Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 491–499

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Is the conservative non-surgical management of medication-related osteonecrosis of the jaw an appropriate treatment option for early stages? A long-term single-center cohort study

Oliver Ristow [a, *], Thomas Rückschloß [a], Michael Müller [a], Moritz Berger [a], Steffen Kargus [a], Christoph Pautke [b], Michael Engel [a], Jürgen Hoffmann [a], Christian Freudlsperger [a]

[a] University of Heidelberg, Department of Oral and Maxillofacial Surgery, (Head of Department: Prof. Dr. Dr. J. Hoffmann), Im Neuenheimer Feld 400, D-69120, Heidelberg, Germany
[b] University of Munich, Department of Oral and Maxillofacial Surgery, (Head of Department: Prof. Dr. Dr. M. Ehrenfeld), Lindwurmstr. 2a, 80337, München, Germany

ARTICLE INFO

Article history:
Paper received 26 July 2018
Accepted 21 December 2018
Available online 29 December 2018

Keywords:
MRONJ
BRONJ
AR-ONJ
Osteonecrosis of the jaw
Conservative therapy
Therapy

ABSTRACT

Purpose: No consensus has been reached regarding the best treatment option for early-stage lesions in medication-related osteonecrosis of the jaw (MRONJ). The purpose of the present study was to evaluate the long-time outcomes of conservative non-surgical management in stage I patients with underlying malignant disease.

Materials and methods: We designed and implemented a retrospective cohort study and enrolled, between 2008 and 2018, a sample of patients with the indication for non-surgical conservative treatment stage I lesions. The primary outcome variable was treatment success defined as mucosal integrity without signs of infection. Secondary outcomes were: (i) worsening stage, (ii) necessity for surgical intervention over time, and (iii) discontinuation of antiresorptive therapy.

Results: The sample included 75 patients with 92 lesions. Eight lesions showed full mucosal coverage, whereas 84 continued with exposed jaw bone (91.3%). Of the treatment-resistent 84 lesions, 67 presented a worsening stage shift over time. Indication for surgical intervention was set in 57 lesions. Of all lesions, 28 developed highly advanced necrotic bone destruction. Antiresorptive medication was paused in all evaluated patients after the first diagnosis of MRONJ.

Conclusion: Conservative non-surgical therapy in MRONJ stage I leads to a healing in rare cases. Conservative management might be a good option to preserve symptoms in patients either unwilling to undergo surgery or in those whose reduced general condition does not allow surgery. Early and consequent surgical advances should be performed throughout all stages of the disease to prevent the possibility of silent disease progression with the risk of large-scale bone loss.

1. Introduction

All treatment strategies, but especially those for early stages of medication-related osteonecrosis of the jaw (MRONJ), remain controversial. With reference to the American Association of Oral and Maxillofacial Surgeons (AAOMS), 2007 classifications (Table 1), stage I disease in particular is often promoted as being best treated non-surgically, namely in a conservative manner (Ruggiero et al., 2014). This treatment is usually legitimized with regard to the underlying oncologic disease of the patient and their associated general condition. In order to preserve the quality of life, advocates of the conservative approach prioritize the support of continued oncologic treatment (Van den Wyngaert et al., 2009; Coropciuc et al., 2017; Khan et al., 2017). Therefore, physicians and surgeons favoring the non-surgical approach define the goal of treatment as the preservation of the symptomatic status quo

* Corresponding author. University of Heidelberg, Department of Oral and Maxillofacial Surgery, Im Neuenheimer Feld 400, D-69120, Heidelberg, Germany. Tel.: +49 6221 56 37314; fax: +49 6221 56 4375.
E-mail address: Oliver.ristow@med.uni-heidelberg.de (O. Ristow).

https://doi.org/10.1016/j.jcms.2018.12.014
1010-5182/

Table 1
Staging criteria as recommended by the AAOMS.

Stage	Definition
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms
Stage I	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection
Stage II	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and ery- thema in the region of the 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 one or more of the fol- lowing: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor

Staging criteria as recommended by the AAOMS in accordance to the definition of the disease: Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws Ruggiero et al. 2014.

without a worsening transition to a higher stage, according to the AAOMS staging criteria classifications (Ruggiero et al., 2014).

By contrast, a plethora of studies has displayed very good results for early surgical treatment in MRONJ therapy reaching 90% or more (Hayashida et al., 2017; Aljohani et al., 2018; Ristow et al., 2018; Schiodt et al., 2018). For those favoring a surgical approach, the primary goal of treatment is the complete removal of the necrosis and long-term mucosal healing in combination with freedom from symptoms in order to attain the retrieval of the physiological condition (Ristow et al., 2015; Grötz and Al-Nawas, 2016). Thereby facilitating the fast and urgently needed resumption of oncological and antiresorptive treatment and, not least, early and adequate prosthetic recovery. Again, the main goal is to maintain the quality of life (Vescovi et al., 2008; Assaf et al., 2013; Carlson, 2014; Otto et al., 2016; Ristow et al., 2017).

The discussions and dissentions regarding the surgical and conservative non-surgical therapy are complicated and maintained by the lack of well-designed prospective randomized clinical trials comparing these two techniques (Rollason et al., 2016; Beth-Tasdogan et al., 2017). However, this deficit has also occurred not least because of the different definition of the outcome measures and, therefore, the definition of the therapeutic success of the two approaches.

The goal of the present long-term follow-up study has been to examine the success rates of a non-surgical conservative therapy in early stage MRONJ patients (according to AAOMS stage I (Ruggiero et al., 2014)) of a single-center cohort and, specifically, to evaluate (i) mucosal integrity, (ii) worsening stage shift (Ruggiero et al., 2014), (iii) the necessity for surgical intervention over time, and (iv) if applicable, the discontinuation of antiresorptive therapy.

2. Materials and Methods

2.1. Patients

This study was approved by the local Ethics Committee of the University of Heidelberg (Ethics number S-402/2012) and carried out according to the Declaration of Helsinki. We designed and implemented a retrospective, single-center cohort study and consecutively enrolled a sample derived from the population of subjects who had been given the working diagnosis of MRONJ and who fulfilled the following inclusion criteria at the Department of Maxillofacial Surgery, University of Heidelberg, between 2008 and 2018: indication for non-surgical conservative treatment in early lesions (stage I according to AAOMS) (Ruggiero et al., 2014); monthly antiresorptive application (bisphosphonates intravenously/denosumab subcutaneously) according to the protocol for the antiresorptive treatment of patients with a underlying malignant diseases; no preceding surgical approach to the lesion. The exclusion criteria were as follows: antiresorptive treatment because of osteoporosis; history of head and neck radiation; metastatic bone disease of the maxillofacial region; and missing follow-up examinations.

