclerotic mandible in the corpus region.
Preoperative computed tomography scan: lysis region 12-13 in respectively axial and coronal views.

Denosumab and/or bisphosphonate use was stopped at first presentation for the duration of the treatment and follow-up. Surgical treatment included thorough surgical debridement with saucerization of the bone until the vital bone margins were reached, and then closing primarily in layers, leaving no dead space (figure 2). Patients were admitted for at least one week for intravenous administration of antibiotics (penicillin G 1,000,000 IU 6 times a day; and metronidazole 500 mg 3 times a day), followed by 3 weeks of oral administration (amoxicillin 500 mg and metronidazole 500 mg, both 3 times a day).

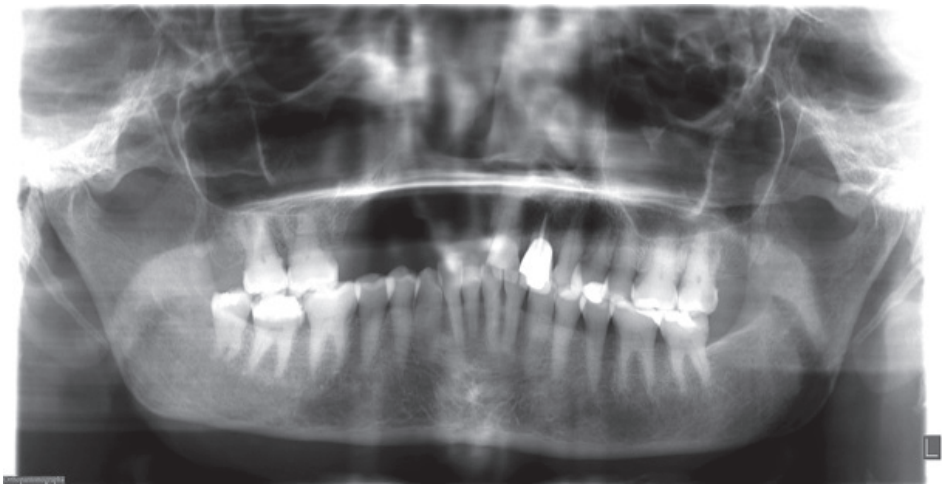
Figure 2. Case DRONJ right maxilla



A: Preoperative image: fistula, probable bone
B: During surgery: after extraction osteolysis can be seen
C: After thorough saucerization, smoothening of the edges, removal of bone to close tensionless primarily in layers

Panoramic radiography was performed immediately after surgery, and repeated at 3 months and 6 months post-surgery, and every 6 months after 1 year.

Figure 3. Case DRONJ right maxilla



Postoperative panoramic radiograph: bone healing, smooth edges

RESULTS

We encountered 11 patients using denosumab, and with exposed bone of the jaw(s).

Patient characteristics

Most patients suffered from malignancies (7/11, 63.6%). Among them, 42.9% (3/7) had (metastasized) breast cancer, and 57.1% (4/7) had prostate cancer. Osteoporosis acccounted for 36.4% (4/11) of the indications for denosumab treatment (Table 2).

The clinical characteristics of the 11 patients are listed in Table 2. Of the 11 patients, 63.6% (7/11) were women, and 36.4% (4/11) were men. Patient age ranged from 59–85 years (mean age, 72.6 years). 63.6% (7/11) had DRONJ of the mandible, 27.3% (3/11) had DRONJ of the maxilla, and 9.1% (1/11) had DRONJ of both jaws.

Table II Summary of the patient and disease characteristics

Nr	Sex	Age	Indication	Location	Stage	Duration complaints
1	F	84	OP	Mandible	3	3
2	F	85	OP	Both	3	2
3	M	82	PC	Maxilla	3	3
4	F	59	BC	Mandible	3	3
5	F	68	BC	Maxilla	3	2
6	M	83	PC	Mandible	2	12
7	M	75	PC	Mandible	3	9
8	F	72	OP	Maxilla	3	8
9	M	64	PC	Mandible	2	8
10	F	68	BC	Mandible	2	2
11	F	63	OP	Mandible	2	6

Nr= Number
Sex: F = female, M = male,
Indication of denosumab: OP=osteoporosis, PC=prostate cancer, BC=breast cancer,
Stages according to AAOMS definition (see Figure 1).
Duration of complaints in months

A dental focus was found in all 11 patients. All but one had had an extraction prior to the start of the complaints. One patient had peri-implantitis.

The duration of denosumab use ranged from 6–18 months, with a mean of 17 months (Table 3). The frequency of the use was either monthly in the case of bone metastases with Xgeva or every 6 months in the case of osteoporosis with Prolia. The time from the last denosumab use to the onset of complaints had an average of 4 weeks with Xgeva and 4-6 weeks with Prolia. The

Table III Summary of the (anti-resorptive) medication use and surgical outcome

Nr	Medication	Duration	Co-med	Time from last dose to onset	Healing	Follow-up
1	Ris/prol	192/18	Pred, mtx	4-6	closed	6
2	Prol	16	Predn	4-6	closed	13
3	Zol/xgev	120/14	None	4	closed	7
4	Pam/zol/xgev	12/18/18	Imm supp	4	closed	12
5	Xgev	12	Cytostatics	4	closed	8
6	Xgev	18	None	4	closed	12
7	Xgev	18	None	4	open	11
8	Ris/prol	48/6	Predn	4-6	closed	34
9	Xgev	7	Predn	4	open	12
10	Xgev	36	None	4	closed	17
11	Al/prol	24/24	None	4-6	closed	6

Anti-resorptive medication Ris= risedronic acid, prol=prolia, xgev=xgeva zol=zoledronic acid, pam=pamidronic acid
Duration=of the use in months of medication respectively mentioned in the medication column
Co-med=co-medication, Pred=prednisolone, mtx=methotrexate, imm sup=immune suppressants
Time from last dose to onset complaints: in weeks
Healing: "closed" mucosa and in case of "open" measurement of remaining defect in millimeters
Follow-up: in months

duration of complaints from the onset until the first presentation in our clinic was 2-12 months with a mean of 27,4 months.

Six patients had used only denosumab (Table 3). Five of the 11 patients had also used biphosphonates previously to denosumab: 2 used intravenous bisphosphonates (1 used zoledronic acid for 120 months; 1 used pamidronate for 12 months followed by zoledronic acid for 18 months); 2 used the oral bisphosphonate risedronic acid for 192 and 48 months prior to denosumab use; and 1 had used the oral bisphosphonate alendronic acid for 24 months. The duration between bisphosphonate use and denosumab use was at least 12 months.

After clinical evaluation together with imaging, there were 2 patients with stage 2 disease; the others had stage 3 disease.

Surgical outcome

The treatment was successful in 9 of 11 patients. These 9 patients healed, i.e. they had a closed mucosa and had no adverse events or complaints post-operatively. Two patients were not cured. They had persistant disease and needed secondary surgery. Despite the second surgery, their complaints and exposed bone persisted, and they died during the follow-up because of metastases. Two of the 9 healed patients also died of metastases during the follow-up, one at 8 and the other at 15 months after surgery. Of these two patients, one had stage 2 and one had stage 3 disease. The follow-up duration was 6–34 months (mean duration, 16.4 months).

DISCUSSION

The purpose of this study was to observe the efficacy of this treatment. Specific aims were characterization of the patients by mapping age, medication use, medical and dental history, (previous) treatment and to investigate the duration of complaints.

In our relatively small study sample in a single-center setting, we were able to cure 9 out of 11 patients (82%). They were free of complaints with a fully healed and closed mucosa. Two patients needed another surgery because of persistent disease refractory to treatment. However, the secondary surgery was unsuccessful in one of these patients, and both died due to metastasis, shortly after their first or secondary surgery. The malignancy may have played a negative role in their overall healing process.

During surgery, the bone in all patients seemed very sclerotic with very little bleeding. Taking the duration of bisphosphonate use or the cumulative dose into account, this supports the idea that even though denosumab may have a reversible effect, the changes in bone may not be reversible within 6 months. This could be due to the decreased rate of bone turnover, which also takes longer than 6 months.

The time between bisphosphonate use and Denosumab use, as mentioned before, was at least 12 months. Therefore, the patients who had used bisphosphonates earlier were in our opinion also DRONJ cases. Although bisphosphonates have a longlasting effect, this time is assumed to be enough to give the bone the opportunity to start metabolizing again[34]. Consequently, previous bisphosphonate use was not likely to be the cause of the necrosis.

We did not find any predictive factors for healing: Co-medication such as steroids, immunosuppressants, or cytostatics seemed to have no influence on the outcome. The patients in whom surgery was unsuccessful did not use any co-medication. Even though a negative influence of co-medications is expected, as they promote bone resorption[13,33], we could not confirm it in this study.

Disease stage also did not influence the treatment outcome. We did not find difference in outcome between the stages II and III. But we realize that our group is too small to draw serious conclusions on this.

The average time from last denosumab use to first complaints was approximately 4-6 weeks: 4 weeks for Xgeva and 4-6 weeks for Prolia. It could be possible that around these 4 weeks after Denosumab use the bone will slowly start to metabolize again. Which could make the bone prone to (dental) procedures like extractions or periodontal or apical pathology.

This minor study showed that the patient group overall seems to be a medically more compromised group. At the end of the study, 5 of the patients died, 3 within months after surgery.

Denosumab is a relatively new antiresorptive medication. Recent publications show that, similar to bisphosphonates, denosumab can also cause osteonecrosis of the jaws[22,23,24,25,26]. Even though

denosumab does not bind to bone, and its effect is supposed to be temporary[13] it is able to cause this difficult problem. Similar to BRONJ, DRONJ also seems to be resistant to treatment.

Denosumab has proven effective in preventing SRE[4,7,14,15]. Hence, its use will continue and more cases of DRONJ will be seen, especially if it turns out to be more aggressive than BRONJ. The incidence of DRONJ is not yet known; some authors claim that it is higher than that of BRONJ[13,16,35], though the difference is not significant. To our knowledge, there are no other case series or cohort studies on DRONJ. So, further research regarding its incidence is necessary.

The most recent literature classifies DRONJ and BRONJ as Medication-Related Osteonecrosis of the Jaw (MRONJ)[18,34,36]. However, we believe that as long as the precise pathogenesis of both conditions remains unclear, some precaution with this term is desirable. Besides that denosumab has a different mechanism of action, and its half-life is not comparable to that of bisphosphonates.

The pathogenesis of DRONJ still remains unclear, as is the case with BRONJ. Further research on a molecular level seems necessary to find out the exact pathogenesis of DRONJ.

CONCLUSION

Since DRONJ resembles BRONJ in clinical features, it seems important to develop good prevention programs and encouraging patients to keep good oral hygiene prior to denosumab use. In conclusion, we found that denosumab is able to cause osteonecrosis of the jaws. This disease might become a serious problem as BRONJ is already, but early surgical treatment shows promising results as shown in this study. This conclusion is based on a relatively small, observational study.

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8

Treatment of pathologic fractures of the mandible in stage III MRONJ- an observational study

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ABSTRACT

INTRODUCTION

The treatment of pathologic fractures in stage III MRONJ remains challenging. The treatment in literature is controversial varying from extensive and aggressive surgery with resections and musculocutaneous free flap reconstruction to conservative treatment with only mouth rinses and/or antimicrobial treatment. The purpose of this study was to analyse the results of the treatment protocol in the Leiden University Medical Center in the Netherlands.

METHODS

Between 2003 and 2017 15 consecutive patients were seen with pathologic fractures in stage III MRONJ. Patient characteristics and treatment were studied.

RESULTS

7 patients were dentate and were all surgically treated according to protocol and 3 were additionally intermaxillary fixated. 8 patients were edentulous of whom 6 were surgically treated: 2 with osteosynthesis and the rest were instructed a soft diet post-operatively for several weeks. One patient showed healing in a later stage and was not treated. Two patients were treated with antimicrobial treatment and a soft diet.

11 patients (73%) showed complete healing of the fracture or a pseudarthrosis and were free of complaints and were able to function.

CONCLUSION

These results show that a relative simple (surgical and/or antimicrobial) approach combined with intermaxillary fixation on occasion can lead to consolidation and/or a pseudarthrosis with a remaining and acceptable function of the jaw.

INTRODUCTION

The treatment of medication related osteonecrosis of the jaws (MRONJ) can be very challenging. MRONJ is defined as exposed bone in the maxillofacial region for more than 8 weeks, with a previous use of anti-resorptive medication like bisphosphonates or denosumab and no history of radiation therapy or obvious metastatic disease to the jaws. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has written a Position Paper[1,2] with an additional staging of MRONJ (table 1).

The stages 0, I and II can be shortly described as respectively: 0- aspecific complaints or clinical and radiological signs without apparent osteonecrosis; I- exposed bone without signs of inflammation (foetor, pus, swelling or hypoesthesia); II- exposed bone with signs of inflammation. The AAOMS suggests to treat these first stages only with symptomatic conservative treatment with chlorhexidine mouthrinse and antibiotics and maybe a very limited local debridement.

Symptoms in stage III are as described in stage II, but extending beyond the region of the alveolar process and/ or involvement of the inferior border of the mandible or the maxillary sinus, cutaneous fistulas, and pathological fractures. The advised treatment strategies in stage III disease are mouthrinses and/or antibiotics and, depending on the symptoms, surgical debridement or resection for longer-term palliation.

In the literature there is still an ongoing debate on the treatment in stage III MRONJ with involvement of the inferior border with or without pathologic fractures. Some authors[2-5] suggest a conservative treatment for as long as possible, whereas other authors[6-19] suggest an aggressive approach with resections and reconstructions of the jaw with for example a free vascularized osseocuteanous flap of the fibula.

