

# Bisphosphonate-associated osteonecrosis of the mandible: reliable soft tissue reconstruction using a local myofascial flap

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**Abstract** For the treatment of bisphosphonate-associated osteonecrosis of the jaw (BP-associated ONJ), poor cure rates are reported. In many cases, repeated osseous exposition and infection may occur. The currently recommended management of affected patients is antibiotic treatment and bony decortication, which is often complicated by soft tissue deficits due to chronic infection. In severe cases osteonecrosis can be managed often only by continuity resections of the mandible. For this purpose, we developed a new surgical procedure, which allows an effective closure of difficult jaw wounds in the lateral mandible. In the last 3 years, 20 patients with BP-associated osteonecrosis of the lower jaw were treated successfully with a modified defect-covering method using a myofascial flap. A mylohyoid muscle flap was detached from mylohyoid line and used to cover the bony defect. During 19 months mean follow-up, 90% of patients were asymptomatic, the oral mucosa was intact, and no exposed bone was observed. In consequence, we are able to demonstrate that a mylohyoid muscle flap provides a reliable wound closure in the lower jaw in patients treated with BPs. Although there are still no consensual therapy guidelines

for patients affected by BP-associated ONJ, the results of the presented study provide evidence for an effective surgical therapy with long-term success. Covering compromised bone with well-vascularized tissue, a muscle flap, increased healing chances by enabling and supporting the necessary nutrition and defense against opportunistic infections. This therapy concept showed a good clinical outcome.

**Keywords** Bisphosphonate · Osteonecrosis · Mandible · ONJ · BRONJ

## Introduction

Since the first report in 2003 [1], the number of publications describing the development of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates (BPs) increased continuously. The introduction of BP was a determining step in the prevention and treatment of skeletal metastases and osteoporosis as well as in the management of multiple myeloma, Paget's disease, and hypercalcemia. An evident correlation between bisphosphonate exposure and osteonecrosis of the jaw is already well recognized, although the pathogenesis is still not completely understood.

The beneficial effects of BPs are to inhibit the resorption of trabecular bone by osteoclasts, preserve its density, and prevent the loss of bone mass and pathological fractures [2, 3]. BPs are divided into two classes according to the presence of a nitrogen side chain on the pyrophosphate group. The non-nitrogen-containing BPs (etidronate, clodronate, tiludronate) lead to apoptosis of osteoclasts by

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disturbance of cellular energy pathways. The nitrogenous BPs (pamidronate, alendronate, zoledronate) inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase pathway and block the building of hydrophobic molecules, which are essential for maintenance of cell membranes, cellular protein connections and trafficking, and hormones production as well. Inhibition of HMG-CoA reductase pathway disturbs proper osteoclastogenesis and apoptosis. Changes into cytoskeletal dynamics of osteoclasts disrupt those adherences to the bony surface [4, 5].

The clinical appearance of BP-associated ONJ is defined as exposed necrotic bone of the oral cavity for at least 8 weeks, in patients without previous radiotherapy in this area [3, 6–8]. Under an intact overlying oral mucosa, BP-associated ONJ can remain asymptomatic. Invasive dental procedures, parodontitis, and constant microtrauma like mechanical stress by ill-fitting dentures can lead to bacterial contamination and infection of the necrotic jawbone, which are accompanied by pain, swelling, non-healing ulceration, and loosening of teeth. In an advanced phase, radiological changes like bone mottling and osteolysis, bony sequestra, and thickened and sclerotic lamina dura can be observed. A reduced bone turnover leads to residual “ghost sockets” after teeth removal, which can persist even after years [9–12]. The prevalence of ONJ, especially by administrating IV BPs has been underestimated in the past. Recent results revealed a range up to 18%, depending on treatment duration [13–19].