2.2. Conservative non-surgical treatment

All patients were treated by using a standardized conservative (non-surgical) protocol consisting of antimicrobial mouth rinsing by applying 0.2% chlorhexidine solution (GlaxoSmithKline Consumer Healthcare GmbH & Co. KG, Munich, Germany) three times a day and the daily topical application of 1% chlorhexidine gel (GlaxoSmithKline Consumer Healthcare GmbH & Co. KG, Munich, Germany). Regular and close follow-up consultations were undertaken at least every 4 weeks in order to perform a controlled manual cleansing of the affected region. Superficial bone sequestra were removed, in cases of spontaneous formation and dissolvement, during the therapy.

Because of the definition of the disease (AAOMS stage I, exposed jaw bone or fistula that extends to the bone in an asymptomatic patient without evidence of infection and the lack of symptoms (Ruggiero et al., 2014)), no antibiotics were utilized. However, in cases of a stage shift with underlying infection as evidenced by pain and/or erythema in the region of the exposed bone with or without purulent drainage (according to AAOMS stage II (Ruggiero et al., 2014)), patients were additionally treated with oral antibiotics Amoxclav 875/125mg 1-0-1, until the absence of infection was achieved resulting in a downshift to stage I (Ruggiero et al., 2014) or the indication for surgery. Patients allergic to penicillin received 600 mg clindamycin (1-1-1) instead. In cases of renal function disturbances, the doses were adjusted accordingly. All patients stopped taking bisphosphonates or denosumab once MRONJ had been diagnosed. It should be note that this decision was always justified and applied by the attending oncologist.

2.3. Data collection

All patients with a history of antiresorptive intake routinely take part in the weekly consulting hour at our unit. Therefore, follow-up examinations and radiographic documentations were performed according to our internal unit standardized protocols and always by the same investigators.

Measurements were acquired at least every 4 weeks after initial diagnosis. The therapeutic success of the non-surgical regimen was defined as complete mucosal recovery without signs of residual infection or exposed bone at the time of evaluation. At every consultation, infection was thoroughly evaluated by the assessment of swelling, redness, bleeding on probing, and purulent discharge. Furthermore, all patients were examined for signs of sinusitis and oro-antral fistula in cases of upper jaw lesions and were checked for extra-oral fistula in cases of lower jaw lesions. To determine any possible underlying progression of the disease, quarterly cone

beam computed tomography (CBCT) scans were acquired from the affected region of interest and evaluated for necrosis progress, osteolysis, sequestrum, and pathologic fracture. Stage shifts (Ruggiero et al., 2014) were thoroughly documented, as was the discontinuation of antiresorptive therapy.

Indication for surgery was defined as treatment failure of the non-surgical conservative therapy. Surgical therapy was initialized for stage II lesions with superinfected purulent drainage not responding to the additional antibiotic regimen in terms of an absence of the downshifting from stage II to stage I according to AAMOS after 2 weeks or for a stage increase to stage III (Ruggiero et al., 2014).

2.4. Statistical analysis

All solely descriptive statistical analysis was performed using IBM SPSS Statistics software (Version 25.0). The primary endpoint of the study was mucosal integrity. Failure of treatment was defined with the indication for surgery. Results are expressed as percentages or as mean values including the standard deviation and range.

3. Results

3.1. Patients

In total, 75 patients with 92 MRONJ lesion-sides were included in this study (42 females (mean age: 68.9; SD: ± 10.8 years) and 33 male patients (mean age: 67.5; SD: ± 8.8 years). Twelve patients died during the observational period (mean time in months after first diagnosis of MRONJ: 21.5; SD: ± 17.9 months).

All included patients suffered from an underlying malignant disease with metastasis or focus of the primary disease (as for the multiple myeloma) to the bone (prostate n = 19; breast n = 33; multiple myeloma n = 13; kidney cell carcinoma n = 7; other n = 3).

Of the 75 patients included, 49 (65%) were treated with nitrogen-containing bisphosphonates; 14 (19%) of the included patients had a history of pure denosumab intake. The remaining 12 patients (16%) reported a subsequent or alternating intake of bisphosphonates and denosumab. The mean duration of intake of the antiresorptive drugs until diagnosis was 44.5 ± 34.0 months (minimum = 3 months; maximum = 180 months).

All included lesions were classified according to AAOMS (Ruggiero et al., 2014) as being stage I (n = 92; 100%) at the time of enrollment. A total of 24 (26%) lesions were located in the maxilla and 68 (74%) lesions in the mandible. Of all patients evaluated during the time period between 2008 and 2018, observational time ranged from a minimum of 12 months to a maximum of 60 months with a mean of 16.1 ± 14.1 months.

3.2. Mucosal integrity

Conservative therapy resulted in 8 out of 92 (8.7%) MRONJ lesions (in 8 patients) with mucosal integrity with full mucosal coverage without signs of residual infection (Fig. 1), whereas 84 out of 92 (91.3%) lesions (in 67 patients) continued to exhibit an