In these medically compromised stage III patients this aggressive approach may not be desirable or possible. Especially for the elderly patients with comorbidities or with (end stage) metastasized disease, major surgery with resection and reconstruction may not be the treatment of choice. However, many patients have pain and a decreased intake, leading to a lower quality of life. Therefore, refraining from treatment is not an option either. In our clinic promising results were seen with a previous reported and relative simple approach[20-22]. The purpose of this study was to analyse this treatment strategy and its follow-up for patients with stage III MRONJ of the mandible with a pathologic fracture.

METHODS

In a cohort of 150 consecutive patients, referred from other clinics, and presenting with stage II/ III MRONJ, treatment and follow-up were studied. Patients were seen between January 2003 and January 2017 in the department of Oral & Maxillofacial Surgery of the Leiden University Medical Center. At presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were noted.

The inclusion criteria for this study was a MRONJ diagnosis according to the criteria stated by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[2]. As previously mentioned this means a recent use of bisphosphonates or denosumab, the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, and no history of radiation therapy to the jaws.

Only patients with a stage III MRONJ with severe osteonecrosis and involvement of the inferior border of the mandible and a pathological fracture were included in this present study.

The primary outcome in this study was to observe the result of treatment for stage III MRONJ with pathological fracture of the mandible. Healing of the bone and mucosa were observed. Healing of the bone was classified as healed or a pseudarthrosis. A pseudarthrosis was defined as a fibrous healing of the fracture without evident mobility of the fracture and with an acceptable function of the mandible.

Healing of the mucosa was defined as a closed or open mucosa in case of dehiscences or fistulas.

The follow-up was done on a regular base the first weeks, then after every month, until at least 12 months. During follow-up the main focus was on pain, on the mucosa, and whether dehiscence or recurrence of the exposed bone had developed.

At presentation, panoramic radiographs were taken of all the patients to localize the lesion, and to gain a first impression of the lesion. A computed tomography (CT) scan (predominantly cone beam CT) was used to determine the extent of the defect. The clinical features and the radiological findings, together, defined the stage of MRONJ, based on the AAOMS classification[2]

Table I: Classification Stages MRONJ and recommendations by Ruggiero et al., 2014 (AAOMS)

MRONJ stage	Description	Treatment strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
Stage I	No symptomatic lesions or bone exposure in the absence of signs of infection	Topical antiseptic therapy Follow-up
Stage II	Bone exposure with pain, infection, and swelling in the area of the lesion	Oral antibiotics, antibacterial mouth rinse, pain control Superficial debridement to relieve soft tissue irritation
Stage III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

(Table 1). Osteolysis in large parts of the jaws beyond the alveolar process and inferior alveolar canal or pathologic fractures were categorized as stage III.

The patients underwent surgical intervention under general anaesthesia as reported before[20-22]. Surgery was performed by senior surgeons. The surgical approach consisted of the removal of sequestra, thorough surgical removal and saucerization of the non-vital bone until reaching the bleeding bone margins. In the case of dentate patients intermaxillary fixation was applied with arch bars (fig. A-E). The defect was closed primarily in layers. This meant closing the periosteum as close to the bone as possible with mattress sutures, leaving no or as little dead-space as possible when closing the overlying mucosa in layers.

During the surgery culture samples were collected, and the resected bone was submitted for histopathological analysis.

The surgical treatment was supplemented by the administration of the antibiotics, penicillin G and metronidazole, intravenously for 1 week, and amoxicillin and metronidazole, orally for 3 weeks.

Panoramic radiographs were taken immediately after surgery, and every 3–6 months, for up to 1 year after the surgery, in order to monitor the condition of the bone margins and the healing of the bone. After 1 year, an annual radiographic follow-up was considered sufficient.

Overlying dentures were not allowed during the first 12 weeks in order to avoid pressure and damage to the mucosa, which could lead to dehiscence of the wound. The patients were instructed to maintain a liquid diet postoperatively for at least 2 weeks, and were otherwise permitted a soft diet after that period.

RESULTS

Fifteen patients could be included in this observational study. The patients were followed for a mean of 24,3 months (6 to 50 months). Two patients could not be followed longer than 6 months because these patients died of metastatic disease.

Fractures

Twelve patients were surgically treated. In 7 cases there was a fracture before or noticed during surgery. In 5 cases there was a spontaneous fracture after surgery.

In the remaining 3 cases the patients presented with pain and a pathological fracture in an edentulous mandible. The fractures showed signs of healing in a later stage, and therefor received no additional surgical treatment.

Patient characteristics (table 2)

The clinical features are listed in Table 2. The ages of the female (53.3%; n = 8) and the male (46.7%; n = 7) patients varied from 47–85 years, with a mean of 71.8 years.

Oral bisphosphonates had been used in 9 cases, with a minimum of 24 months and a maximum of 120 months (mean = 72.1). Intravenous bisphosphonates had been used in 3 cases, with a minimum of 6 months and a maximum of 30 months (mean = 18 months). In 8 patients, steroids, such as prednisone, or methotrexate were used as co-medication.

Table II: Clinical features

Gender		
	Female	8
	Male	7
Indication		
	Osteoporosis	11
	Multiple Myeloma	1
	Prostate Cancer	2
	Breast cancer	1
	Other	-
Intravenous use bisphosphonates		3
	Zoledronic acid	2
	Pamidronic acid	1
Oral use bisphosphonates		11
	Alendronic acid	10
	Risedronic acid	1
Subcutaneous use Denosumab		
	Xgeva	1
	Prolia	-
Co-medication		8
	None	8
	Steroids	7
	Immunosuppressants	2
	Cytostatics	2
	Combination	4

Dentate

There were 7 dentate patients of whom 5 patients had osteoporosis and oral medication use and 2 patients had metastasized cancer and intravenous use of medication.

Edentulous

There were 8 edentulous patients of whom 6 patients had osteoporosis with oral medication use. Two patients had cancer of whom one patient used xgeva and one patient used intravenous bisphosphonates.

Surgical outcome (table 3)

Dentate

7 patients were dentate and were all surgically treated according to protocol and the three patients with a pre-operative fracture were intermaxillary fixated for 6-8 weeks (fig 1). The remaining four patients developed the fracture after initial surgery, due to loss of vertical height of the mandible. These patients were instructed a soft diet. Four patients healed with a closed mucosa. Three patients had a pseudarthrosis, two with closed mucosa and one with a small mucosal dehiscence, but free of pain. No further treatment was installed.

Two of the three patients with a pseudarthrosis had intravenous use of bisphosphonates with a mean of 18 months and one patient had oral use of bisphosphonates of 24 months duration.

Edentulous

8 patients were edentulous and 5 patients were surgically treated. four presented with a fracture and 1 developed a fracture after surgery. Two patients were treated with osteosynthesis (one

Table III: Treatment results

Patient	Indication	Duration	Dentate	Treatment	IMF	Healing bone	Closed mucosa	Co-med
1	OP	24	+	seq+ab	-	+	+	+
2	OP	24	+	seq+ab	-	pseud	-	+
3	OP	59	+	seq+ab	+	+	+	+
4	OP	120	+	seq+ab	-	+	+	-
5	Canc	30	+	seq+ab	+	pseud	-	-
6	Canc	6	+	seq+ab	+	pseud	+	-
7	OP	40	+	seq+ab	-	+	+	+
8	Canc	24	-	seq+ab	-	pseud	+	-
9	OP	84	-	seq+ab	-	pseud	+	-
10	OP	36	-	seq+ab	champy	pseud	-	-
11	Canc	12	-	seq+ab	reconstr	pseud	+	-
12	OP	120	-	seq+ab	-	+	+	+
13	OP	120	-	ab	-	+	+	-
14	OP	120	-	ab	-	+	+	+
15	OP	46	-	-	-	+	+	-

OP= osteoporosis with oral use of bisphosphonates
Canc=cancer with monthly treatment with intravenous bisphosphonates or subcutaneous xgeva (denosumab)
Duration in months
IMF: intermaxillary fixation
Pseud= pseudarthrosis
Ab= antibiotics
Seq= sequestrectomy under general anaesthesia
Co-med= co-medication such as immunosuppressants, steroids or cytostatics
Champy= one patient was treated with champy miniplates
Reconstr= one patient was treated with a reconstruction plate

2.0 4 hole champy plate and one reconstruction plate). All patients were instructed a soft diet post-operatively for several weeks.

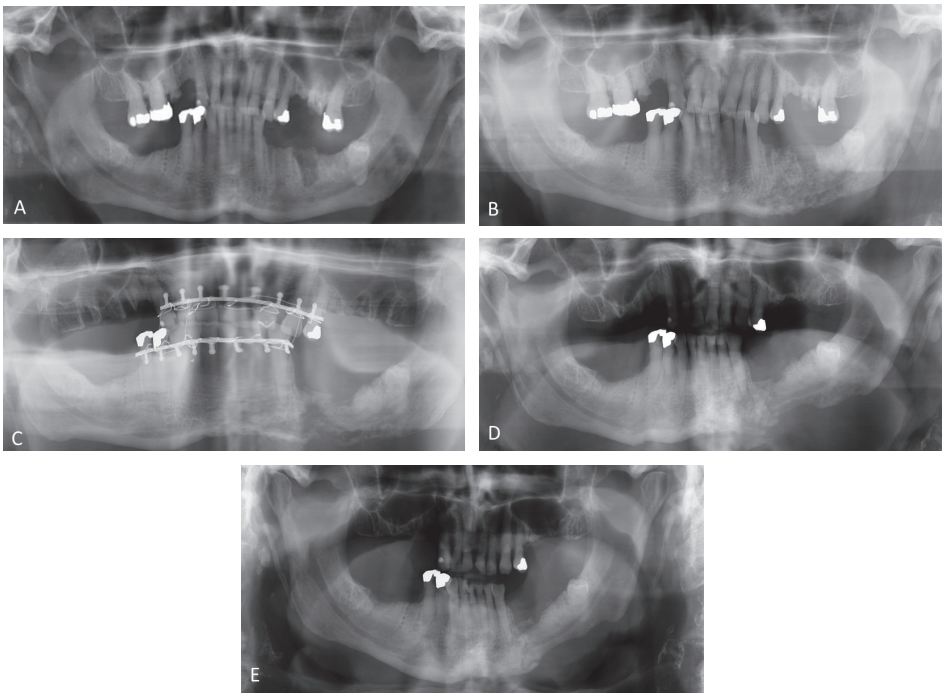
Two of the four patients with a pseudarthrosis had an oral use of bisphosphonates with a mean of 60 months, one patient had intravenous use of bisphosphonates of 12 months and the last patient had xgeva use of 24 months.

Of the 15 patients, 11 patients (73%) showed complete healing or a pseudarthrosis of the fracture and were free of complaints. 4 patients had a remaining dehiscence or fistula, but without discharge and pain.

Ten patients had an uneventful follow-up. The panoramic radiographs taken during follow-up showed healing of the bone (fig 1), without further progression of the disease. 1 received a soft diet only, 2 antibiotics only and 7 underwent a sequestrectomy.

Five patients had a sequestrectomy with persistent complaints. One healed after a second surgery. Another showed an persistent fistula without further complaints.

Figure 1: Illustrations



A: Panoramic radiograph after removal 36 at start of complaints: except empty alveolus no signs of lysis
B: severe lysis visible after a few months. Lysis beyond mandible canal and into inferior border of mandible
C: after surgery with IMF: wisdom tooth not involved in necrosis and left in place to not further compromise healing and cause possible fracture
D: Fracture and healing visible after 6 months
E: after 24 months evident healing, with no palpable mobility

Three had three surgical interventions. These patients remained with a small dehiscence, but died of their primary disease within six months after their last intervention.

DISCUSSION

In this study fifteen patients with stage III MRONJ and a pathologic fracture of the mandible were treated without extensive surgery. Patients were treated with a limited sequestrectomy in combination with intravenous antibiotics or with antibiotics and a soft diet.

In total 11 patients (73%) showed complete healing or a pseudarthrosis of the fracture and were free of pain. Four patients had a remaining dehiscence, but with no pus discharge and no further complaints.

Our results show that with a relatively simple surgical approach healing and functional improvement can be achieved. In the medically compromised patients the gain of this relative less aggressive surgical treatment is high compared to the mutilating and very invasive resection and reconstruction procedure. Removal of sequesters, assessment of vital bone margins and primary closure is essential in the treatment.

Applied intermaxillary fixation with arch bars demonstrates good results in dentate patients. A good healing of the bone was seen in half of the patients, the other half remained with a pseudarthrosis but with an acceptable function.

In edentulous patients, especially with atrophied mandibles, curation was more difficult to reach. In the patients with post-operative fractures after surgery a soft diet was sufficient. Two patients with a preoperative fracture were treated first with one 2.0 4-hole champy plate. The usual treatment with 2 champy plates was not possible due to loss of vertical height of the mandible leaving room for only one plate.

Not unexpectedly these patients developed a dehiscence on top of the plate, due to a compromised healing as a consequence of the extensive inflammation in the soft tissues and the bone and infection of the plate. Surprisingly these dehiscences were a few millimetres and sometimes only a fistula to the plate. Subsequently the plate was removed. A pseudarthrosis was achieved in these patients. These patients were free of pain complaints and one was able to function with an overdenture.

Some patients had no denture, but were satisfied with the ability to have a liquid or soft diet without having pain or any other complaints.