The incidence of osteonecrosis of the jaw by oral BPs administration is higher in patients with more than 4 years of exposure as concluded in a recent study of Lo et al. [10]. Generally, the prevalence ranges of ONJ among oral BP-treated populations are estimated by 0.001% up to 0.2% [10, 15, 20, 21]. The relative proportion of patients with ONJ associated with oral BPs therapy due to all BP-associated ONJ patients ranged from 0.02% to 7.8% [22–25]. Otto et al. suggested classifying the intake duration of oral BPs in excess of 3 years as an independent risk factor when elective dentoalveolar surgeries are impending [22].

The hypotheses according to the development of BP-associated ONJ are controversially discussed. Different theories attempt to explain such a devastating side effect of the BPs exclusively to the jaw, like interferences in the regular remodeling processes of the jaw by disturbing function and apoptosis of osteoclasts [26–28]. Other authors postulate as further theories the toxicity of BPs on fibroblasts and endothelial cells [29], bony microcracks [30], and bacterial infection of the jaw, especially by actinomyces, but also novel forms of yeast, spirochetes, and treponemes [31, 32]. Lehrer et al. hypothesized that a metalloproteinase 2 polymorphism or expression may play a role in the development of BP-associated ONJ [33]. The

risk of ONJ might be associated with IV bisphosphonate and increased duration of treatment [6, 26, 34]. A review of 2,400 BP-associated ONJ patients this year revealed as predisposing factors extractions in 67% and spontaneous development in 26% of cases [35]. Furthermore, chemotherapy (55%), steroids (32%), parodontopathies (16%), hormone therapy (9%), smoking (3%), diabetes (2%), hyperlipidemia (2%), and ethylism (1%) could be identified by Filleul et al. as comorbidities [35], results of which could be confirmed by other reviewers [14, 36–38].

Recent press releases report BP-associated ONJ-like lesions in patients treated with other drugs, like denosumab, a high-affinity, highly specific IgG2 monoclonal antibody, that specifically binds human RANK, which results in an increased bone mineral density and suppression of bone turnover markers [39, 40]. A new term for osteonecrosis of the jaw associated to the administration of therapeutic agents as “drug-induced osteonecrosis of the jaw” was proposed [41].

Regarding clinical findings, four stages of BP-associated ONJ can be identified [6]:

- Stage 0 No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms
- Stage I Exposed and necrotic bone in asymptomatic patients without evidence of infection
- Stage II Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage
- Stage III Exposed and necrotic bone in patient with pain, infection, and one or more of the following findings: exposed and necrotic bone extending beyond the region of alveolar bone (inferior border and ramus of the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral–antral/oral–nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor

The mandible is affected by BP-associated ONJ twice as often as the maxilla [34]. The treatment of BP-associated ONJ is difficult; the reported cure rates are poor [42–44].

At present, monitoring and prevention of surgical procedures and trauma are the most important measures in risk patients [45–47]. In severe cases, however, surgical procedures are necessary despite their controversial status in the literature. Recommended therapeutic modalities range from cautious sequestrectomies up to the resection of the affected mandible or maxilla [6, 26, 48, 49].

The clinical course of BP-associated ONJ-affected patients is often complicated by a progression of the osteonecrosis. The gold standard for stage III and advanced

stage II is the surgical removal of necrotic bone tissue, a sufficient tension-free wound closure with a mucoperiosteal flap and intravenous antibiotic treatment [6]. A progress of BP-associated ONJ can require extended bony resections and controversial procedures with a high morbidity, which can lead to loss of aesthetics, functionalities (speech, alimentation), and quality of life in patients [35].

Pathogenesis of the osteonecrotic bone is, however, a process associated with insufficient vascular supply. Every curative surgical option must take into account that the inflammatory response is limited in necrotic bone. Mainly the surrounding soft tissues must thus provide nutritional support and support an inflammatory response. For this reason, it is essential that progress is made in new surgical procedures that result in secure soft tissue closure by mobilizing well-vascularized tissue.

Trauner described in 1952 the detachment of mylohyoid muscle from the mylohyoid ridge area and its inferior reposition to achieve an effective deepness of mouth floor and improvement of denture position [50, 51]. We use the mylohyoid muscle as a less complicated but effective possibility for reliable locale defect cover in the horizontal, edentulous part of the mandible.

