Autofluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw (MRONJ): a retrospective single-center study

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Objective. Medication-related osteonecrosis of the jaw (MRONJ) has become a serious concern for patients under antiresorptive treatment, especially in the oncological setting. Different approaches have been described in the management of MRONJ, including innovative autofluorescence-guided surgery. However, until now, there has been a lack of data regarding the outcome. In this study, we evaluated the efficacy of minimally invasive autofluorescence-guided resection in MRONJ.

Study Design. Seventy-five patients with 82 lesions were included in this retrospective, single-center study. All included patients were diagnosed with MRONJ according to the American Association of Oral and Maxillofacial Surgeons guidelines and underwent autofluorescence-guided surgery with a minimum follow-up of 3 months. The primary outcome was complete integrity of the mucosa and absence of bone exposure.

Results. The MRONJ stages were stage 0 (3.7%), stage 1 (3.7%), stage 2 (75.6%), and stage 3 (17%). Overall, complete mucosal healing of all lesions after the first surgery was 81.7% (67 of 82), whereas it was 90.2% (74 of 82) after revision surgery.

Conclusions. The study showed that autofluorescence-guided surgery is a safe and successful treatment option that can be considered for all stages of MRONJ. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:519−526)

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse side effect caused by antiresorptive drugs (ARDs) such as bisphosphonates, denosumab, or antiangiogenics.[1] Patients diagnosed with MRONJ are mainly those under antiresorptive treatment who have metastatic bone lesions or multiple myeloma and patients with osteoporosis treated with ARDs.[2]

Although a nonexposed variant of the disease has also been recognized,[3] MRONJ is diagnosed mainly by the presence of exposed bone in the oral cavity with gingival ulceration for more than 8 weeks in patients with previous or current use of 1 or more of these medications and no history of radiation therapy.[4] As the disease progresses, it may lead to severe pain, purulent drainage, extraoral fistula, and pathologic fracture with consequent significant reduction in the quality of life.[5] Progression of the condition can lead to tooth loss and necrosis of entire sections of the jaw, including pathologic fractures of the mandible.[6]

Although there is a broad consensus about the staging of MRONJ and treatment, recommendations vary vastly between conservative treatment[7] and surgical resection with safety margins.[8] Interestingly, conservative management of MRONJ is still partially recommended in the literature, even though evidence suggests that surgical treatment is significantly more effective than conservative treatment.[9]

Incomplete removal of necrotic bone leads to progression or recurrence and consequently a worse outcome,[10] with difficulty encountered in determining the margins of osteonecrosis.[11] A major challenge for maxillofacial surgeons is the demarcation of affected and healthy bone, which is required for a successful long-lasting surgical treatment. Radiologic imaging only supports navigation, but the affected areas of the bone

Statement of Clinical Relevance

Autofluorescence-guided surgery might be a safe and promising minimally invasive tool for complete removal of necrotic bone in patients with MRONJ. Autofluorescence-guided surgery is suitable not only for MRONJ but also for osteoradionecrosis and osteomyelitis.

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are often underrepresented compared with the clinical picture.[12] Common surgical practice is to assess the vitality of the bone on the basis of bony bleeding. However, this depends mainly on the surgeon's experience, which is not a valid way of accurately assessing the bone, because either necrotic bone is left or too much bone is removed.

Fluorescence-guided surgery is a surgical strategy that provides more preservation of bone and leads to promising and reliable outcomes.[13] Recently, the use of autofluorescence of the bone as a possible suitable guide to visualize necrotic bone during surgical debridement or resection was proposed.[14] In physiologic conditions, vital bone shows very strong autofluorescence. Conversely, pathologic tissues are characterized by a loss of autofluorescence and appear much darker than the surrounding areas.[15] The molecular sources of the phenomenon of autofluorescence are the specific amino acids of the collagen molecules that show autofluorescence when irradiated by ultraviolet or blue light.[16]

Therefore, the aim of this study was to evaluate the efficacy of autofluorescence-guided resection and minimally invasive surgical treatment of MRONJ.