Three patients presented with a fracture, but very few clinical symptoms and the CBCT scan showed sequestra, but also signs of healing of the fracture. In these cases the patients had already started with antibiotics elsewhere and we decided to continue this treatment unless the symptoms would deteriorate. In that case a surgery would be planned. But improvement was seen in these patients and no further surgery was necessary. Subsequently these patients healed and developed a pseudarthrosis. This conservative treatment is not the first choice of

treatment, because not surgically removing necrotic bone often leads to deterioration of the disease. However it was estimated that the progression of the healing process at first presentation could be awaited.

For the indication of the anti-resorptive medication or the duration of this medication no relation was found with the outcomes. Cancer patients may seem to have a lesser surgical outcome –pseudarthrosis- than the osteoporosis patients, but the number of patients is limited. Besides this, there is a functional and complaint free situation in an often medically compromised patient.

In addition although long term anti-resorptive medication is associated with more morbidity and therapy resistant disease, the four healed edentulous patients had a very long mean use of oral bisphosphonates of 101,5 months. This may suggest that the duration is less of influence than expected. In this limited number of patients it is difficult to draw conclusions. Therefor in our study no association could be found between indication and duration of anti-resorptive therapy and the outcome.

Patients with co-medication seemed not to have a lesser outcome than the ones without. Statistical analysis was not performed in this limited group of patients.

Pathologic fractures in stage III MRONJ of the mandible can be difficult to treat. In the literature there is no consensus on treatment of these patients. So far conservative treatment with mouth rinses and/or antibiotics have been proven ineffective. The majority of authors including the AAOMS promote resection of the jaw with reconstruction with free vascularized osseocutaneous flaps[2,6-11,13-18]. These surgeries may lead to serious comorbidities in an already medically compromised population, next to the fact that in the oncologic patient the donor site should be free of bone metastases. The arguments against these major surgical procedures are clear[9].

Reasons not to perform regular sequestrectomy are the fear to damage the bone causing or increasing the necrosis. Or the possibility that due to the bisphosphonates there will be problems with the union of the bony margins[8,12,19,23].

The use of reconstruction plates is also mentioned in literature[24,25]. An extra-orally approach leading to more (surgical) risks for the already medically compromised patient, potential contamination of the intra-oral defect and the need for removal often due to infection of the plate can make the use of these plates less favourable.

To our knowledge there are no other reports on the treatment of stage III MRONJ with pathological fractures.

Given the fact that the treatment of pathologic fractures with MRONJ is still challenging, this treatment shows promising results. In medically compromised patients these less invasive but thorough early surgical interventions should be considered as alternative to major surgeries with resection and reconstruction.

CONCLUSION

This study shows that a relatively simple (surgical and/or antimicrobial) approach combined with intermaxillary fixation in individual cases can lead to consolidation and/or a pseudarthrosis with a remaining and acceptable function of the jaw in 11 from the 15 patients (73%).

The results show that performing aggressive surgery like the use of reconstruction plates or a resection of the jaw with the additional morbidity in a medical compromised population is not always necessary. Further research is mandatory.

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3D analysis of a surgical technique in successfully treated stage II/III MRONJ-patients

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ABSTRACT

INTRODUCTION

The aim of this study was to analyze the surgical treatment protocol used in our hospital for successfully treating medication-related osteonecrosis of the jaw (MRONJ) patients.

METHODS

It was a retrospective study where MRONJ patients were divided into 2 groups for analysis. Group 1 comprised 15 MRONJ patients who have had unsuccessful surgical treatments outside of our hospital between the years 2009 and 2018. Group 2 comprised 15 MRONJ patients who had no history of any treatment, and who were then surgically treated at our hospital with our treatment protocol. (Cone beam) computed tomography (CB)CT scans of group 1 patients were analyzed at the time of presentation in our hospital. The surgical technique used for treatment was categorized as either sufficient or insufficient based on the evaluation of the basic principles of bone treatment such as removal of necrotic bone, removal of buccal and lingual cortex, presence of dead space and frontal aspect, on pre- and postoperative CBCT scans, respectively. The clinical outcome was also evaluated. A successful clinical outcome involved a closed mucosa, without any complaints such as pain.

RESULTS

Group 1 had low scores on the basic surgical principles for MRONJ, whereas group 2 had high scores in all features.

CONCLUSION

The surgical technique with high success rate in all stages of MRONJ is based on relatively simple surgical principles, comprising extensive saucerization and rounding off in combination with primary closure.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is one of the serious side effects of medications, such as antiresorptive drugs, which are used in the treatment of osteoporosis and bone metastasis. The first case of bisphosphonate-related osteonecrosis of the jaw (BRONJ) was reported by Marx in 2003[1]. Later, it was reported that besides bisphosphonates, the osteonecrosis of the jaw (ONJ) could also be caused by denosumab in a condition known as denosumab-related ONJ (DRONJ)[2,3]. ONJ can be very difficult to treat, and the debate on its etiology and treatment continues in the literature. The American Association of Oral and Maxillofacial Surgeons (AAOMS) stated a position paper with guidelines for the diagnosis and treatment of MRONJ[4]. MRONJ is described as exposed or probable bone in the oral cavity, present for longer than 8 weeks, without any history of radiotherapy or malignant disease in the jaws and previous or current use of anti-resorptive drugs. The treatment of MRONJ is based on the stage of the disease, which varies from stage 0 to stage 3, with increasing deterioration of symptoms and invasion of the disease throughout the entire jaw. The suggested treatment modalities vary from conservative therapy including mouth rinses, antibiotics, or removal of loosened sequestra in in the initial stages, to major and/or sometimes aggressive surgery in stage 3, involving resection with or without reconstruction. Initially most authors promoted conservative treatment for the condition, because in their opinion, any intervention would lead to worsening of symptoms, and eventually to loss of parts of the jaw[5-7]. However, more authors recently seem to promote an early surgical intervention[8-12]. These authors report an average success rate of more than 80%. The surgical modalities vary from saucerization to continuity resection of the jaw with free flap reconstruction. The basic principles of the treatment reported by several authors include thorough saucerization, smoothing of sharp edges, and closing primarily in the layers[9-11,13,14].

Our previously reported surgical protocol showed high success rates (92%) with relatively conservative surgery, such as saucerization but without segmental mandibular resection[9]. Nevertheless, there are still failures. It is important to analyze the reason of the failures and whether the surgical technique could be the cause. 3D radiological analysis of the surgical technique could give more insights into the possible causes of failure of surgical treatment of MRONJ. On a cone beam computed tomography (CBCT) scan, the extent of the MRONJ can be clearly seen in three dimensions, and it is a useful addition to panoramic radiography[15-19]. Loss of bone can be easily visualized and assessed on a CBCT scan. Therefore, the aim of our study was to evaluate the surgical technique, with a success rate of more than 90%[9]- with 3D technology. The hypothesis stated that the surgical technique used on patients treated elsewhere with unsuccessful results was different from that used in our hospital.

METHODS

In the department of oral & maxillofacial surgery of the Leiden University Medical Center (LUMC), 200 patients with MRONJ were seen and treated between January 2003 and December 2018. The criteria of the Position Paper by AAOMS[4] applied to all patients. It included the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, history of treatment with antiresorptive medication (bisphosphonates or denosumab), and no history of radiotherapy or metastatic disease to the jawbone. The clinical and radiological features together indicated the stage of MRONJ according to the criteria reported by Ruggiero et al. in 2014[4]. Patients below 18 years of age, and without a preoperative CBCT scan, were excluded. The research was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Patients

The patients were divided into two groups. For group 1, the patients were selected retrospectively. Group 1 included 15 patients with MRONJ of the mandible, who were referred from elsewhere between 2009 and 2018, and who had undergone a previous unsuccessful surgical treatment for MRONJ in other referring hospitals.

Group 2 included 15 patients with MRONJ of the mandible from the same time span as group 1, but who were not previously treated for MRONJ. These patients were treated with the standard surgical approach. The CBCT scans of group 1 patients were taken at the time of their visit to our department, and were compared with the postoperative CBCT scans of group 2 patients.

Computed tomography (CT)

For patients treated until the year 2012, a conventional CT was made, with the Aquilion One CT scanner (Aquilion One® Canon Medical Systems, Zoetermeer, the Netherlands; 120 kV; 80 mA; 500 ms; FOV 164 mm; voxel size 1 mm). The images were stored in the Picture Archiving and Communication System (PACS) of the hospital, and incorporated into the digital medical chart of the patients.

CBCT

In 2012, a CBCT scan was available, and became a part of the diagnostic protocol. Therefore, for the patients treated after 2012, the Promax 3D Planmeca CBCT scanner was used (Promax® 3D Max, Planmeca USA, Roselle, IL; 96 kV; 5.6 mA; 12 s exposure time; FOV 13x5.5 cm; voxel size 200 µm). The scan volumes were exported in Digital Imaging and Communications in Medicine (DICOM), and imported into the dental imaging software (Planmeca Romexis 5.1.1.1 Dental imaging software, Helsinki, Finland).

Surgery

In all patients, antiresorptive medication use either was stopped by the time of their presentation, or was stopped after consultation with their prescribing doctor. The surgical intervention

was performed in general anesthesia. The surgery followed the previously mentioned principles, and it was performed by two surgeons specialized in osteomyelitis. The surgical approach included removal of the diseased bone, thorough saucerization of the non-vital bone until clean bone was reached, with visually (some) bleeding bone margins, and closing in multiple, preferably periosteal, submucosal, and mucosal layers[9,20,21]. This meant minimizing the dead-space as much as possible, for tensionless closure of the overlying periosteum and mucosa. Several 'soft' criteria for the treatment included cortical rounding off until the lowest part of medullary defect, estimated absence of dead space after primary closure of the periosteal layer, sufficient total height of healthy soft tissue in primary closure above the defect.

According to the protocol, culture samples were collected during the surgery, and the diseased bone was submitted for histopathological analysis in all patients.

The surgical treatment was supported by the administration of penicillin G and metronidazole intravenously for 1 week, and amoxicillin and metronidazole orally for 3 weeks.

As per the protocol, CBCT scans of both groups were taken 2 or 3 days post-operatively during their stay in our hospital.

Analysis surgical technique

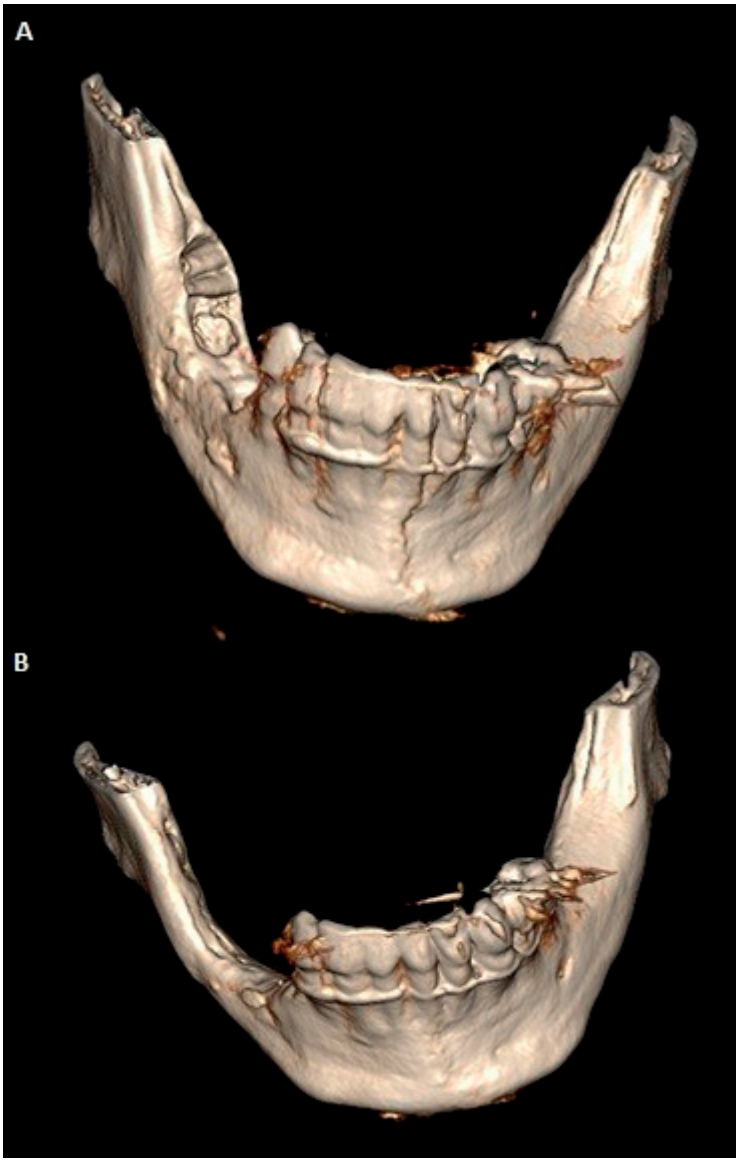
The primary aim of our study was to analyze the surgical technique in both groups. The 3D reconstructions and separate coronal, axial, and sagittal views of the (CB)CT scans from the mandible before and after surgical treatment were compared.

The surgical technique was scored based on several characteristics. The following features were scored on a 2-point scale: removal of diseased bone/sequestra, treatment of the buccal cortex, treatment of the lingual cortex, and presence of dead space/persisting alveolus in frontal aspect of the mandible. Treatment of these features was scored as either present ("1") or absent ("0"). Whether the treatment of the feature was performed sufficiently was not taken into consideration to not obscure the results when the treatment was insufficient. The treated percentages of all the scores were calculated. Scores were assigned by two surgeons together, who specialized in treatment of osteomyelitis, and were blinded for the patient group. The treatment features are shown in figures 1-4.