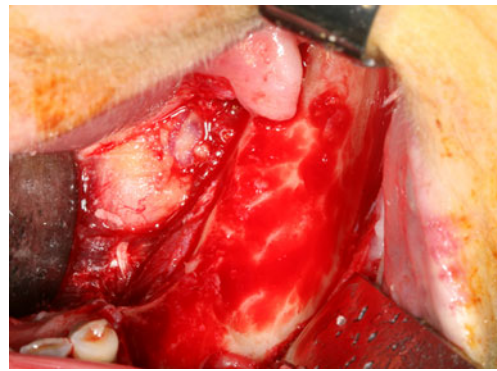
## Materials and methods

The aim of the study was to evaluate the reliability of a well-vascularized local flap as soft tissue closure after removal of osteonecrotic bone of the lower jaw in BP-associated ONJ patients. Between May 2008 and January 2010, all patients diagnosed with BP-associated ONJ stage I to II [6] (symptom less or painful infected exposed bone in the lateral mandible) in the lateral mandible underwent a modified surgical treatment.

Surgical intervention with decortication of the necrotic bone and reliable soft tissue closure was proposed. Resection of the necrotic bone and leveling the sharp bone borders using a rotating bur (Figs. 1 and 2) as well as tooth



**Fig. 1** Extended necrosis of the lower jaw

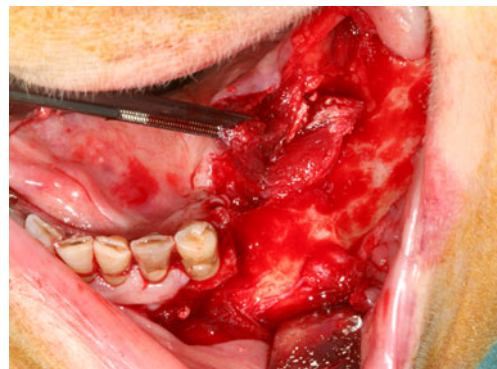


**Fig. 2** Decortication of necrotic bone up to a bleeding bone surface

extraction in necessary cases was performed by an intraoral approach under general anesthesia. A myofascial flap was designed for soft tissue closure by exposing and detaching the mylohyoid muscle from its insertion at the ipsilateral mylohyoid line (Fig. 3). Care was taken to preserve the submandibular duct and lingual nerve (Fig. 4) during the mobilization of the mylohyoid muscle. The flap was then placed in a tension-free manner over the decorticated mandible and fixed with deep sutures (Figs. 5 and 6). An additional tight soft tissue mucosal closure using mattress knots was performed (Fig. 7).

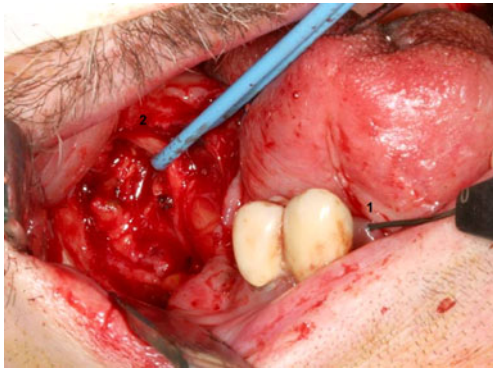
The patients were advised to eat soft food and not to wear dentures for the following 4 weeks. During the hospital stay and already preoperatively, an antibiotic intravenous therapy with penicillin 20,000 IE daily or alternatively in allergic patients clindamycin 1.8 g daily was performed. Additionally oral antiseptic rinses completed the therapy. After discharge, the antibiotic therapy was continued in oral form for mean 12 days.