MATERIAL AND METHODS

Patient characteristics and study design

This retrospective, single-center study was approved by the local ethics committee of Ludwig-Maximilians-University, Munich, Germany (LMU Munich ethics number 19-611) and was carried out according to the Declaration of Helsinki. The study is reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[17]

All patients were treated at the Department of Oral and Maxillofacial Surgery and Facial Plastic Surgery, Ludwig-Maximilians-University, Munich, Germany, between 2008 and 2018. The information was collected from the medical charts of the patients.

Inclusion and exclusion criteria

Patients were included in the study if they were diagnosed with MRONJ according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) guidelines.[4] Autofluorescence-guided surgery was performed to remove MRONJ lesions, and the minimum postoperative follow-up period was 3 months.

Patients were excluded if they had a history of radiation therapy to the head and neck area with obvious metastatic infiltration of the jaw, and the management of the MRONJ lesion was limited to a nonsurgical approach.

The clinical features, medical and dental history, and drug history (with a focus on antiresorptive and chemotherapeutic drugs) were documented. Panoramic radiographs were obtained for all the patients to locate and gain the initial features of their lesions. In selected cases, a computed tomographic scan or cone beam computed tomographic scan was also used to determine the extent of the defect.

Autofluorescence-guided bone surgery

The surgical procedures were performed by experienced oral and maxillofacial surgeons (SO and MT) following a standardized protocol and with the patients under general anesthesia. A mucoperiosteal flap was reflected in all lesions with the exposure of the bone. The VELscope system (Visually Enhanced Lesion scope; LED Dental, White Rock, British Columbia, Canada) was used to visualize the necrotic bone and set resection margins. The VELscope emission light used was at an approximately 400- to 440-nm wavelength that enables visualization of the autofluorescence properties of healthy bony collagen. With these properties of the bone, one is able to differentiate between necrotic (pale or no fluorescence) and vital bone (bright green light).

Resection margins relied on the clinical and autofluorescence properties of the bone (greenish fluorescence: vital bone; reduced or vanished green fluorescence: necrotic bone; red fluorescence: infected bone). The osteonecrosis was surgically removed, and the sharp edges of the bone were smoothened. Bone biopsies were routinely taken for histologic and microbiologic evaluation. All teeth within the necrotic bone were extracted. The mucoperiosteal flap was repositioned and sutured using SERAFIT 3/0 resorbable sutures (SERAG-WIESSNER, Naila, Germany).

All the patients received amoxicillin/clavulanic acid (875 mg/125 mg) twice daily for 1 week before admission. In patients with penicillin allergy, clindamycin 600 mg 3 times daily was prescribed. During the inpatient stay, antibiotics were administered intravenously for 3 days. Postoperatively, the antibiotic treatment was continued for 2 weeks orally.

Data collection

The follow-up was done on a regular basis at 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after surgery. During the follow-up, the main focus was on pain, the mucosa, and whether dehiscence or recurrence of the exposed bone had developed.

Primary outcome

The primary outcomes were the complete integrity of the mucosa, the absence of bone exposure, and the absence of clinical signs of MRONJ.

Statistical analysis

The results were expressed as percentages, median or mean ± SD, and/or range. The level of significance was set at $P \leq .05$.

RESULTS

Patient characteristics

Three hundred sixty-six patients diagnosed with MRONJ between 2008 and 2018 were eligible for the study. Of those patients, 201 patients were excluded because treatment of the lesions was performed by the conventional method of bone removal. The remaining 165 patients with MRONJ were treated by fluorescence-guided bone resection, 86 of whom received tetracycline-guided bone resection and thus were excluded from the study, leaving 79 patients treated with autofluorescence-guided bone resection. Four patients did not attend their follow-up and were excluded from the study. Finally, 75 patients diagnosed with 82 MRONJ lesions were included in this retrospective, single-center cohort study. The patients were surgically treated by autofluorescence-guided bone resection.

Twenty-six patients (34.7%) were male and 49 patients (65.3%) were female, with a mean age of 71.3 ± 10.4 years. Zoledronate was the most frequently used ARD (n = 37; 49.3%). The average duration of ARD intake was 34 ± 19.7 months. Breast cancer was the most common indication for ARD intake. The demographic and clinical characteristics of the patients and ARD-related potential risk factors are presented in Table I.