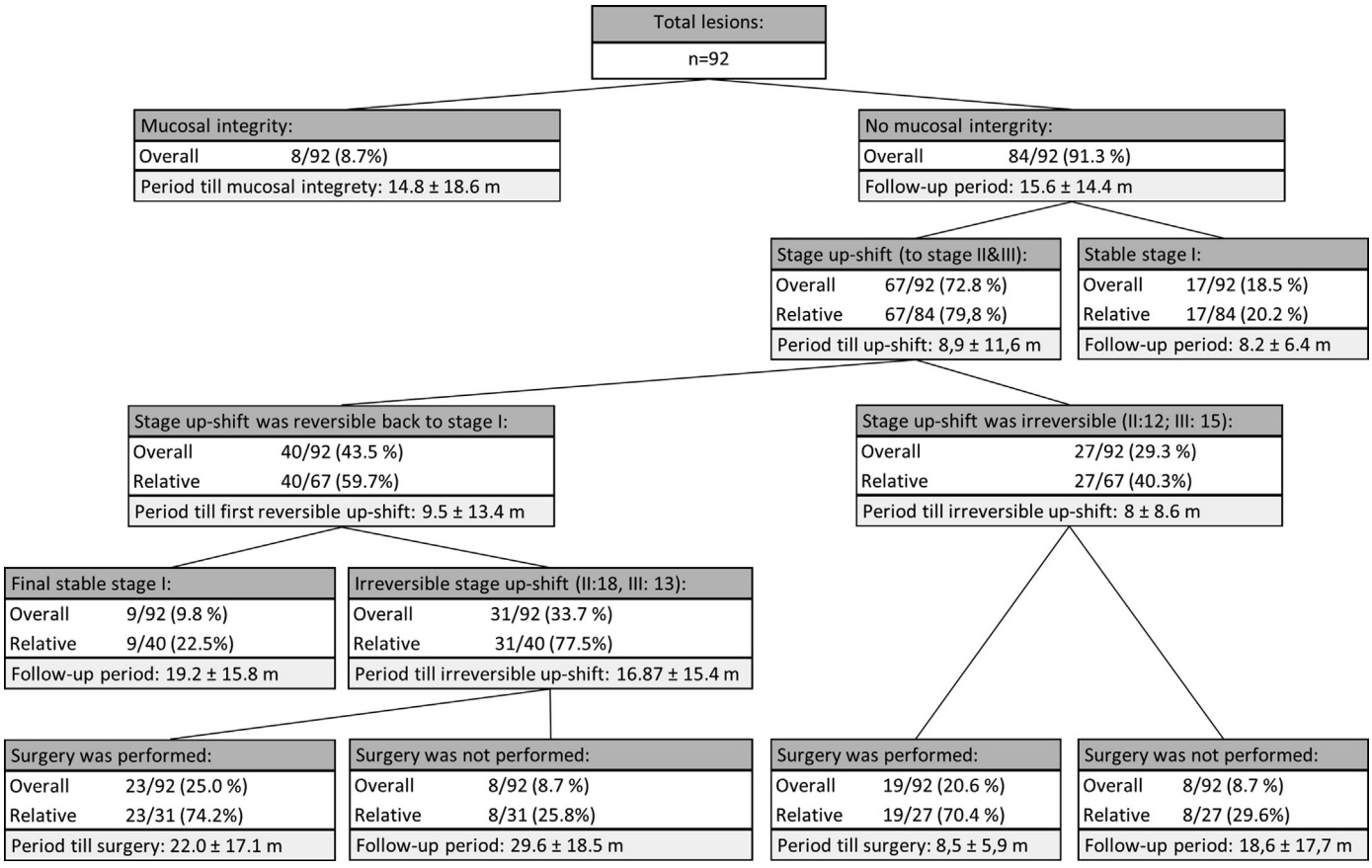

Fig. 1. Flowchart for all enrolled 75 patients with 92 MRONJ lesion-sides. Displayed are the lesions' courses during conservative non-surgical treatment over a 10-year observational period in overall and relative measures. Mean follow-up period with standard deviation is presented in months (m) for every period. Overall, an indication for surgery was given in 57 lesions for all lesions included, over the entire observational time.

exposed jaw bone or fistula that extended to the bone over the entire observational time (mean: 15.6; SD: ±14.4 months).

Of the 8 lesions showing therapy success with the non-surgical conservative treatment, complete mucosal coverage was achieved after a minimum of 1 month to a maximum of 50 months (mean: 14.8; SD: ±18.6).

Of those lesions with persistent os libere (n = 84; 91.3%), after a mean of 8.9 ± 11.6 months, 67 lesions underwent a stage shift with underlying infection (pain and/or erythema in the region of the exposed bone with or without purulent drainage according to AAOMS stage II (Ruggiero et al., 2014)).

However, 40 (59.7%) of those infected lesions returned to an absence of infection, and a downshift to stage I (Ruggiero et al., 2014) was achieved by additional treatment with oral antibiotics in the first course. Nine (22.5%) of those 40 lesions returned to an absence of infection, and a downshift to stage I (Ruggiero et al., 2014) was achieved as a stable condition until the end of observation.

In contrast, 31 of these 40 lesions (77.5%) exhibited a worsening stage shift according to AAOMS stage II (n = 18) and III (n = 13) (Ruggiero et al., 2014), which was irreversible and nonresponsive to antibiotics this time. Therefore, the indication for surgical intervention was given as the patient being a non-responder to conservative therapy.

Of note, in 23 of these 31 lesions (74.2%), surgery was performed and observation ended. However, in 8 lesions (25.8%), surgical intervention was not conducted, either because of the general condition of the patient or their oncologic situation did not allow it (n = 4) or because the patient was unwilling to consent to surgical intervention (n = 4). In these cases, conservative treatment and observation was continued.

The other non-healing lesions, 27 of 67 (40.3%), directly processed either to an irreversible stage shift to stage II (n = 12) according to AAOMS (Ruggiero et al., 2014), with superinfected purulent drainage non-responding to the additional antibiotic regimen or to stage III (n = 15) according to AAOMS (Ruggiero et al., 2014), were therefore counted as non-responders to the therapy with treatment failure. The mean time to stage shift was 8.0 ± 8.6 months.

Indication for surgical intervention was given in 26 of these lesions. One patient died shortly after stage shift. Surgery was performed in 19 lesions. However, in 7 lesions, surgical intervention was not conducted, either because the general condition of the patient, the patient's oncologic situation did not allow it (n = 4), or the patient was unwilling to undergo surgical intervention (n = 3). In these cases, conservative treatment and observation was continued.

Of the 67 lesions, indication for surgery was given in 57, and 9 lesions were successfully downshifted, remaining stable at stage I (Ruggiero et al., 2014) for the entire observational time. Of those with operative indication (57 lesions), surgery was performed in 42 lesions, but in 16 lesions surgery was not applicable.

Of the 67 (89.3%) lesions with an unstable stage, 28 (28/92: 30.4% of all lesions) developed highly advanced necrotic bone destruction causing major bone and/or tooth loss. Four individuals (5.3% of all patients) had to undergo in discontinuation surgery after 14.8 ± 7.2 months.

Notably, 10 of the 28 lesions that ended up with a stage III grading (Ruggiero et al., 2014) had a silent progression of the bone destruction despite presenting with a stable status quo of the mucosal conditions (overlapping stage shift) (Fig. 2).

A pause in the antiresorptive medication was initialized by oncologist in all evaluated patients after the first diagnosis of MRONJ. In 5 (7%) patients, the treating physician resumed antiresorptive therapy after a mean of 9.7 months (±15.04), whereas in the other 70 other patients (93%), therapy was interrupted during the entire observational period. This decision was always made by the treating oncologist.