Another aim of the study was to evaluate and compare the surgical outcome of our surgical treatment in group 1 with the previous surgery received elsewhere, and with group 2, without any previous surgical treatment. Both groups were consequently treated with our surgical protocol.

A post-operative closed mucosa without dehiscence, after 3 weeks, was considered healed. During follow-up, the presence of fistula, dehiscence, or recurrences were evaluated. The patients were seen for at least 6 months: postoperatively after 1 week, 1 month, 3 months, and then every 6 months up to 2 years.

Figure 1: 3D reconstruction of CBCT of pre- en post-operative result showing surgical technique group 1 patient



A: Right lower jaw shows persisting extraction alveoles, some lysis and subperiosteal bone formation
B: Right lower jaw shows rounded off and smooth edges and sufficient removal of buccal and lingual cortex

Statistics

Statistical analysis was performed in SPSS software for Windows (Version 25; SPSS Inc., Chicago, IL, USA). For continuous variables, median and range were reported; for binary variable, the percentages were computed. Data was reported in median, unless reported otherwise. A p-value <0.05 was considered statistical significant.

RESULTS

In this retrospective study, 30 consecutive patients with MRONJ were included in 2 groups. 15 patients had a previous surgical treatment elsewhere (group 1) and 15 patients were treated only with the surgical technique used in the LUMC (group 2). The patient characteristics are listed in table 1.

Patients

There were 11 males and 19 females. Fourteen patients used antiresorptive medication for osteoporosis, with no statistical difference in both groups (p=0.464). Age was unevenly distributed. Group 1 had a median age of 70 (51-87) years and group 2 had a median age of 72 (60-90) years.

Sixteen patients had cancer, of which seven had breast cancer, eight had prostate cancer, and one had multiple myeloma.

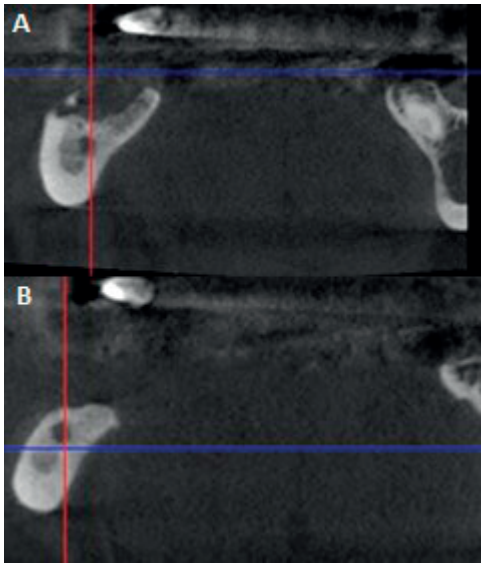
The follow-up was 3-26 months (mean 11.3±5.1). Group 1 patients mainly had stage III MRONJ; whereas, group 2 patients had stage II (p=0.008).

The median duration of medication was 77.4 months in group 1 and 19.88 months in group 2.

3D analysis of surgery

The surgical technique is illustrated in figures 1-4. The results of the study showed that in most cases of group 1, treatment of the buccal cortex was performed in 14 of 15 patients (93.7%). The

Figure 2 Pre- and postoperative treatment principle features of buccal & lingual cortex



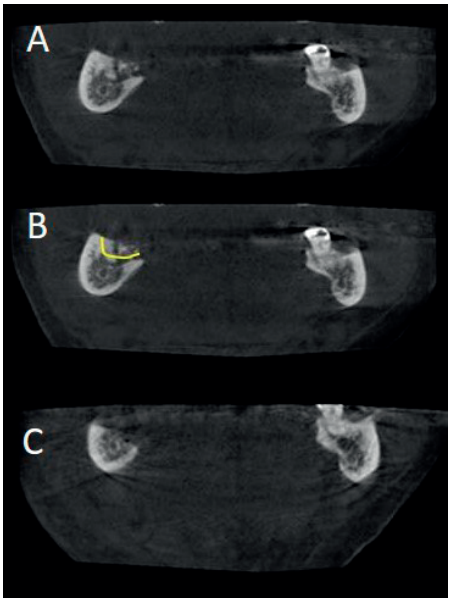
A: Pre-operative frontal view of sharp buccal edge, sequestrum and persisting lingual cortex.
B: Buccal subperiosteal bone has been minimally removed. Rounded off frontal aspect and smooth edges are reached.

Table I Clinical features

	Group I	Group II	Total	p-value
Gender				0.256[C]
Female	7	4	11	
Male	8	11	19	
Indication				0.464[C]
Osteoporosis	6	8	14	
Cancer	9	7	16	
Breast cancer	4	3		
Prostate cancer	5	3		
Multiple Myeloma			1	
Anti-resorptive medication				
Bisphosphonates			21	
Intravenous use		9		
Zolendronic acid monthly	4	3		
Zolendronic acid yearly		2		
Oral use		12		
Alendronic acid 70mg weekly	6	6		
Denosumab			9	
Xgeva 120mg monthly	5	4		
Stage[1]				0.008*[C]
II	6	13	19	
III	9	2	11	
Duration of medication (months)	77.4 (18-180)	19.88 (3-36)		
OP	90.67	24.44		
Cancer	67.5	14.0		
Follow up (months)	11.5±6.1	11.1±4.1		0.807[#]

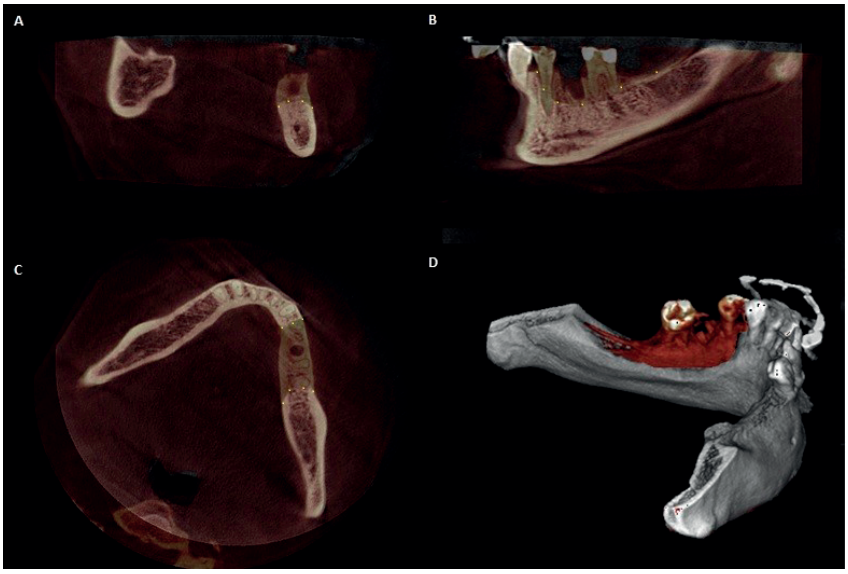
[C]=Chi-square-test
*p<0.05 was considered statistical significant
[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)
#=t-test

Fig 3 Pre- and postoperative treatment principles features of frontal view



A: An evident sequester on top of the alveolar process on the right mandible
B: Supposedly planned resection of the sequestrum and sclerotic bone
C: Post-operative view after saucerization and rounding off of sharp edges of both lingual and buccal cortex

Fig 4 Superimposed pre- and postoperative CBCT of LUMC treatment



CBCT scan of stage II MRONJ patient in the left lower jaw. The yellow dots represent the margins of the LUMC treatment.
A Frontal view: removal of bone with LUMC treatment of buccal and lingual cortex and clear rounded off frontal aspect.
B Sagittal view: evident lowering of the mandible and removal of the 34 and 36.
C Transversal view: removal of bone.
D 3D reconstruction of CBCT: extent of LUMC treatment is shown in red.

Table II Post-operative analysis treatment elsewhere vs LUMC treatment group I

Scan	Removal diseased bone (cumulative percentages)	Buccal cortex (cumulative percentages)	Lingual cortex (cumulative percentages)	Dead space/ Alveolus (cumulative percentages)	Transversal (cumulative percentages)
After surgery elsewhere	0=100% (0%)	0=6.7% 1=93.3% (93.3%)	0=100,0% (0%)	0=100% (0%)	0=0% (0%)
After LUMC treatment	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)

Table III Post-operative analysis of LUMC treatment group II

Scan	Removal diseased bone (cumulative percentages)	Buccal cortex (cumulative percentages)	Lingual cortex (cumulative percentages)	Dead space/ Alveolus (cumulative percentages)	Transversal (cumulative percentages)
After LUMC treatment	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)

other features, such as removal of diseased bone, treatment of lingual cortex, and the presence of dead space, were scarcely scored in most of the cases, as shown in table 2.

The results of the patients of group 2 showed maximum scores of treatment of the buccal cortex in all fifteen cases (100%), as indicated in table 3. Removal of diseased bone, treatment of buccal cortex, and the presence of dead space had nearly maximum scores.

Surgical outcome of LUMC treatment

Group 1 showed healing and a closed mucosa in 14 of 15 patients (93.3%). However, two patients from this group developed a pathologic fracture after treatment in the LUMC. One patient had full recovery after a soft diet, and the other continued to have an extraoral fistula with denuded bone extraorally, but with a closed mucosa intraorally, and died a few months later due to metastatic disease.

Complete healing was found in all patients of group 2 (100%) with a closed mucosa and no further complaints. The follow-up of this group was also uneventful.

DISCUSSION

In this study (CB)CT scans from patients with MRONJ and a previous surgical treatment were compared to scans from patients who were treated at our department, according to our previously reported surgical technique[9,21].The hypothesis was that there is a difference in surgical

technique in unsuccessful results of patients treated elsewhere. A 3D analysis was performed, and the bone was evaluated for several surgical principles of the treatment. In addition, the clinical outcome of the used surgical technique was analyzed.

The results of this study showed that in other institutes except for the buccal cortex, the other surgical features, such as treatment of removal of diseased bone, the lingual cortex, and the frontal aspect, were scarcely treated in patients who had undergone surgery previously outside of our department. This may have resulted in sharp bony edges, dead space and insufficient primary closure thus giving inferior results. The findings confirm our hypothesis that a difference in surgical technique plays an important role in its success rate.

The primary goal of the surgical treatment of MRONJ is to remove as much as necessary but as little as possible[14]. During the surgical procedure for treatment of MRONJ, the diseased bone is removed, which is followed by saucerization with rounding off of the edges of the bone to provide an easy tension-free primary closure. Furthermore, the rounding off helps prevent the development of secondary mucosal lesions.

The first step during the surgery is the determination and removal of the diseased bone. Clearly discolored and necrotic bone is removed. Secondly, as much sclerotic bone is removed as possible, and rounded off in order to obtain primary closure, and as little dead space as possible without challenging the remaining strength of the jaw.

According to the literature, the use of autofluorescence as an aid to find the healthy bone margins has been suggested[22-25]. In this technique, tetracycline is administered to the patient, which is incorporated in the healthy, viable bone. This can be made visible with ultraviolet (UV) light during surgery, indicating the viable bone margins by lighting them up. This is an old technique and can sometimes be difficult to interpret[26].

The reactive sclerosis, which is caused by MRONJ, but also the sclerosis caused by the antiresorptive medication, may cause difficulties in interpreting the viability of the bone.

The present study showed that treatment of the buccal cortex seemed to be done mostly in group 1. After removal of the diseased bone, removal of the buccal cortex is the next step in the procedure for most surgeons. It is probably the easiest step of the procedure. Removal of bone up to the lowest medullar level of the defect is necessary. The lingual cortex can sometimes be difficult to reach due to the small opening of the mouth and the angulation of the bur. Removal of the lingual cortex also facilitates coverage of the mandible with the floor of the mouth. Similarly, this also counts for removal of the buccal cortex, facilitating coverage of the mandible with the vestibulum. Closure of the wound in layers, with the periosteum as first layer, is easier and tension-free if the lingual cortex has been lowered and rounded off. The wound can then be closed up in 2 layers if possible[10-14]. With a non-lowered lingual cortex, primary closure is difficult, because automatically dead space is introduced.

It seems that surgical a center with less experience in ONJ or osteomyelitis, may lead to insufficient surgical treatment. The insufficient treatment of the scored features automatically leads to suboptimal circumstances for closure primarily, and thus healing, as seen in the results

of the group 1 patients. Sometimes the surgery can be difficult and certain (lingual) angles can be clinically hard to reach with the bur. The presence of present edges, but smoothened, may not necessarily be of clinical relevance. Nonnenmuhlen et al. (2019) also confirmed this with their study on different mucosal flaps for closure of the wounds[27]. Therefore, these patients showed uneventful healing, showing that some treatment of the lingual cortex in combination with optimal treatment of the other features could still lead to complete healing. This supports the hypothesis that healing is dependent on the combination of the surgical principles.

Since in this group of patients the expected physiological bone resorption will not take place due to altered bone metabolism caused by the antiresorptive drugs, regardless of whether it concerns the surgical treatment of MRONJ or a dental extraction, it is advisable to remove bone to the level of the expected normal physiological bone resorption after 6 months. If this is not taken into account, extraction alveoli, or sharp edges will remain, and cause recurrent problems, starting with mucosal dehiscence. This counts especially for the alveolar process and extraction alveoli. Special attention is needed for the amount of removed bone. As mentioned earlier, surgeons should aim to remove as much as necessary, but as little as possible, to not compromise the surgical or functional result.