Table I. Demographic data and antiresorptive drug-related potential risk factors

Variable	*Category*	*No. of patients (%)*
Age, years		71.3 ± 10.4 years
Sex		
	Male	26 (34.7)
	Female	49 (65.3)
Type of ARD		
	Zoledronate	37 (49.3)
	Pamidronate	3 (4)
	Ibandronate	3 (4)
	Combination of different bisphosphonates	7 (9.3)
	Denosumab 120 mg/month	9 (12)
	Denosumab 60 mg/month	6 (8)
	Alendronate	1 (1.3)
	Zoledronate and denosumab 120 mg/month	7 (9.3)
	Zoledronate and bevacizumab	2 (2.7)
Duration of ARD intake		34 ± 19.7 months
Primary disease		
	Breast cancer	25 (33.3)
	Multiple myeloma	12 (16)
	Osteoporosis	10 (13.3)
	Prostate cancer	20 (26.6)
	Other malignancies	8 (10.8)
Comorbidities		
	Metastasis to the bone	50 (66.7)
	Chemotherapy	50 (66.7)
	Cardiovascular disease	47 (62.7)
	Long-term corticosteroid therapy	13 (17.3)
	Type 2 diabetes mellitus	13 (17.3)
	Rheumatoid arthritis	7 (9.3)
Preceding oral events		
	Tooth extraction	16 (19.5)
	Apical periodontitis	17 (20.7)
	Marginal periodontitis	13 (15.9)
	Periimplantitis	1 (1.2)
	Unknown	19 (23.2)
	Denture pressure sores	7 (8.5)
	Extraction and endodontic treatment	4 (4.9)
	Extraction and marginal periodontitis	4 (4.9)
	Ridge augmentation	1 (1.2)

ARD, antiresorptive drug.

Treatment outcomes

Fifty-one lesions were located in the mandible, and 31 were in the maxilla. MRONJ stage 2 was identified in 62 lesions (75.6%), and stage 3 was diagnosed in 14 lesions (17%), whereas a frequency of 3.7% was observed for both stages 0 and 1 (n = 3).

The mean follow-up period was 11.41 ± 9.37 months, and the median follow-up period was 7 months. Complete mucosal healing in the absence of inflammation and pain was established after surgical treatment in 67 (81.7%) of 82 lesions after 3 months. Complete healing of MRONJ lesions in the mandible and maxilla is presented in Figures 1 and 2, respectively. Wound dehiscence requiring a second surgical intervention occurred in 15 (18.3%) of 82 lesions. Complete healing after relapse of MRONJ in the mandible is presented in Figure 3. Of these 15 lesions, 7 showed complete postoperative mucosal healing after the second surgery, and 8 lesions continued to exhibit exposed bone. Thus, the success rate after the second surgical approach was 90.2% (74 of 82). Four lesions demonstrated complete postoperative mucosal healing with persisting oroantral communication. Rehabilitation was achieved with obturators without any complications. Location, stage, and treatment outcomes of MRONJ lesions are shown in Table II.

DISCUSSION

The management of MRONJ is still controversial. Although some authors have promoted mucosal integrity and absence of bone exposure as primary aims of