4. Discussion

The purpose of this study was to demonstrate our experience with the non-surgical conservative treatment of early lesions (stage I according to AAOMS (Ruggiero et al., 2014)) in MRONJ patients over the long term. In particular the variables success rates (defined as full mucosal rehabilitation), the necessity for surgical intervention during conservative therapy, and the discontinuation of antiresorptive therapy were analyzed.

Mucosal integrity was only achieved in 8 of 92 (8.7%) lesions over the entire observational time, whereas 84 of 92 lesions (91.3%) retained an exposed jaw bone (or fistula that extended to the bone). Of the treatment-resistant 84 lesions 67 (79.8%) presented a worsening stage transition to a more severe stadium of the disease (in accordance with AAOMS stage II or III) (Ruggiero et al., 2014) under conservative non-surgical therapy. However, 17 lesions (20.2%) exhibited a stable stage condition stage I over the entire course of the observation.

Antibiotic treatment and anti-inflammatory rinsing resulted in a downshift from infected to non-infected stable MRONJ lesion (in accordance with AAOMS stage I) (Ruggiero et al., 2014) in every third case (32%). In all of these cases, antiresorptive treatment was discontinued by the treating oncologist, dental recovery was not possible because of unresolved mucosal integrity in these cases. Thus, patients were always at risk for silent progression of the disease.

However, in the majority of cases (68%), the indication for a surgical intervention had to be set, often associated with major bone and teeth loss.

Undoubtedly, in MRONJ patients with a skeletal malignant disease, the major goal of treatment is the prioritization and support of continued oncologic therapy and the preservation of quality of life. Therefore, a multidisciplinary approach with a detailed assessment of the patient's general health and life expectation is indispensable. However, the best way to achieve these aims is unclear and remains under intense discussion (Groetz et al., 2012; Ruggiero et al., 2014; Khan et al., 2017; Yoneda et al., 2017). Nevertheless, it should be taken into account that a long-lasting conservative therapy without success in combination with a lack of dental rehabilitation might reduce the quality of life of the patients.

Since the first guidelines for bisphosphonate-related osteonecrosis of the jaw, the AAOMS has promoted a stage-dependent management of the disease (2007, Ruggiero et al., 2009; Ruggiero et al., 2014). Conservative non-surgical treatment is recommended, especially for early stage I disease, and also for stage II disease conservative non-surgical treatment is a recommended therapy option (Table 1). Most notably, the symptom-correlated treatment in early stage I disease is arguable, since, by definition, stage I disease involves exposed bone without symptoms.

Almost concomitantly with the first AAOMS guidelines, Khan et al. published, on behalf of the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS) (Khan et al., 2008) and the International Osteonecrosis of the jaw task force, multiple recommendations for MRONJ management (Khan et al., 2015, 2017). The authors determined their treatment on the basis of the disease stage (according to the AAOMS (Ruggiero et al., 2014)) and on the size of the lesions. In their opinion, conservative therapy should be continued as long as (1) no obvious progression of the disease occurs, (2) pain is not being controlled by conservative means, or (3) antiresorptive therapy is discontinued by the treating oncologist

