



**Universiteit  
Leiden**  
The Netherlands

## **Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment**

Pichardo, S.E.C.

### **Citation**

Pichardo, S. E. C. (2020, September 22). *Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment*. Retrieved from <https://hdl.handle.net/1887/136855>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/136855>

**Note:** To cite this publication please use the final published version (if applicable).



|12

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 prosthesis 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 prosthesis, which raises the question whether the swelling was the cause for the ill-fitting prosthesis, 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 course 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 or 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.