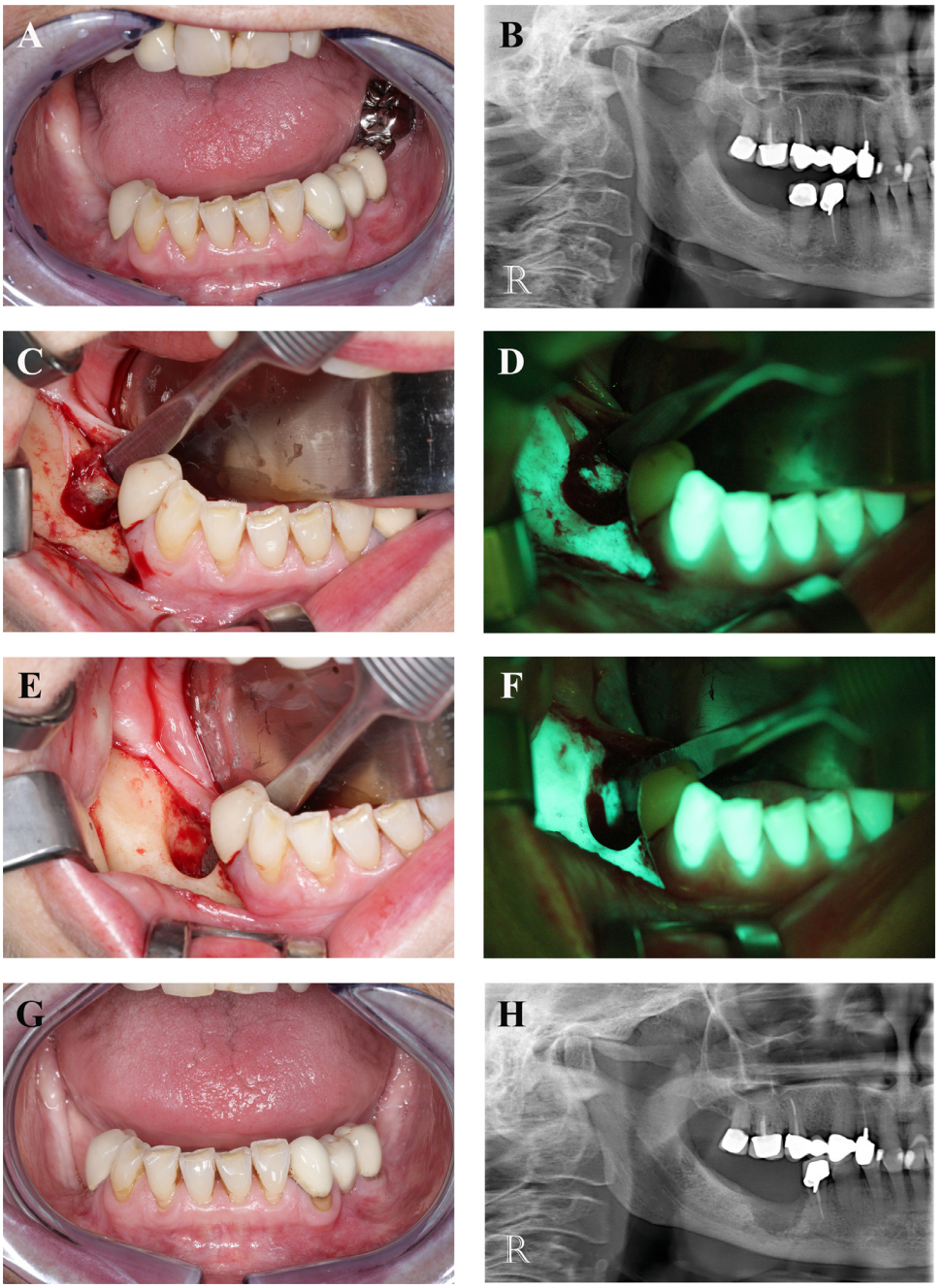

Fig. 1. Complete healing of medication-related osteonecrosis of the jaw lesion in the mandible of a female patient aged 76 years at her first visit to our clinic. She was administered intravenous zoledronate. (A, B) Clinical and radiologic images before extraction of tooth 45. (C, D) Intraoperative images obtained before autofluorescence-guided surgery. (E, F) Intraoperative images obtained after autofluorescence-guided surgery. (G, H) Clinical and radiologic images obtained 1 year after autofluorescence-guided surgery.

the treatment,[18] others have had the aim of relieving pain and controlling the infection. The management of MRONJ had varied among the maxillofacial surgeons between the conservative management of MRONJ, which includes the use of antibiotics, analgesics, and mouthwash, or undergoing surgical treatment, either conservative or aggressive.[19] Evidence suggests that surgical treatment is significantly more effective than conservative treatment if the aim is mucosal integrity and relief of recurrent infection.[20,21] This means that patients treated under a conservative protocol have a higher risk for long-lasting bone exposure, which might limit further treatment options of oncology patients and might affect their quality of life.[22]