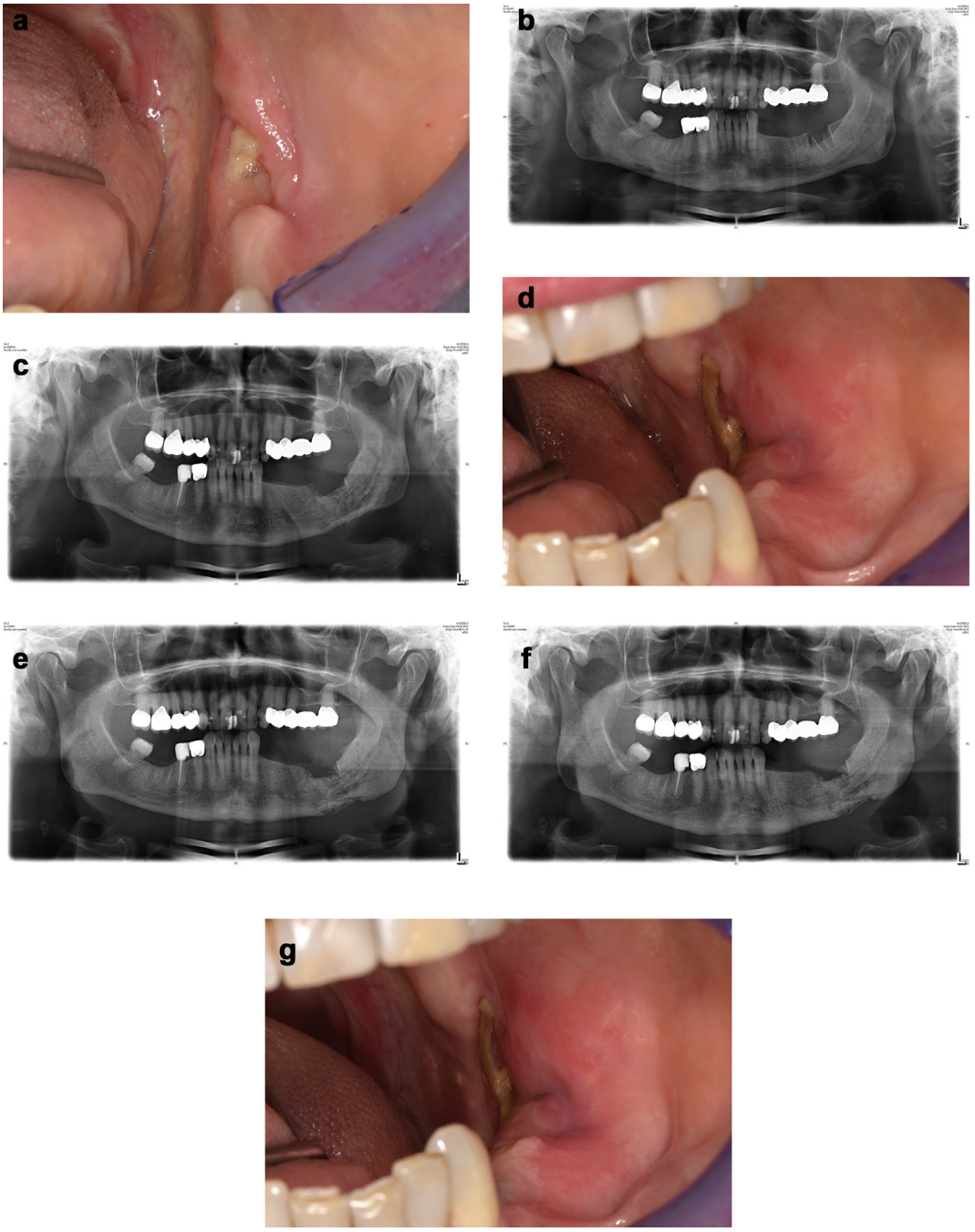

Fig. 2. Illustration of a 70-year old woman with breast cancer who has received intravenous treatment with zoledronate over 60 months and who presented at initial consultation with exposed necrotic bone stage I (Ruggiero et al., 2014) of the left mandible after tooth extraction alio loco 1 year ago. **(A)** clinical picture and **(B)** orthopanthomogram. Disease presented as stable stage I for 14 months by conservative non-surgical therapy, then a spontaneous bone sequestrum came loose. **(C)** Orthopantomogram after removal of a spontaneous bone sequestrum. **(D)** Clinically disease presented as stable stage I for further eight months by conservative non-surgical therapy. However, **(E)** radiograph already implicates a silent progression of the bone destruction despite presenting with a stable status quo of the mucosal conditions (overlapping stage shift to stage III). Patient was unwilling to undergo surgical intervention; therefore, furtherer conservative non-surgical therapy was performed for 6 months, ending in highly advanced necrotic bone destruction radiographically **(F),** while mucosal condition again was stable **(G)**.

because of MRONJ. In summary, the authors recommended surgery at the earliest in stage II (Ruggiero et al., 2014).

Based on those criteria with reference to this present study, antiresorptive treatment was paused by the treating oncologist in all included patients (except for 7%, as long as mucosal integrity was not present). Furthermore, 28 lesions with an unstable stage developed highly advanced necrotic bone destruction causing major bone and/or tooth loss. Four patients even ended up with partial jaw resection surgery. Of the 28 lesions that resulted in stage III (Ruggiero et al., 2014), 10 had silent progression of the bone destruction, despite presenting with a stable status quo of the mucosal conditions over course of time.

This indicates that the progression of the diseases is not necessarily obvious but very likely. Furthermore, the results of this study show that the size of the lesion, or of the mucosal defect, is neither an indicator of the dimension of the underlying necrotic

bone nor of the prognosis of the disease. Indeed, the exposed bone can often be considered as only the tip of the iceberg. Further studies will be necessary to confirm this assumption.

As shown in this present study and in earlier studies, in cases of infection (AAOMS stage II) (Ruggiero et al., 2014) antibacterial measures (e.g., rinsings, antibiotics) usually lead to a stage downshift (to AAOMS stage I) (Ruggiero et al., 2014; Ruggiero and Kohn, 2015; Otto et al., 2016; Hayashida et al., 2017; Ristow et al., 2018). Therefore, a fluent transition occurs between those lower stages, resulting in a lack of any clear information about the real severity of the disease or the extent of the bone destruction.

Accompanied by this achieved freedom of infection, some authors describe the declining of the mucosal defect and, sometimes, even the total rehabilitation of the mucosal integrity. Therefore, consider the temporary absence of infection or transitory declining of the mucosal defect as success of conservative therapy (Bodem et al., 2015; Klingelhoffer et al., 2016; Hadaya et al., 2018; Nisi et al., 2018). However, as the results of this present long-term study imply that the improvement of mucosal rehabilitation should not be misinterpreted, as it can sometimes be misleading. Of the initially 40 downshifted stage I lesions, 31 (78%) ended up with a recurrence to stage II ($n = 18$) or even progressed to a higher stage (stage III; $n = 13$) (Ruggiero et al., 2014) over time.

The mucosal situation can be improved, but this should not be misinterpreted as the disease being resolved. Necrotic bone will neither be resolved nor be revitalized. It will always hamper the full mucosal rehabilitation dependent on the status of the immune system. The analysis of our data suggests that the necrotic bone defect seems to show tendencies to enlarge rather than to diminish.

Not least, this highlights that the clear definition of the therapeutic success plays a crucial role in the interpretation of MRONJ data. The major outcome of treatment in MRONJ should be defined as complete mucosal healing in combination with freedom from symptoms after removal of all necrotic bone (Ristow et al., 2015; Grötz and Al-Nawas, 2016; Schiodt et al., 2018). This represents the physiologic condition and is the only long-term possibility for the resolution of the diseases. It facilitates the urgently needed resumption of oncological and antiresorptive treatment as well as the early dental rehabilitation contributing to the maintenance of the quality of life (Vescovi et al., 2008; Assaf et al., 2013; Carlson, 2014; Otto et al., 2016; Ristow et al., 2017).

In contrast, 30.5% of all MRONJ lesions included in the present data ended up irreversibly in stage III (Ruggiero et al., 2014) after an initial, solely conservative, non-surgical treatment. The management of stage III patients is known to be a major challenge, and the outcomes are often worse than in earlier stages, possibly leading to multiple necessary surgical approaches to achieve the treatment goal (with or without partial jaw resections and complex reconstructions) (Ruggiero and Kohn, 2015; Otto et al., 2016; Ristow et al., 2017, 2018; Schiodt et al., 2018). Indeed, AAOMS stage III is the only grade that indicates the severity of the disease and that gives more detailed information about its extent, since pathologic fractures, extra-oral fistula, and oro-antral communications, etc. are the symptoms of advanced necrotic bone destruction (Bedogni et al., 2014; Fedele et al., 2015).

This agrees with data recently presented by Ruggiero et al. (Ruggiero and Kohn, 2015). In a large retrospective cohort over 10 years, these authors observed a significant difference in outcome with respect to the disease stage, with stage I and II disease being more likely to have better outcomes than stage III. Furthermore, patients who underwent surgery were 28 times more likely to have a positive outcome than patients who had received non-operative therapy. In contrast to the authors' recommendations in the latest AAOMS guidelines (Ruggiero et al., 2014) and earlier reports by the group, Ruggiero et al. concluded that patients with a less severe disease and operative treatment were most likely to have an improvement or complete healing of their MRONJ lesions (Ruggiero and Kohn, 2015).

This implies and alerts one to a possible selection bias of studies because the earlier stages (Ruggiero et al., 2014) (supposedly minor cases) were often treated conservatively and non-surgically and the more severe cases surgically.