Some authors promote resection of the affected area and reconstruction with a microvascular fibula flap in stage III MRONJ[28-32]. Considering our success rate, resection of the mandible seems a very drastic surgical approach with a relative high comorbidity. It can certainly be of use in ultimum refugium cases, but also as an alternative in case the above mentioned surgical technique fails. Due to the recent reported success rates using comparable surgical techniques and a less invasive character of the surgery, the approaches of these authors should be the first choice of treatment in stage II and III MRONJ[9-14]. Many patients are medically compromised making major surgery not preferable or even not possible[33].

The results also promote early intervention, instead of a wait and see policy. In an early stage, sufficient treatment is less difficult than in an advanced stage III (with or without pathologic fracture). The stage did not seem to influence the outcome with our surgical approach. Even though underlying diseases could also worsen the surgical outcome, this was not the case with a success of more than 90% in group 1. Basic principles of treatment remained the same: removal of diseased bone, saucerization, and primary closure. Viable and smooth bone margins are necessary for tension-free primary closure. One of the two pathologic fractures was cured with conservative treatment and a soft diet, proving the reason why the basic principles should always be followed. The clinical outcome of the surgical treatment in both groups was 93.3% and 100%, respectively. This suggests that prior treatment does not influence the current treatment result, but could lead to a possible higher incidence of pathological fractures due to the loss of vertical height. Our results are in line with other authors[10-14]. In literature there are no other studies addressing specifically the surgical technique of the bone. This is the first study to perform a radiological analysis in order to obtain more insight on the possible factors for failure of the surgical treatment.

One of the limitations of this study was the relative small sample size, especially for group 1. Further studies are being performed in a larger cohort of patients in our hospital, with and without previous surgical treatment.

Another limitation was the statistically significant difference in the stages between the two groups. There were more stage III patients in group I. That could also be a reason for primary failure of the surgery elsewhere. Patients with severe oncologic conditions may have a decreased healing and thus worse outcomes. Despite the staging, underlying diseases, and duration of therapy, the first group was successfully healed with our surgical technique.

In addition, the circumstances of previous surgeries, such as an underlying disease, could have led to an initial surgical treatment under local instead of general anesthesia. Therefore, extensive surgery could not be performed, which could have affected the outcome. However, being able to heal these patients shows that when the basic principles of surgery are followed, complete cure can be achieved.

This study seems to support the hypothesis that the surgical technique of MRONJ is based on the treatment of diseased bone, buccal, and lingual cortex, and if treated sufficiently, altogether provides an easy primary closure without dead space leading to complete healing of the bone. Further research is necessary regarding the ongoing debate on the best treatment for MRONJ.

CONCLUSION

The surgical technique with high success rate of more than 93.3% in all stages of MRONJ is based on a few simple surgical principles comprising of extensive saucerization and rounding off in combination with primary closure. Therefore, this relative conservative surgical approach should be the first choice in the treatment of MRONJ. Further research toward the surgical technique to prevent deterioration, recurrence or failure of MRONJ is recommended.

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‘Autoreconstruction’ of the mandible: report of a case

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ABSTRACT

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first mentioned in the literature in 2003. Since then, several reports have been published referring to this disease. The etiology of BRONJ still remains unclear. The treatment of BRONJ also remains a topic of discussion between those who are in favor of a conservative treatment and those who are convinced that surgical treatment gives the best results. In this case report, a patient is presented with BRONJ in the mandible which has been treated surgically in combination with antibiotic treatment. During surgery it appeared that a large part of the jaw was sequestrated full-thickness with, at the same time, formation of a substantial amount of subperiosteal bone that was formed around the BRONJ, supporting the sequestrated part of the mandible and, after sequestrectomy, serving as a neo-mandible. This case shows the capacity of the jawbone despite bisphosphonate use to regenerate itself.

INTRODUCTION

Bisphosphonate related osteonecrosis of the jaw was first mentioned in the literature in 2003[1]. Since then several reports and research have been published referring to this disease. In the literature authors are divided about the treatment. Some suggest to stay as conservative as possible, for surgical intervenience could worsen the disease leading to loss of (parts of) the jaw[2,3]. Other authors plead for a prompt surgical approach to stop the disease from extending in the jaw thus preventing loss of continuity[4-6].

Subperiosteal bone is formed as a response to injury caused by an inflammation, trauma to the bone, cancer or chronic irritation of the periosteum. It takes at least a few weeks before subperiosteal bone apposition is visible on an X-ray. Usually subperiosteal bone consists of a thin layer and is being resorbed in the normal bone turnover whenever the original stimulus has gone. Only in the relatively rare proliferative periostitis[7-9] or Garré's osteomyelitis, larger quantities of subperiosteal bone are found[10]. In older literature however, cases of phosphorus necrosis of the jaw with abundant formation of subperiosteal bone are formed. Thus, apart from the chronicity of the osteomyelitis seen in BRONJ, possibly the use of bisphosphonates plays a role in acquiring a large quantity of subperiosteal bone.

So far, it has never been seen or reported, that BRONJ may lead to sequestration of a large part of the jaw with at the same time a presence of a substantial amount of subperiosteal bone that was formed around the BRONJ, supporting the sequestrated part of the mandible and after sequestrectomy, serving as a neo-mandible.

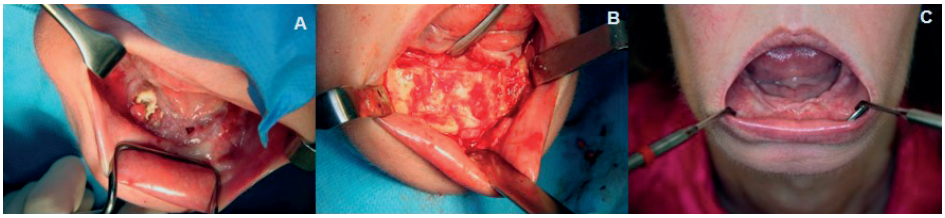
To our knowledge this case report is the first in literature to report about this phenomenon.

CASE REPORT

A 55 year old woman with metastasized breastcancer for more than three years and multiple intraoral fistulas since 6 months was referred to the department of Oral and Maxillofacial Surgery of the Leiden University Medical Center. The medical history further showed deep vein thrombosis, appendectomy, hypercholesterolemia and hepatitis. The patient used Bactroban, Paracetamol/Codein, Zoladex, Innohep and Tamoxiphen. The patient also used Pamidronate for 27 months with a dose of 90mg per month and Alendronate for 37 months orally with a dose of 70mg per week. Before surgery both anti-resorptive agents were stopped for one month, after surgery they were not continued. The patient smoked 10-20 sigarettes a day, did not use alcohol, stopped using drugs (marihuana, heroin) 32 years before. The patient did not receive radiotherapy in the head or neck region in the past.

At presentation pain, intraoral fistulas (fig 1A) and a extraoral fistula in the submental region were found. Two months before she had extractions of all her teeth in general anaesthesia elsewhere, because of caries and periodontitis, a productive submental fistula and pain. Afterwards she had antimicrobial treatment of 10 days Augmentin 625 (amoxicillin and clavulanic acid) and Perioaid mouth rinse. Despite the extractions the pain and the fistulas persisted.

Figure 1 Photographs before, during and after surgery



A= multiple intraoral fistula and denuded bone
B= subperiosteal bone before closure of the surgical wound
C= intraoral view 6 weeks after surgery with closed mucosa

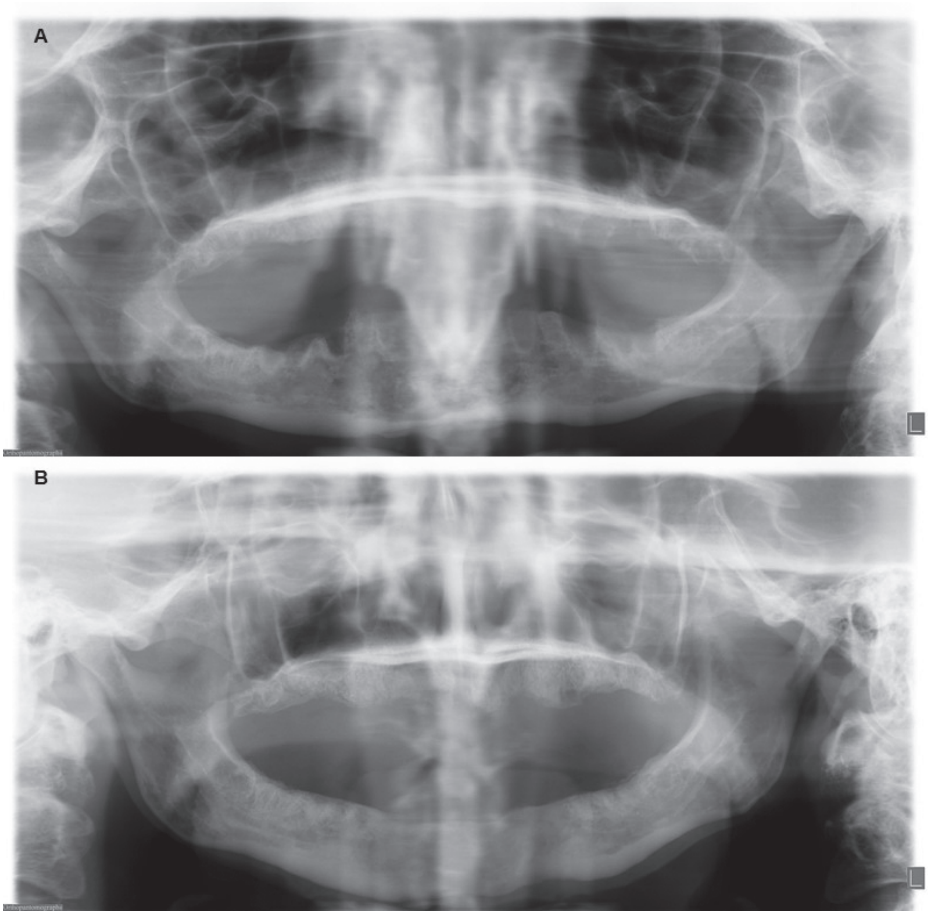
The panoramic radiograph showed osteolysis of the ventral part of the mandible (Fig 2). The CT scan (fig 3A) showed massive osteolysis and sequestration of the ventral part of the mandible from region 34 to 45 matching an osteomyelitis and BRONJ. The continuity of the mandible seemed intact just because of subperiostal bone formation (fig 3A).

A diagnosis of bisphosphonate related osteonecrosis of the jaw was made.

The patient was treated according to a protocol reported earlier by Alons[4] with a sequestrectomy in general anesthesia in combination with intravenous antibiotics. During surgery the original mandible from region 34 to 45 appeared to be completely necrotised and sequestrated. The mental nerve could not be identified on the right side, on the left side it could be identified. When the sequestrae were removed a large quantity of subperiostal bone was found around the defect especially at the former lingual border of the mandible. This subperiosteal bone seemed vital and perfused. After partial removal its buccal shape was lowered and rounded off. Finally the subperiosteal bone was shaped in order to make primary closure without dead space possible and seemed to have sufficient thickness to provide continuity of the mandible (fig 1B). The wound was closed primarily in layers[4]. The patient received anti-microbial treatment according to protocol (Penicillin G (6 x 1 million EH) and Metronidazole (3 x 500 mg) were administered for five days intravenously followed by Amoxicillin orally 3 x 500 mg for three weeks and Metronidazole 3 x 500 mg for three weeks.)

Histologic examination of the bone showed non-vital bone, signs of chronic inflammation and the extensive presence of microorganisms. Streptococcus constellatus, a mixed-cell infiltrate and Actinomyces were seen; there were no signs of metastases of the breast cancer in the mandible.

Figure 2 Radiologic findings before surgery and 9 months after surgery



A: Panoramic radiograph with extensive osteolysis, extending from the region of 46 to 34 up to the inferior border in the region of the symphyse
B: Panoramic radiograph 9 months post-operatively with healed, smooth edges of the mandibular corps

The patient's recovery was good without further complaints, intraoral dehiscences or fistulas (fig 1C). During follow-up no pathological fracture of the subperiosteal bone occurred. The panoramic radiograph showed continuity of the mandible and a cortex like structure. The CT scan 6 weeks after surgery showed a lingual neo-cortex of the mandible without any signs of resorption (fig 3B). At follow-up after 9 months the patient was still free of complaints.

DISCUSSION

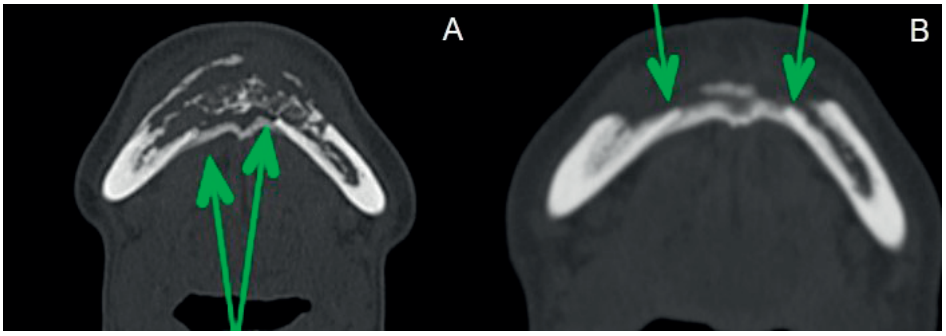
Bisphosphonates are built in in bone tissue and are released after cessation of therapy over a prolonged time. Therefore, bisphosphonates stay effective for years. Since bisphosphonates inhibit the osteoclasts, bone resorption is decreased, hence in this case probably also the subperiosteal bone resorption.