All patients were informed in detail, educated about the risk of progress of the osteonecrosis and the necessary prophylaxis during and after BP treatment, and were placed in a regular recall schedule. We did not require a drug holiday. Five patients, which gave up the BP treatment



**Fig. 3** Detachment of mylohyoid muscle from its insertion at the ipsilateral mylohyoid line





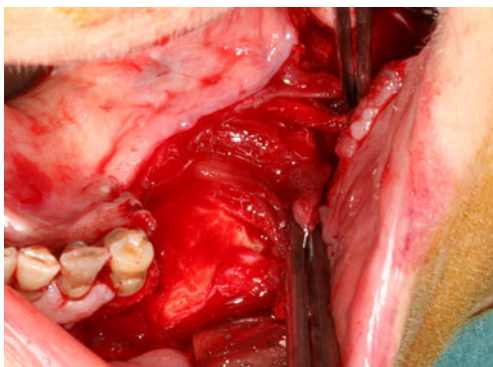
**Fig. 4** Preserved submandibular duct (1) and lingual nerve (2) during the mobilization of mylohyoid muscle

postoperatively, took the decision themselves or in consultation with the oncologist. During the described follow-up, the BP treatment was not restarted. Mean duration of BP treatment until ONJ was diagnosed was 3.1 years (range 1.4 to 5.4 years).

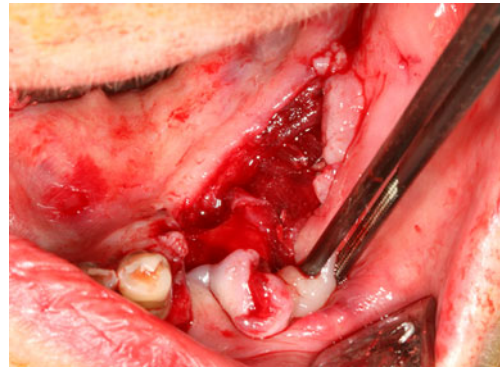
## Results

Between 2003 and 2010, a total of 130 patients with BP-associated ONJ were diagnosed and treated in our department. The mandible was affected in 57% of cases, the maxilla in 36% of cases. In 7% of patients the upper and lower jaw were simultaneously affected. Twenty patients with BP-associated ONJ stage I and II [6], in whom a mylohyoid flap for defect cover was used, were identified (Table 1).

The patients' mean age was 68 years; the patient group included 11 women and 9 men. Nineteen patients had a history of taking intravenous BPs, consisting of zoledronate ( $n=13$ ), bondronate ( $n=4$ ), alendronate ( $n=2$ ), and pamidronate ( $n=1$ ). In two patients, the initial BP treatment with zoledronate changed into ibandronate, respectively pamdr-



**Fig. 5** Placement of the mylohyoid flap in a tension-free manner over the decorticated mandible



**Fig. 6** Fixation of the flap with deep submucosal sutures

onate. Mean duration of BP treatment until ONJ was diagnosed was 3.1 years (range 1.2 to 5.4 years).

At the time of surgery, BP treatment has been discontinued in one patient for 3 years. Five patients stopped BP treatment directly postoperatively. All other patients continued on their BPs medications. In the majority of patients, BPs was administrated to treat bone metastases: breast cancer (35%,  $n=7$ ), kidney cancer (20%,  $n=4$ ), myeloma (15%,  $n=3$ ), prostate cancer (15%,  $n=3$ ), and pancreatic cancer (5%,  $n=1$ ). Only two patients received BPs to treat osteoporosis (10%). The hospital stay ranged from 5 to 22 days (mean 8.1 days). Seventy percent of patients were discharged during the first week postoperatively.

The intravenous antibiotic treatment started 1 day before surgery and continued during the whole hospital stay. We administered penicillin 10,000 units twice a day in 12 cases and clindamycin 600 mg three times a day in seven patients with penicillin intolerance or allergy. Cefuroxime 500 mg twice a day was administrated in one patient. After discharge, the antibiotics were prolonged in oral form for mean 11 days. Clinical symptoms were correlated with radiological findings in orthopantomogram ( $n=20$ ) and in three-dimensional computed tomography (CT or cone beam CT,  $n=11$ ).