In contrast to the results of this present study, Coropciuc et al. retrospectively evaluated the success rate of conservative treatment in 107 lesions and reported an overall improvement of 79.73% (complete healing or down-staging) after 24 months follow-up, with only two lesion evolving to a higher stage during treatment (Coropciuc et al., 2017). Interestingly, the authors defined conservative therapy as being medical and/or minimally invasive surgical (such as debridement and sequestrectomie). Based on their presented data, approximately half of the patients actually received minimal surgical treatment. The authors promote conservative therapy (as defined by their group) to be the mainline treatment for stage I and II lesions, as indicated by the AAOMS guidelines (Ruggiero et al., 2014).

However, these data require cautious interpretation. The construction of the various therapy options might be misleading and thus might lead to false recommendations. Conservative (non-surgical) therapy and surgical therapy should be clearly defined and distinguished.

Indeed, the extent of the surgical intervention is usually predetermined by the nature of the disease, the extent of the osteonecrosis and its progression. Therefore, the major benefit of early surgical therapy is that the dimension of necrosis in early MRONJ lesions is usually smaller. Consequently, the surgical approach has to be less invasive and extensive bone loss can be avoided. Furthermore, this practice also obviates the potential protracted progression of the disease (Bedogni et al., 2011; Fliefel et al., 2015; Otto et al., 2016; Hoefert et al., 2017; Ristow et al., 2017).

As almost annually pointed out in the Cochrane Database (Rollason et al., 2016; Beth-Tasdogan et al., 2017), there is a lack of methodologically well-designed prospective randomized clinical trials comparing conservative (non-surgical) with the surgical therapy in MRONJ patients. This refers to both conservative and surgical approaches. Moreover, methodological trials are undoubtedly needed finally to reach a consensus with regard to the challenging discussions about the most effective MRONJ management approaches.

Assorted reasons presumably exist as to why such methodical trials are still lacking: not only intra-institutional routine clinical practice and ethical dilemmas, but also available empirical data.

The available data on conservative (non-surgical) treatment approaches range from 14.9% (outcome measure: mucosal integrity) (Nicolatou-Galitis et al., 2011; Heufelder et al., 2014) up to 65% (outcome measure: decrease of mucosal lesion; no stage transmission) (Badros et al., 2008; Van den Wyngaert et al., 2009). In contrast, a plethora of studies display good results up to/over 90% (outcome measure: mucosal integrity) for surgical approaches in MRONJ therapy in long-term follow-ups (Hayashida et al., 2017; Ristow et al., 2017, 2018; Aljohani et al., 2018; Schiodt et al., 2018). In a systematic review and meta-analysis, El-Rhabbany et al. have suggested that there are higher odds of resolving MRONJ with surgical treatment compared with medical treatment (El-Rabbany et al., 2017). Schiodt et al. have reported on findings from 141 patients with MRONJ, with a high cure rate (93%) in patients undergoing surgery, and a low cure rate (17%) in patients

receiving conservative non-surgical treatment (Schiodt et al., 13–16 September 2016. London (UK)).

Therefore, national associations are increasingly dissociating themselves from conservative strategies when the general condition of the patient allows surgery and the patient is willing to undergo an operation (Schiegnitz et al., 2018; Groetz et al., 2012; Yoneda et al., 2017). This practice might not only prevent the possibility of silent disease progression but might also obviate the potential protracted progression of the disease with the possibility of large-scale bone loss. What is more, it might improve the oncological therapy by minimizing the time of discontinuation of oncological and antiresorptive treatment.

The data of this present study thus suggests that the perennial assertion that conservative treatment is the method of choice in early MRONJ stages needs to be critically scrutinized.

A drawback of this study might be the retrospective set-up of the study design. However, we have done our best to collect long-term data (over 10 years) from a homogeneous study group and enrolling only stage I patients with a malignant underlying disease. Our specialized consultation hour for MRONJ patients with a standardized follow-up protocol keeps any possible bias as low as possible.

Furthermore, the heterogeneous intake of antiresorptive medication might be considered as a limitation. Therefore, the application of multifactorial regression models, considering covariance as a medication type and/or underlying disease, might be the aim of a subsequent prospective study in the future. Especially relevant might be the covariance medication type, considering the subgroup exclusive denosumab intake. Because of the special pharmacokinetics and the short serum activity of the antibody (approximately 6 months), conservative non-surgical therapy might play a more important role in the future (Fig. 3) (Ohga et al., 2018). However, again, this implies a long-term discontinuation of antiresorptive treatment.

Another covariance of interest is the underlying disease. This retrospective evaluation exclusively included patients with a malignant primary disease. However, with an increasing number of MRONJ in osteoporosis patients (overall incidence is still low), the definition of treatment options for this study group should remain in focus (Hayashida et al., 2017; Kim et al., 2017). Such patients usually have good life expectations and a stable general condition. Therefore, the role of early surgical approaches aiming to prevent any silent progression of the disease and any possible large bone loss and, thus, to enable resolution, is considerable. Future