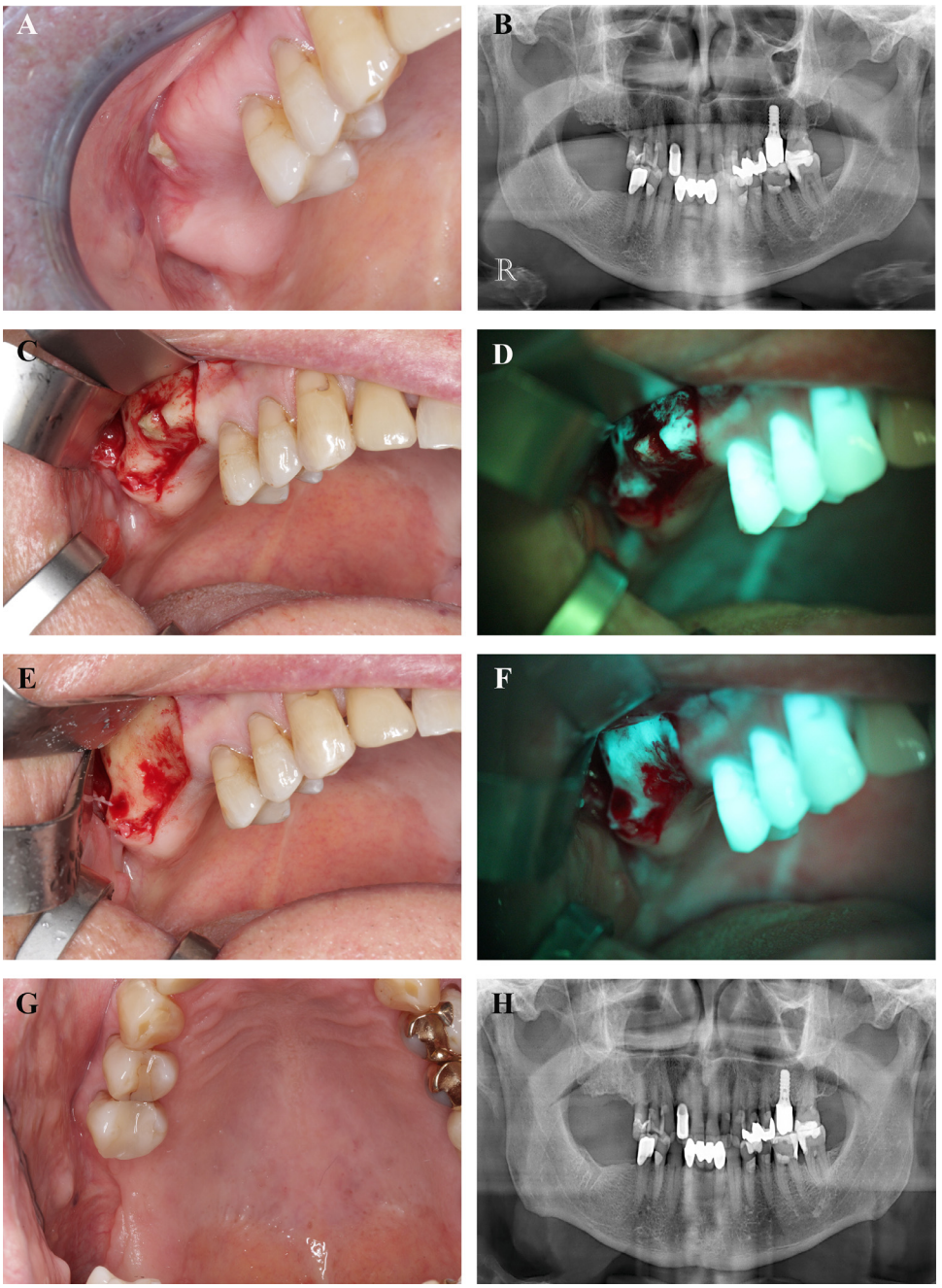

Fig. 2. Complete healing of medication-related osteonecrosis of the jaw (MRONJ) lesion in the maxilla of a male patient aged 75 years at his first appointment in our clinic. He was administered intravenous zoledronate. (A, B) Clinical and radiologic images obtained at the first presentation of MRONJ in the right maxilla at region 17 in our clinic. (C, D) Intraoperative images obtained before autofluorescence-guided surgery. (E, F) Intraoperative images obtained after autofluorescence-guided surgery. (G, H) Clinical and radiologic images obtained 1 year after autofluorescence-guided surgery.