In 30% of cases ( $n=6$ ) teeth removal was necessary. In two patients (10%) we observed a progress of BP-



**Fig. 7** Tight wound closure of intraoral mucosa using mattress knots

**Table 1** Patient characteristics and treatment results

Patient	Age	Sex	Primary disease	BP	BP administration form	Duration of BP treatment (years) at diagnosis	BP treatment stopped before ONJ occurred	BP treatment postoperatively stopped	Cause for BP-associated ONJ	Location of ONJ	Stage	Treatment result	Follow-up (months)
1	58	F	Breast cancer	ZOL/IBA	IV/oral	4.8	No	No	PA	36–38	2	+	26
2	63	M	Prostate cancer	ZOL	IV	2.5	No	Yes	Ex	36–37	2	+	33
3	56	M	Kidney cancer	ZOL	IV	2.6	No	Yes	Ex	46–47	1	+	30
4	71	M	Prostate cancer	ZOL	IV	3.4	No	No	PR	47–48	2	+	29
5	75	F	Multiple myeloma	PAM	IV	4.0	No	No	PR	48	1	+	29
6	72	F	Pancreatic cancer	ZOL	IV	2.8	No	No	PA	44–45	2	+	27
7	63	F	Breast cancer	IBA	IV	1.8	No	No	Ex	45–46	2	+	27
8	73	M	Prostate cancer	ZOL	IV	5.2	Yes	–	Ex	45–47	1	+	21
9	68	M	Kidney cancer	ZOL	IV	1.4	No	Yes	Ex	41–48	1	+	19
10	73	M	Breast cancer	IBA	IV	3.6	No	No	SP	48	1	+	19
11	54	F	Breast cancer	IBA	IV	4.6	No	Yes	PR	35–36	2	+	18
12	84	F	Osteoporosis	ALE	Oral	3.2	No	No	Ex	45–48	1	+	18
13	58	M	Kidney cancer	ZOL	IV	1.4	No	No	Ex	36–37	2	+	18
14	73	F	Multiple myeloma	ZOL	IV	1.2	No	Yes	Ex	34–33	2	–	6
15	72	F	Breast cancer	ZOL	IV	2.1	No	No	Ex	34–36	1	+	17
16	77	F	Multiple myeloma	ZOL	IV	1.9	No	No	PA	35–37	1	+	15
17	72	M	Osteoporosis	ALE	IV	1.0	No	No	Ex	37–38	1	+	13
18	64	M	Kidney cancer	ZOL/PAM	IV	5.4	No	No	PA	36–38	1	+	13
19	67	F	Breast cancer	IBA	IV	4.0	No	No	C	46–48	2	+	11
20	69	F	Breast cancer	ZOL	IV	1.5	No	No	PR	37–38	1	–	3

F female, M male, ZOL zoledronate, IBA bondronate, ALE alendronate, PAM pamidronate, IV intravenous, Ex extraction, C caries-destroyed tooth, PR pressure denture sore, SP spontaneously, PA chronic periodontitis, + successful treatment—intact oral mucosa or no symptoms, – unsuccessful treatment

associated ONJ after 3 months (Nr. 20) and 6 months (Nr. 14), respectively. Both patients received intravenous BPs. One of them stopped the BPs medication postoperatively (Nr. 14), the other one patient received BPs continuously (Nr. 20). One patient underwent repeated bony debridement and removal of one tooth (Nr. 14), and in the other patient, a continuity resection of the mandible was necessary (Nr. 20).

The rest of the patients were asymptomatic ( $n=18$ , 90%), the oral mucosa was intact, and no exposed bone was observed. The mean follow-up for the 18 patients was 19.2 months, 11 up to 33 months. Two patients had postoperative transient hypoesthesia of the tongue, as a sign of temporary injury of lingual nerve (10%). However no permanent paraesthesia of the tongue was observed.

## Discussion

The presented modified soft tissue reconstruction using the mylohyoid muscle shows a surgical treatment option that takes into account the pathophysiology of ONJ. Recurrences are avoided by using the functions of the surrounding soft tissue in order to improve healing mechanisms in the affected bone.