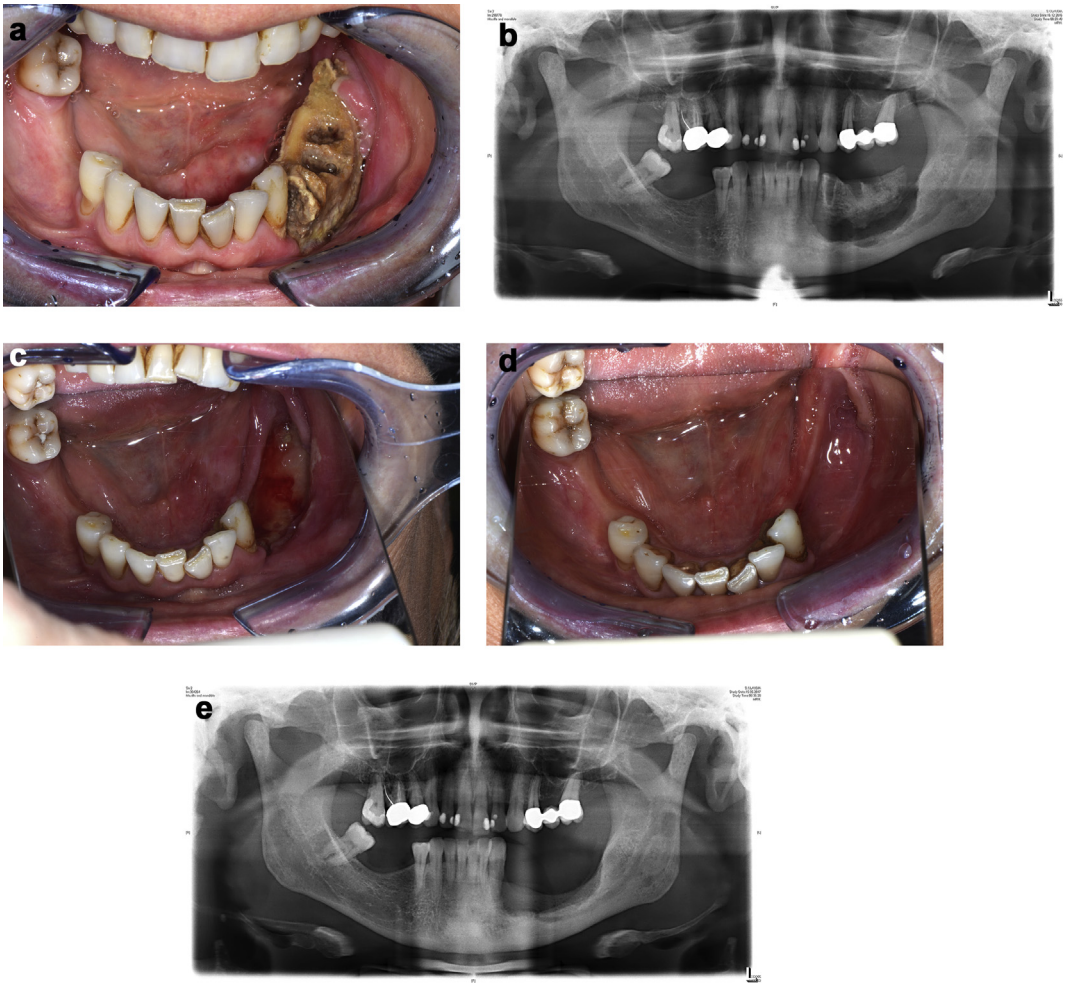

Fig. 3. Illustration of a 55-year old woman with breast cancer who received exclusively a subcutaneous monthly treatment with denosumab over 17 months. At initial consultation, the patient presented **(A)** clinically with extended exposed necrotic bone and **(B)** a large sequestrum of the left mandible in the orthopanthomogram. Etiology and time to onset of MRONJ are unclear; however, antiresorptive treatment has already been paused for over 12 months at this juncture. **(C)** After removal of the large bone sequestrum, an already starting resolution of mucosal integrity can be observed. **(D)** Clinical and **(E)** radiographic control after 6 months. Total mucosal integrity is achieved without signs of infection. Note that antiresorptive treatment is still discontinued at this point of time.

recommendations should be distinct concerning this subgroup of MRONJ patients.

5. Conclusion

To preserve symptoms, conservative non-surgical therapy in the management of MRONJ lesions should be restricted to patients who are either unwilling to undergo surgery or whose general condition does not allow surgical intervention.

In order to prevent the possibility of silent disease progression and the protracted progression of the disease with the risk of large-scale bone loss, early and consequent surgical advances should be considered throughout all stages of the disease. This should always occur with the patient's general, oncological, and osteological condition in mind.

Early surgical intervention in MRONJ patients certainly promises a benefit in outcome, and thus ensures a fast re-uptake of anti-resorptive and oncologic treatment and possible prosthetic rehabilitation, thereby contributing to quality of life.

Methodologically clear clinical trials are needed to substantiate the present empirical data with a clear definition of the therapeutic strategies (non-surgical vs. surgical) and outcome measures and a minimization of selection bias.

Funding

This work has neither been funded nor financially supported.

Conflicts of interest

We declare that we have no conflicts of interest. This research was not supported by any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

References

Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. AAMOS: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65: 369, 2007

Aljohani S, Gaudin R, Weiser J, Troltzsch M, Ehrenfeld M, Kaeppler G, et al: Osteonecrosis of the jaw in patients treated with denosumab: a multicenter case series. J Cranio Maxillo Fac Surg 46(9): 1515–1525. https://doi.org/10.1016/j.jcms.2018.05.046, 2018 Sep Epub 2018 May 31

Assaf AT, Zrnc TA, Riecke B, Wikner J, Zustin J, Friedrich RE, et al: Intraoperative efficiency of fluorescence imaging by Visually Enhanced Lesion Scope (VELscope) in patients with bisphosphonate related osteonecrosis of the jaw (BRONJ). J Cranio Maxillo Fac Surg 42(5): e157–e164. https://doi.org/10.1016/j.jcms.2013.07.014, 2014 Jul Epub 2013 Sep 4

Badros A, Terpos E, Katodritou E, Goloubeva O, Kastritis E, Verrou E, et al: Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 26: 5904–5909, 2008

Bedogni A, Fedele S, Bedogni G, Scoletta M, Favia G, Colella G, et al: Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease. Br J Oral Maxillofac Surg 52(7): 603–608. https://doi.org/10.1016/j.bjoms.2014.04.009, 2014 Sep Epub 2014 May 22

Bedogni A, Saia G, Bettini G, Tronchet A, Totola A, Bedogni G, et al: Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. Oral Oncol 47: 420–424, 2011

Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O: Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev 10: CD012432, 2017

Bodem JP, Kargus S, Engel M, Hoffmann J, Freudlsperger C: Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw. J Cranio Maxillo Fac Surg 43: 1139–1143, 2015

Carlson ER: Management of antiresorptive osteonecrosis of the jaws with primary surgical resection. J Oral Maxillofac Surg 72: 655–657, 2014

Coropciuc RG, Grisar K, Aerden T, Schol M, Schoenaers J, Politis C: Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2. Br J Oral Maxillofac Surg 55: 787–792, 2017

El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A: Effectiveness of treatments for medication-related osteonecrosis of the jaw: A systematic review and meta-analysis. J Am Dent Assoc 148: 584–594 e582, 2017

Fedele S, Bedogni G, Scoletta M, Favia G, Colella G, Agrillo A, et al: Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed. Br J Oral Maxillofac Surg 53: 13–17, 2015

Fliefel R, Troltzsch M, Kuhnisch J, Ehrenfeld M, Otto S: Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int J Oral Maxillofac Surg 44: 568–585, 2015