The reason of the subperiosteal bone growing to this volume is probably because of the long duration of chronic irritation of the periosteum caused by the former dentition with multiple inflammatory foci and the longterm use of bisphosphonates. However, subperiosteal bone is supposed to be resorbed entirely in the normal bone remodeling process. But in this case it did not. A possible explanation for this could be due to the bisphosphonates, which decrease (subperiosteal) bone resorption. In normal patients these amounts of subperiosteal bone formation would not have been reached due to the normal bone remodeling process and normal (subperiosteal) bone resorption. In our opinion there is not necessarily more subperiosteal bone formation in BRONJ patients compared to normal patients, but rather a decreased bone resorption due to bisphosphonates.

The pre and post-op CT scan confirmed this finding that the continuity of the original lingual cortex of the region from 34 to 45 was gone and replaced by subperiosteal bone (fig 3B).

The CT scan also showed that the subperiostal bone developed a cortex-like structure (fig 3B). The distinction between the former cortex of the mandible and the cortex of the neo mandible was visible on the CT scan (fig 3B). Where the first CT scan made at presentation clearly shows a distinction between the subperiosteal bone and the lingual cortex, the second CT scan made several weeks after presentation appears to have no such clear dinstinction anymore. It seems as if a new cortex has been formed.

Figure 3 Comparison CT scans before (A) and 3 months after surgery (B)



A= lingual subperiosteal bone can be seen and seems to connect both parts of the mandible
B= the difference between the cortex of the mandible and the subperiosteal bone is decreasing

It appears that this phenomenon is not entirely new. Older literature going back to the mid nineteenth century already showed subperiosteal bone formation in phossy jaw-patients during and after surgery[11,12]. Workers in matches industry were at risk for developing the phossy jaw caused by the inhalation of phosphorus vapours in the factories. These phosphorus vapours had a similar effect on the jawbone as bisphosphonates do[13,16]. Several written case reports of the phossy jaw patients are comparable in clinical features with the current BRONJ with in several cases abundant subperiosteal bone formation[11,12,17]. In this case the subperiosteal bone mass appeared sufficient to retain mandibular continuity during a follow up of more than 9 months.

CONCLUSION

This report of a case of BRONJ of the mandible with excessive subperiosteal bone formation shows a practical and patient friendly use of the excessive amount of this subperiosteal bone in BRONJ.

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Discussion and future perspectives

DISCUSSION AND FUTURE PERSPECTIVES

Aims of this thesis

This thesis aimed to provide more insight in the diagnosis of MRONJ and to study the best treatment for MRONJ. In order to give more insight in the different aspects of the diagnosis of MRONJ, part I focuses on origin, clinical and radiological features with a special interest for dental implants. This was performed through retrospective cohort studies and an observational study.

Part II focuses on the surgical treatment of MRONJ. Surgical treatment of BRONJ and DRONJ is challenging since no consensus is found in the literature. Cohort studies were performed on the outcome of our surgical treatment. Our surgical technique was analysed with 3D imaging. The results of the challenging treatment of stage III MRONJ were discussed with an observational study.

PART I - DIAGNOSIS

Origin

Part I concentrates on the diagnosis of MRONJ. The origin of MRONJ is still debated in literature. MRONJ has not been reported in other bones other than the jaws. A possible explanation for this is the presence of teeth and/or a very thin mucosa in edentulous patients shortening the distance between the bone and the oral environment. There remains a controversy in literature between the spontaneous cause of MRONJ, the so-called “inside-out”-theory, and the dental related cause known as the“outside-in”-theory[1-10] The first cause is assigned to an infection in the jaw bone that then spreads to the surrounding tissues. The latter is an infection of dental origin or a porte-d’entrée due to denture-related pathology in edentulous patients, with a secondary infection of the jaw bone. All patient cohorts described in this thesis were closely examined in order to analyse all luxating moments of the MRONJ (CHAPTER 2). The results show a certain or presumable dental focus, such as extractions, placing of implants, dental treatments, periodontitis, apical granuloma, in nearly all patients. Pressure sores due to ill-fitting dentures, or caused by a knife edge ridge or a prominent mylohyoid ridge were assigned as a presumable dental focus. This thesis therefore shows that MRONJ is precipitated by dental pathology, a dental/surgical procedure or a pressure sore. An actual defect in the mucosa due to e.g. a pressure sore can cause a porte- d’entrée to the jaw thus leading to invasion of bacteria and development of jaw necrosis. This may well be an explanation for the so-called ‘spontaneous osteonecrosis’ as found in several reports in the literature.

Now a dental origin of MRONJ seems to be established, there should be a more prominent role for prevention of MRONJ. For dental clinicians, but also for the prescribing doctors (e.g. internists such as oncologist and hematologists, general practitioners) this would mean a focus

on informing patients of the possible disease and dose depending risks for MRONJ. But primarily emphasizing the necessity and importance of prevention and adequate-preferably rapid- treatment of dental pathology. Dental check-ups before initiation of the anti-resorptive therapy might be advisable and maintenance of a good dental hygiene is of upmost importance.

Implant survival & risk factor

CHAPTER 3 focuses on dental implants and its relation to and survival with MRONJ. A precipitating event causing MRONJ can be implant associated. The relationship between implants and MRONJ but also the exact pathogenesis still remain unclear. However, the number of reports on implant-related MRONJ and its causes is increasing. They show that 10-15% of MRONJ should be considered implant-related[11-14]. This concerns a serious amount of patients and has clinical implications.

The majority of reports and cases in the literature concern patients who received their dental implants before the start of anti-resorptive medication (CHAPTER 3). Osseointegration will therefore be concluded before the start of the medication making peri-implantitis the main risk-factor for the development of MRONJ around dental implants[15-17]. The loss of implants seems directly related to the local factors or the spread of the MRONJ. Whenever a zone of healthy bone is present between implants and the MRONJ, the prognosis of the remaining implants seems to be normal (CHAPTER 3). Peri-implantitis seems to act, as is the case in other dental inflammations like apical granuloma or periodontitis, as a cause for the development of MRONJ (CHAPTER 2&3). The other cause for implant-related MRONJ is the insertion of dental implants. These patients received implants during their anti-resorptive therapy and lost their implants within 6 months after insertion.

CHAPTER 3 shows that implants adjacent to a necrosis, but not involved could be preserved. This also supports early intervention in MRONJ to save adjacent implants. Furthermore, these findings support the outside-in theory with development of the MRONJ. Most patients with implant-related MRONJ seem affected by peri-implantitis[17] (CHAPTER 3).

Currently there is no consensus on the placement of implants[18]. There are several reports on development of MRONJ in predominantly intravenous use of bisphosphonates[12, 15, 17, 19-22] and to a lesser extent oral bisphosphonates[20, 21]. Also, reports are present on survival of implants in patients who use oral bisphosphonates, in whom little to no MRONJ developed[23-25]. Our study shows that both intravenous and oral bisphosphonate users can develop MRONJ. Therefore there is a serious increased risk for failure of implants with anti-resorptive therapy. Recent literature shows a difference in favour of oral BP use[23, 25]. Supposedly there is no increased risk for MRONJ with oral BP use. However in this thesis it is shown that both oral as iv BP can cause MRONJ, although time to event with the latter is much shorter. Considering that implants are more prone to failure, inserting implants when the use of anti-resorptive medication equals or exceeds the duration of time for the drugs to cause MRONJ, 2 years of oral BP use and 1 year intravenous BP use, should be reconsidered and appropriate measures should be undertaken[6, 13, 14, 26].

The relevance of literature findings is difficult to interpreted due to the heterogeneity of the studies and further (prospective) studies are necessary emphasizing the importance of the findings of this thesis. This means that dental hygiene should be optimal in patients using anti-resorptive medication and eligible for implants to prevent development of peri-implantitis, which can lead to MRONJ. In addition the decision for insertion of implants should be made on an individual level and preferably in a specialised centre because of the increased risk of development of MRONJ in long term users.

Radiological features

A diagnosis of MRONJ cannot be made properly without imaging. A panoramic radiograph is advised as a first choice in literature[27, 28]. In addition, many authors report of frequent use of 3D imaging with (cone beam) CT. This gives a better view on the mandibular bone in general as well as important features of the MRONJ[28-36] as the size of the lesion, the presence of sequesters, subperiosteal bone formation, lysis of the cortical border and sclerosis.

In general no distinction is made between the radiographic images of BRONJ and DRONJ[28-36]. However, based on clinical impressions of more sclerosis and less sequesters in DRONJ a study was performed on the radiological findings on CBCT in DRONJ and BRONJ (CHAPTER 5). This study showed that denosumab necrosis showed significant less sequestra and lysis of the cortical border than bisphosphonate related osteonecrosis. Subperiosteal bone formation was equally present in denosumab necrosis and bisphosphonate necrosis. This difference could possibly be due to the different mechanism of action.

The immediate absence of osteoclast function with denosumab possibly leads to the inhibition of sequestration. In bisphosphonate cases with evident sequestration, the body already demarquates the healthy bone margins. It may be difficult to find viable bone margins without evident sequestration. This difference in the presence of sequesters could lead more easily to insufficient treatment in denosumab cases, because underestimation of DRONJ can occur. The absence of sequestra or lysis may even unintentionally suggest that there is no necrosis. Furthermore, the theory that denosumab necrosis would be self-limiting, because its effect is gone after six months, may lead to underestimation. It may unintentionally lead to the choice of a relatively conservative treatment, which on its turn may lead to serious deterioration of the disease[37, 38]. The effect of denosumab may be gone after 6 months, but the changes in bone structure (i.e. sclerosis) will take longer to resolve to its original state. A complicating factor is that cessation of denosumab treatment should always be performed in collaboration with the prescribing physician as after stopping of denosumab bone loss and an increased risk for vertebral fractures has been described[39-41].

A combination of clinical and radiological examination should dictate the diagnosis and treatment. DRONJ may unintentionally be undertreated because it does not present itself as clearly as BRONJ.

PART II - TREATMENT

In the literature there is still a lot of discussion on the optimal treatment of MRONJ. Shortly after the first reports on MRONJ, conservative treatment with mouth-rinses and anti-microbial treatment was recommended. Several authors claimed worsening of symptoms when intervening surgically, e.g. pathological fractures or loss of parts of the jaw[5, 13, 18]. Consequently, in the first stages of MRONJ only removal of loose sequestra was advised. Surgery was used only in severe cases needing resection and reconstruction. In later years several reports appeared in the literature suggesting that a 'wait and see' conservative policy could lead to larger, more therapy resistant lesions and that early intervention could be successful[37, 42-45].

More recently the majority of reports on treatment of MRONJ show high cure-rates with a combination of sequestrectomy and antibiotics.

The surgical treatment/sequestrectomy in the LUMC is based on the treatment protocol of chronic suppurative osteomyelitis[46]. This surgical approach with high curation rates in chronic suppurative osteomyelitis of the mandible was also used as a treatment regimen for MRONJ, because of the resembling clinical features. The initial results were promising and it became the standard protocol of care[42, 43, 47]. This surgical technique has similar success rates as other authors report in the literature[11, 45, 48-50].

Surgical treatment in stage II & III patients

Surgical techniques are widely discussed. CHAPTER 6 describes a 92,3% success rate following the previously reported surgical protocol[42, 43, 47]. This thorough intra-oral sequestrectomy and saucerization followed by primary closure prevented segmental resection and reconstruction with free vascularized osteocutaneous flaps. These results suggest that early intervention will prevent deterioration of the disease with loss of parts of the jaw as a consequence. This is in-line with many, mostly European, studies which recently showed similar success rates of more than 80% up to nearly 100%[11, 45, 48-52]. Several authors report success with local flaps such as the buccal fat pad or with mylohyoid muscle flap to close defects in the upper and lower jaw respectively[53, 54].

Patients where a pathologic fracture of the mandible is already present, stage III MRONJ (CHAPTER 8), offer a bigger challenge. Essential for the treatment again, is a sequestrectomy with removal of diseased bone and primary closure in layers combined with antibiotics in line with others[55]. Depending on the dental status, these patients can additionally be treated with arch bars or a soft diet only (edentulous patients). We accomplished acceptable results (CHAPTER 8) with even restoration of continuity in several patients and succeeded to prevent any resections of the jaw. The latter is especially important because patients suffering from this severe stage of MRONJ with a fracture, usually are elderly with multiple comorbidities and/or metastatic disease. In these patients the international guidelines (AAOMS) advise resection with free microvascular flap reconstruction. However these approaches come with a risk for infection

and complications and are therefore not always preferable. Our success rates (73%) shown in CHAPTER 8 are very acceptable considering the severe stage III of MRONJ and in the light of average success rate of 80% of the surgical treatment of stage II/III MRONJ in literature[11, 45, 48-50]. Therefore a limited approach should be considered as a serious treatment option in a fragile patient population.

In order to illustrate the principles of the surgical technique of the bone surgery, reported in several publications from the LUMC, pre-and post-operative 3D scans were studied to visualise the amount of bone removal (CHAPTER 9). 3D analysis in 30 patients (CHAPTER 9) clearly showed the differences in treatment of the bone between this technique and that of other referring surgeons. Removal of diseased bone followed by saucerization of the bone until reaching viable bone margins and then eliminating dead space as much as possible through rounding off of sharp edges, frequently leads to necessary extractions of neighbouring teeth just in order to get primary closure. Finally tensionless primary closure of the wound in layers can easily be done. The experience of the surgeon has a major role in the success of the treatment. Removal of diseased bone until reaching viable bone margins may be difficult especially in cases with extensive sclerosis where the difference between bleeding bone and avascular bone is vague. The distinction between sclerosis due to the medication or reactive bone hyperplasia due to the chronic osteomyelitis, remains difficult. Several authors[50, 56-62] have reported on claimed successes with tetracyclin autofluorescence as an aid. But this method is oldfashioned[63], and it can still be difficult to interpret. With autofluorescence bone is labelled with tetracycline. Tetracycline has a high affinity to calcium and can easily bind to the bone matrix. With a fluorescence lamp viable bone can be detected. Its value remains questionable if similar or even higher success rates are reached without[50, 56, 61, 64].