Several studies following a surgical protocol showed success rates exceeding 85%: Carlson and Basile[10] reported 92% mucosal integrity in a case series of 95 patients. However, other authors found healing rates up to 89% after 12 months.[23] In 2016, our research group found complete mucosal healing in 87% of patients and 86.2% of lesions.[18] Prospective studies also indicate the advantage of surgical treatment,[24,25] but differences in underlying study cohorts, surgical protocol, evaluation, and postoperative follow-up did not allow direct comparison.

Furthermore, it could be detected that for successful surgical treatment of MRONJ apart from complete removal of necrotic and infected bone, pre- and

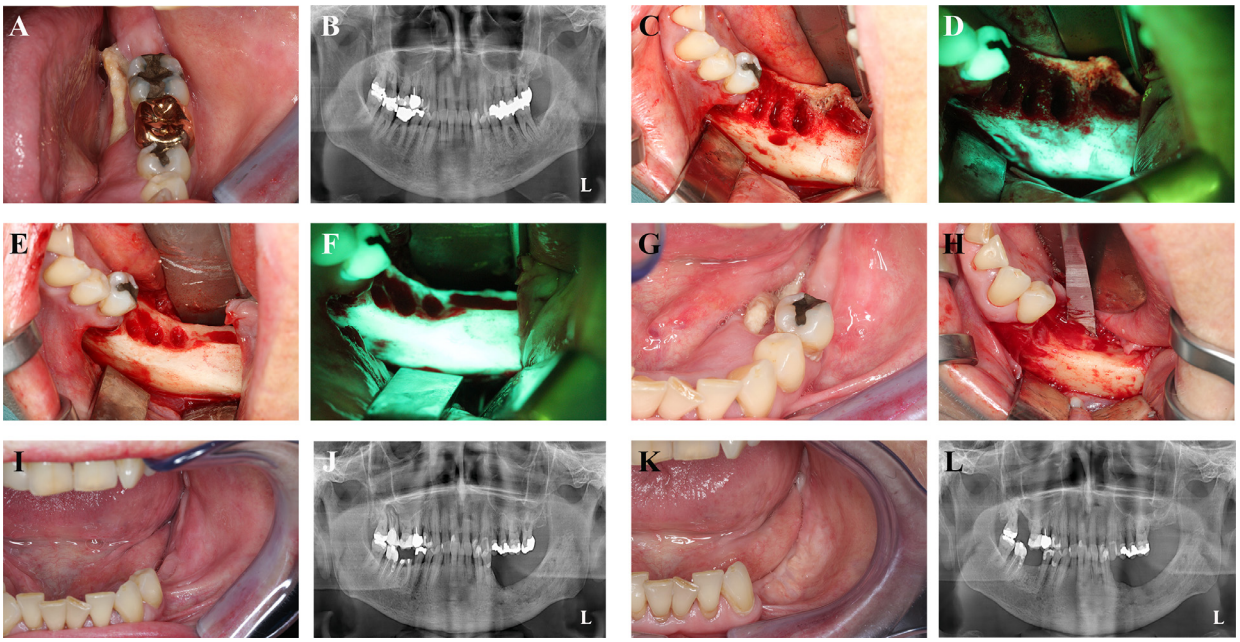

Fig. 3. Complete healing after relapse of medication-related osteonecrosis of the jaw in the mandible in a female patient aged 65 years at her first visit in our clinic. She was administered intravenous zoledronate. (A, B) Clinical and radiologic images obtained at the first visit in our clinic. (C, D) Intraoperative images obtained before autofluorescence-guided surgery. (E, F) Intraoperative images obtained during autofluorescence-guided surgery. (G, H) Pre- and intraoperative clinical images of autofluorescence-guided surgery obtained 2 years later upon relapse. (I, J) Clinical and radiologic images obtained 3 years after the first surgical treatment. (K, L) Clinical and radiologic images obtained 6 years after the first surgical treatment.

postoperative antibiotic treatment, smoothening of sharp bony edges, and reliable plastic wound closure with mucoperiosteal flaps are vital.[26]

Although several guidelines, including those in the AAOMS position paper and the American Society for Bone and Mineral Research (ASBMR) expert panel, recommend conservative treatment for early stages of MRONJ,[4,27] the authors of this paper promote surgical treatment for all stages with exposed bone.[28] Former studies by our research group showed complete mucosal healing with minimal morbidity in a predictable and reasonable time frame in stages 0 and 1 lesions.[18] Early surgical treatment can prevent these lesions from becoming more severe and thus can reduce the necessity of extended surgical approaches in the long run,[29] and conditions are better due to lack of infection.