Groetz KA, Piesold J-U, Al-Nawas B: Bisphosphonat-assoziierte Kiefernekrose (BP-ONJ) und andere Medikamenten-assoziierte Kiefernekrosen: AWMF online (wwwawmforg); 2012

Groetz KA, Al-Nawas B: Antiresorptiva-assoziierte Kiefernekrose. MKG-Chirurg, 207–217, 2016

Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, et al: Nonsurgical management of medication-related osteonecrosis of the jaws using local wound care. J Oral Maxillofac Surg. https://doi.org/10.1016/j.joms.2018.05.025, 2018 May 29 pii: S0278-2391(18)30500-7. [Epub ahead of print]

Hayashida S, Soutome S, Yanamoto S, Fujita S, Hasegawa T, Komori T, et al: Evaluation of the treatment strategies for medication-related osteonecrosis of the jaws (MRONJ) and the factors affecting treatment outcome: a multicenter retrospective study with propensity score matching analysis. J Bone Miner Res 32: 2022–2029, 2017

Heufelder MJ, Hendricks J, Remmerbach T, Frerich B, Hemprich A, Wilde F: Principles of oral surgery for prevention of bisphosphonate-related osteonecrosis of the jaw: oral surgery, oral medicine. Oral Pathol Oral Radiol 117: e429–e435, 2014

Hoefert S, Yuan A, Munz A, Grimm M, Elayouti A, Reinert S: Clinical course and therapeutic outcomes of operatively and non-operatively managed patients with denosumab-related osteonecrosis of the jaw (DRONJ). J Cranio Maxillo Fac Surg 45: 570–578, 2017

Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al, International Task Force on Osteonecrosis of the Jaw: Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 30: 3–23, 2015

Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, et al, International Task Force on Osteonecrosis of the Jaw: Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the international task force on ONJ. J Clin Densitom 20: 8–24, 2017

Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F, et al: Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 35: 1391–1397, 2008

Kim HY, Lee SJ, Kim SM, Myoung H, Hwang SJ, Choi JY, et al: Extensive surgical procedures result in better treatment outcomes for bisphosphonate-related osteonecrosis of the jaw in patients with osteoporosis. J Oral Maxillofac Surg 75: 1404–1413, 2017

Klingelhoffer C, Zeman F, Meier J, Reichert TE, Ettl T: Evaluation of surgical outcome and influencing risk factors in patients with medication-related osteonecrosis of the jaws. J Cranio Maxillo Fac Surg 44: 1694–1699, 2016

Nicolatou-Galitis O, Papadopoulou E, Sarri T, Boziari P, Karayianni A, Kyrtsonis MC, et al: Osteonecrosis of the jaw in oncology patients treated with bisphosphonates: prospective experience of a dental oncology referral center. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112: 195–202, 2011

Nisi M, Karapetsa D, Gennai S, Ramaglia L, Graziani F, Gabriele M: Conservative surgical treatment of medication related osteonecrosis of the jaw (MRONJ) lesions in patients affected by osteoporosis exposed to oral bisphosphonates: 24 months follow-up. J Cranio Maxillo Fac Surg 46: 1153–1158, 2018

Ohga N, Sato J, Asaka T, Morimoto M, Yamazaki Y, Kitagawa Y: Successful conservative treatment of jaw osteonecrosis caused by denosumab in patients with multiple bone metastasis. J Oral Sci 60: 159–162, 2018

Otto S, Ristow O, Pache C, Troeltzsch M, Fliefel R, Ehrenfeld M, et al: Fluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw: a prospective cohort study. J Cranio Maxillo Fac Surg 44(8): 1073–1080. https://doi.org/10.1016/j.jcms.2016.05.018, 2016 Aug Epub 2016 May 24

Ristow O, Otto S, Geiss C, Kehl V, Berger M, Troeltzsch M, et al: Comparison of autofluorescence and tetracycline fluorescence for guided bone surgery of medication-related osteonecrosis of the jaw: a randomized controlled feasibility study. Int J Oral Maxillofac Surg 46: 157–166, 2017

Ristow O, Otto S, Troeltzsch M, Hohlweg-Majert B, Pautke C: Treatment perspectives for medication-related osteonecrosis of the jaw (MRONJ). J Cranio Maxillo Fac Surg 43: 290–293, 2015

Ristow O, Ruckschloss T, Bodem J, Berger M, Bodem E, Kargus S, et al: Double-layer closure techniques after bone surgery of medication-related osteonecrosis of the jaw–a single center cohort study. J Cranio Maxillo Fac Surg 46: 815–824, 2018

Rollason V, Laverriere A, MacDonald LC, Walsh T, Tramer MR, Vogt-Ferrier NB: Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ). Cochrane Database Syst Rev 2: CD008455, 2016

Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws–2009 update. J Oral Maxillofac Surg 67: 2–12, 2009

Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo TL, Merhotra B, et al: American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg 72(10): 1938–1956. https://doi.org/10.1016/j.joms.2014.04.031, 2014 Oct Epub 2014 May 5

Ruggiero SL, Kohn N: Disease stage and mode of therapy are important determinants of treatment outcomes for medication-related osteonecrosis of the jaw. J Oral Maxillofac Surg 73: S94–S100, 2015

Schiegnitz E, Al-Nawas B, Hoefert S, Otto S, Pautke C, Ristow O, et al: Antiresorptiva-assoziierte Kiefernekrosen (AR-ONJ) AWMF-Register-Nr. 007–091: AWMF online, www.awmf.org; 2018

Schiodt M, Otesen C, Dalsten H, Oturay P, Kofod T: Surgical treatment outcome of 141 consecutive patients with medication-related osteonecrosis of the jaws (MRONJ) from the Copenhagen ONJ cohort. London (UK): European Association for Cranio Maxillo-Facial Surgery (EACMFS). London, 13–16 September, 2016

Schiodt M, Vadhan-Raj S, Chambers MS, Nicolatou-Galitis O, Politis C, Coropciuc R, et al: A multicenter case registry study on medication-related osteonecrosis of the jaw in patients with advanced cancer. Support Care Canc 26: 1905–1915, 2018

Van den Wyngaert T, Claeys T, Huizing MT, Vermorken JB, Fossion E: Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome. Ann Oncol 20: 331–336, 2009

Vescovi P, Manfredi M, Merigo E, Meleti M: Early surgical approach preferable to medical therapy for bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 66: 831–832, 2008

Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al: Antiresorptive agent-related osteonecrosis of the jaw: position paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. J Bone Miner Metabol 35: 6–19, 2017