Treatment with BPs may lead to osteonecrosis of the affected bone especially in the jaw [26]. This is induced by a decrease in osteoclastic activity, which reduces bone resorption [2]. BPs are thus effective for treating bone metastasis and multiple myeloma. The benefits of this treatment with significant improvement of quality of life in patients by reducing the bone pain and the incidence of pathologic fractures [52] far outweigh the risk of developing BP-associated ONJ and make the widespread use of BPs explicable. The well-recognized risk of BP-associated ONJ should lead to a careful reevaluation of indications for BPs treatment and duration of treatment in patients with osteopenia/osteoporosis and cancer [45].

Given the pharmacokinetics of BPs, it is noteworthy that the half-life dose in tissues strongly differs. While the plasma half-life is only between 20 min and 3 h, it is between several months and years for the bone. The bone turnover still remains compromised for more than a year after taking 2.5 to 5 mg alendronate daily during 1 year, compared with 5 years after taking 20 mg alendronate daily during 1 year [53]. The bone half-life time for oral alendronate is 10.9 years [54]. Moreover, these drugs have a high affinity to bone and are thus absorbed there for more than 50% of the applied dose [55]. As BPs show a very long half-life concentration in bone, discontinuation of BPs treatment is unlikely to be successful. Discontinuation of IV BPs seems not to offer a short-time benefit [56] but remains controversial [46]. However, some authors report a reduction of clinical symptoms and decreased risk to develop a

new BP-associated ONJ [57–59]. In our own patient group, we observe a progress of BP-associated ONJ after surgery in two patients, one of them interrupted postoperatively the BPs treatment, obviously without a short-time benefit or an improved outcome. The treating oncologist, in consultation with the maxillofacial surgeon, should weigh the risks and benefits of discontinuation of BPs treatment individually [6, 36, 46, 60]. Since the clinical appearance of ONJ was first described in 2003 [1], its pathophysiology is still not understood in detail.

Reid supposes an interaction of factors contributing to the development of BP-associated ONJ [27]. While BPs tightly bonded to hydroxyapatite in bone, they are not available to act on non-bone cells. Driven by infection with dissolution of bone, BPs are released into the immediate environment. The mobilized BPs are taken up by epithelial, vascular, mesenchymal, and immune cells, resulting in toxicity mediated through its inhibition of the mevalonate pathway [61]. A vicious cycle is created, in which the presence of infection to further bone resorption releases cytotoxic BPs and leads as final result to a sustained progression of infection [27]. Other authors assume also a multifactorial etiology of BP-associated ONJ development [46, 62].

Despite the unknown processes involved, there is agreement that local vascular insufficiency is a major risk factor for local osteonecrosis. It has been shown that BPs inhibit endothelial cell function in vitro and in vivo [63]. Furthermore, it has been demonstrated that bone blood flow is limited by BPs [64]. This leads to a decline of angiogenesis and, in the long term, to microvascular failure in the affected tissues. The authors recommend a stable, well-vascularized tissue closure in order to maintain optimal nutritive support to the jaw. Since microvascular density in mandibular jaw is comparatively low, it is strongly affected by ONJ [12, 34, 42, 57, 65, 66]. This was also showed by the presented case, where the upper jaw revealed no such lesions despite the fact that dental status showed periodontal insufficiencies.

In most cases, intraoral wounds heal after periodontal or surgical treatment without infection of the bone. When blood flow is limited due to radiation or drug therapy, however, there is an increased risk to develop a nonhealing wound with exposed bone [12]. Antibiotic treatment and chlorhexidine mouthwash are the recommended treatment guidelines in such cases for stage I and II patients [6]. In our patient group, antibiotic treatment leads to an improvement of local soft tissue wound sites, but as predicted, there was no evidence of bone healing. For this reason, the authors decided in favor of surgical treatment. Successes after surgical treatment in the past are poorly described in the literature, but in the mean time, an increasing number of publications report better results with surgery. Van der