CHAPTER 9 also shows that insufficient treatment of the bone may indirectly cause failure of the treatment. Bony edges prevent easy tensionless closure and may therefore lead to (persisting) mucosal defects. The same goes for sharp, bony edges of the alveolar process after extractions that cause mucosal lesions, eventually leading to non-healing exposed bone and MRONJ.

These findings stress that surgical treatment in MRONJ is different in comparison to regular chronic suppurative osteomyelitis.

Considering the high success rates of the reported LUMC-technique in stage II/III–MRONJ patients as shown in CHAPTER 6-9 with a limited approach [11, 24, 45, 48-51, 55], we propose early surgery as the treatment of first choice for MRONJ.

CHAPTER 10 illustrates the unusual characteristics in this patient group. Although bone remodelling is severely inhibited, the bone formation is less suppressed leading to, in many cases, large amounts of subperiosteal bone. The case-report shows a rare case of an 'autoreconstruction' of the mandible due to a large amount of subperiosteal bone around a necrotic mandible. The mandible was necrotic between the mental foraminae and needed resection, but in this particular case the body had provided in its own reconstruction. Therefore the excessive amount of subperiosteal bone that was formed on the lingual side was sufficient to maintain the

continuity of the mandible after removal of the entire necrotic symphysis of the mandible during surgery. The patient lived one year after surgery with a healed mucosa and without complaints. The patient died due to metastatic disease, one year after surgery.

The case shows the ability of the patient to make use of the body's own provisional reconstruction. Subperiosteal bone is healthy viable bone which can be maintained in order to serve as continuity. In case of excessive amounts of subperiosteal bone, this advantage should be considered and used whenever possible.

FUTURE PERSPECTIVES

This thesis focuses on diagnosis and treatment of MRONJ. MRONJ remains a topic of discussion. It can be difficult to treat, but with our protocol good results are achieved. We therefore propose this surgical protocol as treatment of first choice in all MRONJ patients. Even patients with a pathologic fracture can be treated with low morbidity and good results.

Further research to the disease's behaviour in bone with quantification of the density of bone with nuclear investigations should be performed in order to get more insight in the changes that occur on tissue level in the bone. These changes are not visible on conventional radiographic techniques as panoramic radiograph or computed tomography. Measurement of serum bone metabolism parameters in patients with anti-resorptive therapy, during MRONJ and after healing of MRONJ may provide information on the body's altered metabolism due to anti-resorptive medication and development of MRONJ. Combining the results of these investigations may create the possibility to draw a risk profile for development of MRONJ. Therefore this could contribute to improvement of guidelines on dental treatments or surgeries during anti-resorptive therapy. Quality of life assessment such as the PROMs should be considered to show the benefit of treatment from the patients perspective.

More awareness should be created among prescribing practitioners and dental specialists for treatments during anti-resorptive therapy and the possible risk for development of MRONJ. More awareness will lead to early detection and thus early intervention and avoiding deterioration of the disease.

In addition, there should be a greater focus on prevention of MRONJ with a dental check-up if possible before the start of anti-resorptive therapy. This is especially applicable for cancer patients. However in the patients with the highest risk, being Multiple Myeloma as well as other malignancies, these screenings are often not feasible due to the underlying nature of the disease. Possible dental interventions should take then place as soon as possible.

There is an increased risk for peri-implantitis and development of MRONJ. Therefore patients with or with intended implants should be informed of this increased risk. This should be addressed by well-informed dental professionals. Dental hygiene instructions and a strict follow-up for these patients to prevent peri-implantitis is important. Furthermore, in long term

antiresorptive users planning of implants should be preferably performed multidisciplinary in a specialized centre.

Guidelines and information leaflets should be created for patients, prescribing physicians, dental clinicians and implantologists on how to deal with extractions, dental pathology or implants and anti-resorptive therapy. These leaflets should take into account the specific working mechanisms of anti-resorptives and the different risks for MRONJ among the different diseases due to variations in dose and time interval.

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Summary

SUMMARY

In this thesis the focus was on diagnosis and treatment of Medication related osteonecrosis of the jaws (MRONJ). *Part I* concentrates on the diagnosis of MRONJ. The origin of MRONJ is still debated in literature. The aim of this thesis is to provide more insight in the diagnosis of MRONJ and the optimal treatment. Furthermore it intends to provide guidance for (dental) practitioners.

CHAPTER 1 is the introduction to this thesis. It starts with a short introduction on the 'phossy jaw', an ancient phenomenon, which strongly resembles the clinical picture of MRONJ. Etiology of MRONJ, mechanism of action of anti-resorptive medication and indications are reviewed. Present diagnostics, imaging and treatment are shortly discussed. Lastly the outline of this thesis is established.

CHAPTER 2 is a study towards the origin of MRONJ. In 45 patients all previous medical and dental histories were studied and the events leading to the MRONJ were analysed. Extractions, placing of implants, dental treatments, periodontitis, apical granuloma were considered certain dental foci. Pressure sores due to ill-fitting dentures, caused by knife edge ridge or a prominent mylohyoid ridge were assigned a presumable dental focus. A certain dental focus was found in 80% of the patients, a presumable dental focus was found in 17.8%. Spontaneous was assigned to patients without any dental history or prothesis complaints. Unknown was ascribed to patients with an unclear history. No spontaneous patients were seen. One patient was considered unknown. This patient presented with a swelling under an ill-fitting prothesis, which raises the question whether the swelling was the cause for the ill-fitting prothesis, or vice versa. The results of the study further show that nearly all patients had a certain or presumable dental focus (97,8%). This suggests that MRONJ is precipitated by a dental cause. In literature more studies confirm these findings. Pressure soars, which initially were considered spontaneous in literature, are now also considered a dental cause for MRONJ. Therefore dental check-ups should be performed before anti-resorptive treatments if possible and special care should be given to the fitting of dentures given the fact that these can cause pressure sores, which can cause MRONJ.

CHAPTER 3 studies the relationship between implants and MRONJ. In a cohort of 150 patients, the patients with implants in the necrosis were analysed. These patients were studied on their luxating moment of MRONJ. 77.8% of the patients had implants before their anti-resorptive therapy. These patients developed peri-implantitis, which led to MRONJ. The remaining 22.2% were inserted during or after their anti-resorptive therapy. These patients experienced MRONJ within 6 months after insertion. All patients were treated with surgery. Implants in the necrosis were lost; most of them were already lost at presentation, the remaining were removed during surgery. Good functioning implants not involved in the necrosis survived. There is great controversy in literature regarding the placement of implants in patients with anti-resorptive therapy. Hard contraindications cannot be found in literature. However, considering the risks for MRONJ and the accompanying morbidity some reserve towards insertion of implants is recommended.

Therefore placement of implants in patients with anti-resorptive therapy should be done with caution and good dental hygiene and follow-up.

CHAPTER 4 shows the results of a comparison of the radiological features of denosumab related osteonecrosis of the jaws (DRONJ) and bisphosphonate related osteonecrosis of the jaws (BRONJ). The presence of sequestra, subperiosteal bone formation and lysis of the cortical border are indicative for osteonecrosis. Therefore these features were scored in 2 groups of 17 patients with DRONJ and BRONJ. Denosumab shows a statistical significant absence of sequestra ($p=0.015$) and lysis of the cortical border ($p=0.033$). There was no difference between presence of subperiosteal bone formation ($p=0.545$) in the denosumab or bisphosphonate group. This was the first study to show a significant difference between radiological appearances of DRONJ and BRONJ. The study stresses that underestimation can occur, when DRONJ does not present itself with a clear (expected) clinical picture such as BRONJ. Underestimation may lead to a conservative treatment, which then could lead to a worse and more difficult coarse of disease.

CHAPTER 5 shows us our first experience with DRONJ. This was one of the first reported cases on denosumab necrosis. This case reports a 74-year-old male patient with a medical history of diabetes mellitus, angina pectoris, coronary bypasses, hypertension, and prostate cancer with multiple metastases to lymph nodes, bone and lungs. The prostate cancer was treated according to the protocol. But he was never treated with bisphosphonates. Instead he was included in a phase III randomized double blind multicentre trial, testing the efficacy of denosumab compared to zoledronic acid in the treatment of bone metastases of hormone resistant prostate cancer. Only 7 months after start of denosumab infectious symptoms developed, followed by infestation of the mandible. Despite surgical treatment, fistula and exposed bone remained. This case illustrates that use of denosumab can lead to a type of osteonecrosis resembling bisphosphonate related osteonecrosis of the jaws.

Part II mainly focuses on the surgical treatment of MRONJ. The surgical treatment of MRONJ remains controversial. The following chapters discuss the optimal treatment for MRONJ.

CHAPTER 6 evaluates the treatment of bisphosphonate related osteonecrosis of the jaws (BRONJ) according to our previously reported protocol. A sequestrectomy is based on the basic principles of the treatment of chronic osteomyelitis. These are removal of necrotic bone, thorough saucerization and rounding off of sharp edges. All patients were treated with a sequestrectomy in combination with intravenously administered antibiotics. Seventy-four stage II/III-BRONJ patients were studied. Success was defined as a closed mucosa with no further complaints. In 92,3% success was achieved with a follow-up of 6-96 months. Despite the relative minor surgical approach – instead of the international guidelines advising a major surgical approach such as resection- patients were cured. These results promote an early and thorough treatment of BRONJ.

CHAPTER 7 shows the first publication in literature of a small cohort of patients with DRONJ. A series of 11 patients was characterized and analysed. All patients were treated according to the basic principles as with BRONJ. Nine of eleven patients were healed with this surgical ap-

proach. Two died of metastatic disease and could not have a second (surgical) treatment. The pathogenesis of DRONJ still remains unclear, as is the case with BRONJ. DRONJ resembles BRONJ in clinical features. In all patients a dental focus for the DRONJ was found. In literature DRONJ is now considered MRONJ together with BRONJ. Initially DRONJ seemed more difficult to treat, however that could not be confirmed in this study or in literature. Considering these results it seems important to develop good prevention programs and encouraging patients to keep good oral hygiene prior to denosumab use. Further research on a molecular level seems necessary to find out the exact pathogenesis of DRONJ.

CHAPTER 8 studies the 3D analysis of our surgical technique in 30 patients. To objectivate the surgical technique several principles of the treatment of the bone were analysed with (CB) CT scans. Two groups of patients were selected. Group 1 comprised 15 patients who were unsuccessfully surgically treated elsewhere and group 2 comprised 15 patients who were successfully treated only with our previously reported technique. The post-operative scans of both groups of patients were scored on treatment of diseased bone, buccal and lingual cortex, presence of dead space and frontal aspect. The patients treated elsewhere showed mainly treatment of the buccal cortex, persisting necrotic bone and dead space. Sufficient removal of diseased bone and treatment of buccal and lingual cortices, with thorough rounding off to smooth edges facilitates primary closure in layers with as less dead space as possible. Nearly all patients were cured with our surgical approach, 93.3% in group 1 and 100% in group 2. Therapy resistant MRONJ remains a problem that plagues several clinicians. The results show that treatment according to our surgical technique has a high success rate in all stages of MRONJ. The technique is based on a few relatively simple surgical principles comprising extensive saucerization and rounding off in combination with primary closure. In literature this technique is in line with others, with comparable success rates.

CHAPTER 9 studies the treatment of stage III MRONJ patients with pathologic fractures of the mandible. The treatment of these patients is very challenging. In our cohort of 150 patients 17 patients presented with a pathologic fracture. These patients were treated depending on their dental state (dental of edentulous) with arch bars or conservative with a soft diet. Essential for the treatment was a sequestrectomy with removal of diseased bone and primary closure in layers combined with antibiotics. Patients suffering this stage of disease with a fracture are usually elderly with comorbidities and/or metastatic disease. The results show that in 84% of the patients healing or a pseudarthrosis was achieved. These patients were saved from a resection with microvascular flap reconstruction-as recommended in literature-, which is not preferable in this group of medical compromised people. The surgical approach with thorough saucerization and temporary fixation with dental arch bars in dentate patients of a conservative treatment in edentulous patients shows very acceptable results.

CHAPTER 10 shows a rare case of an ‘autoreconstruction’ of the mandible. It illustrates a patient with a large amount of subperiosteal bone and a necrotic mandible. The mandible was necrotic up to the inferior border, but in this particular case the body seemed to have provided in

its own reconstruction. The amount of subperiosteal bone formed on the lingual side was sufficient to maintain the continuity of the mandible after removal of the entire necrotic symphysis of the mandible. For one year the patient had a healed mucosa without complaints, but then died due to metastatic disease. This case shows the capacity of the jawbone, despite bisphosphonate use, to regenerate itself.

CHAPTER 11 discusses the conclusions, clinical implications and future perspectives of this thesis.