Table II. Location, stage, and treatment outcomes of medication-related osteonecrosis of the jaw lesions

Variable	*No. of lesions (%)*
Location	
Maxilla	31 (37.8)
Mandible	51 (62.1)
Stage of MRONJ	
Stage 0	3 (3.7)
Stage 1	3 (3.7)
Stage 2	62 (75.6)
Stage 3	14 (17)
Treatment outcomes	
Complete mucosal healing after first surgical attempt	67 (81.7)
Complete mucosal healing after revision surgery	74 (90.2)
Relapse	8 (9.8)
Special cases	
Complete mucosal healing with oroantral communication and obturator	4 (4.9)
Persisting hypoesthesia in lower lip	3 (3.6)
Protection plate	3 (3.6)

MRONJ, medication-related osteonecrosis of the jaw.

Fluorescence-guided surgery has been used as a promising technique.[11,18] Despite tetracycline only was used for fluorescence in former studies, newer studies showed that vital collagen of bone has autofluorescent properties.[11] A recent study in a minipig model demonstrated that a vital part of bone fluorescence is autofluorescence and not tetracycline-induced fluorescence.[14] Because of this physiologic fluorescence, it is possible to distinguish between vital and necrotic bone independently of tetracycline administration while having similar fluorescence.[30]

In this study, the overall healing rate of all lesions treated with autofluorescence-guided surgery after the first surgical attempt was 81.7% (67 of 82), whereas it was 90.2% (74 of 82) after revision surgery in 15 cases compared with 86.2% and 95.4%, respectively, in our former study of tetracycline fluorescence,[18] indicating

that autofluorescence-guided bone surgery is a reliable and promising treatment option for patients with MRONJ.

Compared with total resection as promoted by some surgeons,[8] the risk of functional impairments such as oroantral communication, hypesthesia, fracture, or continuity resections of the mandible or the necessity of protection plates can be reduced through autofluorescence-guided surgery because only the necrotic areas are removed.

In selected severe cases of MRONJ, ablative surgery including continuity resections of the mandible and microvascular reconstructions might be necessary, whereas in early stages, conservative treatment might be an option. However, the authors of this paper see autofluorescence-guided bone surgery as a promising opportunity to strike a balance, especially because surgical treatment of MRONJ in general leads to higher healing rates.[9]

Limitations

This retrospective, single-center observational study had limited convergence of data and a small number of participants. Because autofluorescence-guided surgery is relatively new, no long-term results can be presented at this point. Because denosumab has a much shorter half-life (26 days) than nitrogen-containing bisphosphonates, conservative treatment approaches in MRONJ in patients treated solely with denosumab might play a more important role. Further prospective studies are needed to confirm these results, because up to now no study has directly compared conservative, conventional surgical, and autofluorescence-guided surgical treatments.

CONCLUSIONS

Our study shows that autofluorescence-guided bone surgery might be a tool to optimize the completeness of removal of necrotic bone parts and is a reliable, minimally invasive, and promising treatment option for patients with MRONJ. Autofluorescence-guided surgery might be suitable not only for MRONJ but also for osteoradionecrosis and osteomyelitis. Therefore, the authors of this paper renew their call for a reevaluation of concepts and aim for a change of paradigms. Long-lasting, unpredictable conservative treatment approaches usually resulting in improvement of symptoms but rarely leading to complete mucosal healing should be replaced by early surgical interventions aiming for complete mucosal healing in a predictable time frame and resulting in optimized functional outcomes. Thus, extended surgeries frequently performed after unsuccessful conservative treatment approaches can be avoided.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2020.10.018.

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