Wyngaert et al. concluded in a meta-analysis 2007 over 2 years that 73% of patients showed residual BP-associated ONJ after conservative and/or surgical therapy [67]. In a later evaluation, the conservative treatment in 53% of patients ( $n=30$ ) brought a stabile mucosal closure, in 10%, however, a progress of disorder [43]. Similar results, 54.1% responders in 37 patients treated with conservative or/and surgical therapy, provided a recent study of Scoletta [42]; just 23% resolved ONJ after conservative therapy in 4,019 observed BP-associated ONJ patients [14]. Better results are reported by Vescovi et al. in 12 patients after surgical therapy performed using a new form of resective therapy, the Er:YAG laser, successful in 87.5% of BP-associated ONJ cases with a mean follow-up of 13 months [56]. Abu-Id et al. reported in a multicenter study on healing after marginal or segmental bone resection in 86% of cases compared with 46% responders after conservative therapy [12]. We could report with the modified surgical technique a complete healing in 90% of cases with a mean follow-up of 18 months.

The myofascial flap is appropriate to cover bone defects in the toothless horizontal part of the mandible or directly after teeth extraction in this area. A flattening of the mouth floor is a tolerable adverse effect, which is, however, less pronounced, because of the reduced height of the alveolar bone due to necessary necrosis removal.

Whereas some authors especially in the past state that surgical treatment is mostly counterproductive [17, 21, 26, 68, 69], more clinicians see however the necessity of surgical treatment and report that healing rates ranged up to 91.6% [12, 48, 49, 70–75]. Recent histopathological and radiologic researches described BP-associated ONJ as an extensive but localized osteomyelitis-like condition [76]. Filleul et al. hypothesized that unsuccessful resective surgical procedures obviously did not assess vital bone margins [35]. We assumed that vital bone substance can be described by bone bleeding. The bony resection margins showed clinically a bleeding bone surface. New treatment approaches like fluorescence-guided bone resection, laser treatment, hyperbaric oxygen and ozone exposure, and parathyroid hormone administration in BP-associated ONJ-affected osteoporotic patients are still controversial and require extended evaluation and long-term follow-up results in larger patient groups [54, 56, 57, 72, 77–80].

There is a consensus among all experts about the difficulty of treating BP-associated ONJ and the importance of prevention. The risk of developing BP-associated ONJ can be decreased by optimizing dental health and regular monitoring of BPs-receiving patients. They should be informed by treating clinicians about the low but existing risk of developing BP-associated ONJ and about the importance and necessity of regular dental visits and prophylactic dental treatment [45].

As the perfusion and nutrition of the jaw strongly depends on periosteum and overlying mucosa, the authors assumed that local mucosal flap surgery in combination with periosteal stripping could lead to bony and mucosal healing complications. This hypothesis is in line with the study of Engroff et al. [81, 82] and further authors [83], who presented the first positive results in surgical treatment by performing even free tissue transfer surgery.

The study presented here used the advantages of local muscle flap surgery, in patients with various comorbidities who are not good candidates for free tissue transfer. We could prove that careful surgical planned treatment leads to a successful clinical outcome for patients affected by BP-associated ONJ.

## Conclusion

Although there are still no consensual therapy guidelines for patients affected by BP-associated ONJ, the results of the presented study provide evidence for an effective surgical therapy with a long-term success. Covering the compromised bone with a well-vascularized tissue, a muscle flap, increased the healing chances by enabling and supporting the necessary nutrition and defense against opportunistic infections. This therapy concept showed a good clinical outcome, despite the insufficiently clarified etiology of BP-associated ONJ.

Considering the treatment difficulty, a tight teamwork between treating oncologists, cranio- and maxillofacial surgeons, dentists, and patients is required. Prevention of BP-associated ONJ, detailed education of patients by involved clinicians, and patient monitoring by regular recalls to control and recognize the development of BP-associated ONJ are strongly recommended.

**Conflict of interest** The authors declare that they have no conflict of interest.

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