13

Dutch Summary
Samenvatting

SAMENVATTING

Dit proefschrift richt zich op de diagnose en behandeling van medicatie gerelateerde osteonecrose van de kaak (MRONJ). Deel I concentreert zich op de diagnose en deel II focust zich vooral op de chirurgische behandeling van MRONJ. Zowel de oorsprong als de behandeling van MRONJ zijn controversieel en nog altijd in de literatuur bediscussieerd. Het is een moeilijk te behandelen aandoening, die tot verlies van delen van de kaak kan leiden en de bijbehorende morbiditeit en invaliditeit. Het doel van dit proefschrift is om meer inzicht te verschaffen in de diagnose en de optimale behandeling van MRONJ en om richtlijnen te bieden voor (tandheelkundige) behandelaars.

HOOFDSTUK 1 is de inleiding van dit proefschrift. De inleiding begint met een korte introductie over de 'phossy jaw', een eeuwenoud fenomeen, dat klinisch sterke overeenkomsten vertoont met de MRONJ. Daarnaast beschrijft het hoofdstuk kort iets over het ontstaan, de werkingsmechanismen en de indicaties voor het gebruik van de anti-resorptieve medicatie. Het klinisch beeld, de diagnose, beeldvorming en behandeling worden kort toegelicht en er wordt stilgestaan bij de tot nu toe bekende literatuur. Ten slotte wordt het kader geschetst waarin dit proefschrift is geschreven.

HOOFDSTUK 2 is de eerste studie naar de oorsprong van MRONJ. In onze groep patiënten werden de medische en tandheelkundige voorgeschiedenis bestudeerd en werden alle luxerende momenten geanalyseerd. Extracties, het plaatsen van implantaten, tandheelkundige behandelingen, parodontitis en apicale granulomen werden beschouwd als 'zeker' dentogeen focus. Drukplekken ten gevolge van slechtzittende prothesen, of veroorzaakt door een zeer smalle processus alveolaris de zogeheten 'knife edge ridge' of een prominente linea mylohyoidea werden gezien als 'vermoedelijk' dentogeen focus. De resultaten toonden bij 44 van de 45 patiënten een zeker, dan wel een vermoedelijk dentogeen focus. Een luxerend moment lijkt te leiden tot MRONJ. Nagenoeg alle patiënten hadden een herleidbaar dentogene oorsprong. Daarom valt een dentogeen focus onderzoek voor de start van anti-resorptieve medicatie aan te bevelen.

HOOFDSTUK 3 bestudeert de relatie tussen implantaten en MRONJ. In een cohort van 150 patiënten werden de patiënten met implantaten in het bijzonder bestudeerd. 77.8% van de patiënten hadden implantaten voor de start van hun anti-resorptieve therapie. Deze patiënten ontwikkelden peri-implantitis, die leidde tot MRONJ. De resterende 22.2% hadden implantaten die tijdens of na anti-resorptieve therapie waren geplaatst. Deze patiënten ontwikkelden MRONJ binnen 6 maanden na het plaatsen van de implantaten. Alle patiënten werden vervolgens chirurgisch behandeld. Implantaten in de necrose gingen verloren; de meeste waren al verloren gegaan tijdens de eerste presentatie, de rest werd verwijderd tijdens de behandeling. Over het plaatsen van implantaten bij het gebruik van anti-resorptieve therapie bestaat in de literatuur grote controverse. Harde contra-indicaties worden niet genoemd. Desalniettemin, met het oog op de risico's op MRONJ en de bijkomende morbiditeit, is enige terughoudendheid met het

plaatsen van implantaten aanbevolen. Daarom zou het plaatsen van implantaten bij deze patiëntengroep met de nodige voorzorg, goede mondhygiëne en follow-up worden gedaan.

HOOFDSTUK 4 toont de resultaten van de vergelijking tussen de radiologische bevindingen tussen denosumab gerelateerde osteonecrose van de kaak (DRONJ) en bisfosfonaat gerelateerde osteonecrose van de kaak (BRONJ). De aanwezigheid van sequesters, subperiostale botvorming en lyse van de cortex zijn indicatief voor osteonecrose. Daarom werden deze kenmerken gescoord in 2 groepen van 17 patiënten met DRONJ en BRONJ. Denosumab toont een statistisch significant verschil voor de aanwezigheid van sequesters (p=0.015) en lyse van de cortex (p=0.033). Er was geen verschil wat betreft de aanwezigheid van subperiostale botvorming tussen de denosumab- en bisfosfonaatgroep. Dit was de eerste studie die een statistisch significant verschil aantoont tussen de radiologische kenmerken tussen DRONJ en BRONJ. Deze studie benadrukt dat onderschatting kan ontstaan, als DRONJ zich niet duidelijk presenteert zoals verwacht bij BRONJ. Onderschatting kan ten onrechte leiden tot een conservatief beleid, dat dan weer zou kunnen leiden tot een slechter en moeilijker beloop van de ziekte.

HOOFDSTUK 5 toont de eerste ervaring met DRONJ. Dit was één van de eerste gerapporteerde casus in de gehele literatuur. Het betreft een 74-jarige man met in de voorgeschiedenis diabetes mellitus, angina pectoris, bypassen, hypertensie en lymfogeen en ossaal gemetasteerde prostaatkanker. De prostaatkanker werd volgens protocol behandeld. Maar hij werd nooit behandeld met bisfosfonaten. In plaats daarvan werd hij geïncludeerd in een fase III gerandomiseerde dubbel blinde multicenter studie, die het effect van denosumab vergelijkt met die van bisfosfonaten bij de behandeling van botmetastasen bij hormoon resistente prostaatkanker. Pas 7 maanden na start van de denosumab ontstonden er infectieuze symptomen, gevolgd door invasie van de mandibula. Ondanks chirurgische behandeling persisteerden fistula's en bloot bot. Deze casus illustreert dat het gebruik van denosumab kan leiden tot een type van osteonecrose zoals die van bisfosfonaatnecrose.

Deel II concentreert zich op de chirurgische behandeling van MRONJ. De chirurgische behandeling blijft nog altijd controversieel. De volgende hoofdstukken bediscussiëren de optimale behandeling.

HOOFDSTUK 6 evalueert de behandeling van BRONJ volgens ons eerder gepubliceerd behandelprotocol. Een sequestrectomie is gebaseerd op de basale principes van de behandeling van chronisch purulente osteomyelitis. Deze zijn verwijdering van de dood bot, grondige 'saucerization' en afronden van scherpe randen. Alle patiënten werden behandeld met een sequestrectomie in combinatie met intraveneuze antibiotica. Er werden 74 patiënten bestudeerd. Succes werd gedefinieerd als een gesloten mucosa zonder verdere klachten. In 92,3% was de behandeling succesvol met een follow-up van 6-96 maanden. Ondanks de relatieve beperkte chirurgische benadering -in plaats van de internationaal geadviseerde grote chirurgie met resectie- werden patiënten toch genezen. Deze resultaten promoten een vroege en grondige behandeling van BRONJ.

HOOFDSTUK 7 toont de eerste publicatie in de literatuur van een klein cohort patiënten met DRONJ. Een serie van 11 patiënten werd bestudeerd. Alle patiënten werden behandeld volgens de basale principes zoals bij BRONJ. Negen van de elf patiënten werden genezen met deze chirurgische behandeling. Twee stierven aan hun onderliggende ziekte en konden geen tweede behandeling krijgen. De pathogenese is nog steeds niet duidelijk, net zoals bij BRONJ. DRONJ lijkt klinisch sterk op BRONJ. Bij alle patiënten kon een dentogeen focus worden gevonden. In de literatuur wordt DRONJ samen met BRONJ beschouwd als medicatie gerelateerde osteonecrose van de kaak (MRONJ). Initieel leek DRONJ moelijker te behandelen, maar dat kon niet worden bevestigd in deze studie. Met deze resultaten in ogenschouw, is het belangrijk om goede preventie programma's te ontwikkelen en om patiënten te blijven motiveren om een goede mondhygiëne en dentitie te hebben alvorens te starten met denosumab. Nader onderzoek is noodzakelijk om de exacte pathogenese te verlichten.

HOOFDSTUK 8 beschrijft de 3D analyse van een chirurgische techniek bij 30 patiënten. De chirurgische techniek werd geobjectiveerd door enkele principes van de behandeling van het bot te analyseren op cone beam CT (CBCT) scans. Twee groepen patiënten werden geselecteerd. Groep 1 bestond uit patiënten die elders niet succesvol waren behandeld. Groep 2 bestond uit patiënten die enkel in onze kliniek met onze gerapporteerde chirurgische techniek-gebaseerd op de behandeling van chronisch purulente osteomyelitis- werden behandeld. De post-operatieve scan werd beoordeeld op de behandeling van aangedaan bot, buccale en linguale cortex, de aanwezigheid van dode ruimte en het frontale aspect. De patiënten van elders toonden voornamelijk behandeling van de buccale cortex, aanwezigheid van sequesters en dode ruimte. Een sufficiënte behandeling van aangedaan bot en behandeling van buccale en linguale cortex met goede afronding van scherpe randen vergemakkelijkt primair sluiten in lagen met zo min mogelijk dode ruimte als mogelijk. Nagenoeg alle patiënten werden genezen met onze chirurgische benadering, 93,3% in groep 1 en 100% in groep 2. Therapie resistente MRONJ blijft een probleem, dat vele chirurgen tergt. De resultaten van deze studie tonen dat de behandeling volgens onze chirurgische techniek een hoog succespercentage heeft in alle stadia van MRONJ. De techniek is gebaseerd op een paar relatief eenvoudige chirurgische principes, zoals uitgebreide 'saucerization' en afronden in combinatie met primair sluiten. Deze techniek vindt aansluiting bij de literatuur en is in lijn met andere auteurs met vergelijkbare uitkomsten.

HOOFDSTUK 9 bestudeert de behandeling van stadium III MRONJ met pathologische fractuur van de mandibula. De behandeling van deze groep patiënten is uitdagend. In ons cohort van 150 patiënten presenteerden 17 zich met een pathologische fractuur. Deze patiënten werden behandeld afhankelijk van hun dentale staat (al dan niet edentaat) met winterspalken of conservatief met een zacht dieet. Essentieel voor de behandeling was een sequestrectomie met verwijdering van dood bot en primaire sluiting in lagen in combinatie met antibiotica. Patiënten met stadium III MRONJ en een fractuur zijn meestal ouderen veelal met comorbiditeiten en/of gemetastaseerde ziekte. De resultaten tonen dat in 84% genezing of een pseudoarthrose kon worden verkregen. Deze patiënten werd een resectie al dan niet met reconstructie -zoals

aanbevolen in de literatuur- bespaard, die ook niet altijd de voorkeur verdient in deze populatie. De uitkomst van deze chirurgische techniek icm intermaxillaire fixatie bij dentaten of een conservatief beleid bij edentaten toont zeer acceptabele kliknische resultaten.

HOOFDSTUK 10 toont een zeldzame casus van een 'autoreconstructie' van de mandibula en illustreert een patiënt met een zeer excessieve hoeveelheid van subperiostale botvorming en een necrotische mandibula. De mandibula was tot aan de onderrand necrotisch, maar bij deze patiënt had het lichaam gezorgd voor zijn eigen reconstructie. De hoeveelheid van subperiostale botvorming aan de linguale zijde was dermate veel, dat na verwijdering van de necrotische mandibula (symfyse) de continuïteit toch gewaarborgd kon blijven. Voor een heel jaar had de patiënt een gesloten mucosa zonder klachten, maar overleed toen aan de onderliggende borstkanker. Deze casus toont de capaciteit van het kaakbot om te regenereren ondanks het bisfosfonaatgebruik.

HOOFDSTUK 11 bediscussieert de conclusies, klinische implicaties en toekomstperspectieven van dit proefschrift.

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CURRICULUM VITAE

Sarina Pichardo werd op 19 juli 1984 geboren in Etten-Leur. Na het behalen van het gymnasium aan het Gymnasium Juvenaat te Bergen op Zoom, studeerde zij geneeskunde aan de Universiteit Leiden. In 2003 deed zij mee aan de Erasmus-uitwisseling van 5 maanden met het Karolinska Institutet te Stockholm. Begin 2009 behaalde zij haar artsenbul, waarna zij als ANIOS werkte in het Leids Universitair Medisch Centrum. In september 2009 startte zij aan de Tandheelkunde Opleiding voor Artsen (TOVA) aan de Radboud Universiteit Nijmegen. De basis voor dit proefschrift werd in het najaar van 2011 gelegd. De specialisatie Mondziekten, Kaak- en Aangezichtschirurgie startte zij in 2012 in het Leids Universitair Medisch Centrum bij prof.dr. JPR van Merkesteyn. In 2014 deed zij een traumastage in het National Maxillofacial Trauma Unit Ireland in het St. James Hospital te Dublin bij prof.dr. LFA Stassen. De opleiding werd in 2015 afgerond met een perifere stage in het Spaarne Gasthuis te Haarlem bij prof.dr. AG Becking.

Sinds 2016 is zij werkzaam als staflid en chef de clinique bij de afdeling Mondziekten, Kaak- en Aangezichtschirurgie van het Leids Universitair Medisch Centrum en coördinator 3D MKA voor chirurgische operatieve en/of patiënt specifieke planning. Zij participeert in een nauwe samenwerking met de neurochirurgie en de oogheelkunde voor de behandeling en reconstructie van botafwijkingen in het middengezicht en de schedel. Tevens is zij lid van het Trauma Team West en lid van het behandelteam van het Centrum voor Botkwaliteit. Sinds 2020 is zij eveneens plaatsvervangend opleider.

Speciale aandachtsgebieden zijn botpathologie, orthognathische chirurgie, implantologie en traumatologie van het aangezicht.