

Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up

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Abstract

Goals of work This is a prospective clinical study aimed at assessing the success rate of osteotomy and primary wound closure in patients with bisphosphonate-associated osteonecrosis of the jaw (BONJ).

Materials and methods Fifty patients who had received bisphosphonates intravenously and subsequently suffered from BONJ were included in the study. All patients underwent osteotomy of the affected jaw bone region and primary wound closure under general anaesthesia. They were followed up bimonthly for a period of 12 months.

Results Macroscopically altered bone could be completely removed in all cases. In two patients with plasmocytoma,

major bleeding occurred postoperatively that required monitoring in an intensive care unit. In two cases, recurrence of BONJ was diagnosed during the first 2 months. In three patients, recurrence appeared between the fourth and the sixth month. In these cases, an additional osteotomy had to be performed. Six patients died during the follow-up period. In the remaining 39 patients, no signs of recurrence could be detected during the follow-up of 12 months. The success rate of the surviving patients was 89% after 1 year.

Conclusion Due to the high success rate of osteotomy and primary wound closure, it should be checked for every patient suffering from BONJ if osteotomy is a viable treatment option.

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Introduction

Bisphosphonates reduce bone metabolism, inhibit angiogenesis and induce apoptosis in tumour cells [18, 26, 29, 31, 33]. They have been successfully applied in the treatment of patients with osteoporosis, Paget's disease and lytic bone malignancies like multiple myeloma, metastatic breast cancer, prostate cancer and hypercalcemia syndrome related to malignancy.

Randomised clinical trials could show that bisphosphonates reduce pain and pathological fracture in patients with bone metastases and may increase lifetime with metastatic bone disease [5, 27]. Due to their beneficial effects, oncologists prescribe bisphosphonates for the prevention and control of bone metastases more commonly. It has been

claimed that IV bisphosphonate treatment is generally well tolerated [13]. To date, the frequency of side effects is not well defined. Side effects include an acute and self-limited febrile inflammatory response, hypocalcemia and kidney dysfunction [8]. However, recently, a serious adverse effect of bisphosphonate administration has been described [7, 19, 34, 37].

Bisphosphonate-associated osteonecrosis of jaws (BONJ) shows certain characteristics. Non-healing extraction sockets or exposed jaw bone with progression to sequestrum formation associated with localised swelling and infection are encountered frequently. These complications are predominantly associated with the use of the new generation of nitrogen-containing bisphosphonates like pamidronate and zoledronic acid (II and III generation) [19, 28].

A diversity of treatment modalities have been published including conservative management, primary surgical intervention [14], bone resection and application platelet-derived growth factors [2], use of recombinant human parathyroid hormone [12], Nd:YAG laser biostimulation, hyperbaric oxygen and local ozone therapy [3].

But to date, there is still uncertainty on the adequate treatment strategy and management of patients with BONJ [1, 3, 14, 15, 21, 25, 32]. Reasons for uncertainty are early failures with surgical revisions, lack of healing with anti-infective strategies and small number of cases from reportedly successful treatment trials. At the moment, prospective studies are rare that are dedicated to one or the other treatment concept (Table 1). It seems that performing an osteotomy to the jaw regions affected by BONJ and carrying out primary wound closure could be a benefit to the patients if this procedure would show a high success rate. Compared to other more conservative treatment approaches where a large number of appointments are necessary and often only little improvements in the clinical situation are achieved, the number of appointments could be reduced significantly if the new concept would turn out to be successful. Therefore, it has been the aim of the present study to assess the success rate of osteotomy and primary wound closure in patients suffering from bisphosphonate-associated osteonecrosis of the jaws during a follow-up period of 12 months.

Materials and methods

Fifty consecutive patients under treatment with bisphosphonate were included from October 2004 until December 2006 in the prospective study. The study was approved by the ethical committee of the University of Erlangen-Nuremberg. All patients gave their informed consent to participation.

According to the definition of the American Association of Oral and Maxillofacial Surgeons (AAOMS) [1], the

criterion for diagnosis bisphosphonate-associated osteonecrosis of the jaw is non-healing exposed bone in mandible or maxilla for longer than 8 weeks.

Patients were included in the study if they had received bisphosphonates intravenously for prevention or control of bone metastases of breast cancer, prostate cancer, multiple myeloma or osteoporosis.

Patients were excluded from the study if there was a history of radiation therapy in the head and neck region. They also were excluded if the overall life expectancy was less than 1 year according to the estimation of the attending oncologist. The oncologists' estimation of life expectancy was based on the stage of the disease and the related average life expectancy.

Another exclusion criterion was contraindications for surgery under general anaesthesia. General anaesthesia was chosen because at the moment, it is not possible to assess the extent of the jaw region affected by BONJ precisely before surgery. Therefore, general anaesthesia was chosen to have the option to carry out mandibulectomy during surgery if it would have been necessary.

Age and gender of the patients were documented. The duration of intravenous bisphosphonate administration before surgery was assessed. Medical history and general state of health of each patient were recorded with an emphasis on pain and oral surgical interventions before occurrence of bisphosphonate-associated osteonecrosis. The American Society of Anesthesiologists classification score was used as a correlate to the general health status.

Jaw and region of occurrence of osteonecrosis were documented. It was documented if the patients were fully dentate, partially dentate or edentulous and had no restorations, removable or fixed restorations. It was checked if the restoration was in contact with the region of osteonecrosis. It was documented if the osteonecrosis occurred after trauma to the gingiva or spontaneously. Clinical symptoms like signs of infection, pain, extension of bony lesion and sensitivity disorders (numbness) were also documented.

These clinical symptoms were used retrospectively to assign the patients to the three different clinical stages of BONJ according to expert guidelines of the AAOMS [1].

All patients received contrast-enhanced computed tomography before surgery. The images were checked for bony lesions of the jaws that could be suspected either as bone affected by BONJ or as metastasis of the underlying disease.

Discontinuation of bisphosphonate therapy was chosen according to the guidelines of the German Society of Dentistry and Oral Medicine (DGZMK) to promote healing of the effected region [11, 22]. Surgery was carried out 2 weeks after the last dose of bisphosphonates. Bisphosphonates were allowed to be administered not before 4 weeks after surgery. Starting from the day before surgical intervention, all patients received 500 mg amoxicillin with clavulanate 125 mg orally

Table 1 Detailed record of prospective studies which were dedicated to surgical treatment on BONJ

Author	No. of patients (<i>n</i>)	BIS (<i>n</i>)	Definition of BONJ	Mean follow-up period (months \pm SD)	Treatment concept (<i>n</i>)	Outcome at the end of follow-up
Montebugnoli et al. 2007	16	P (3)	Area of devitalised exposed bone without bleeding on probing	Group 1: 12.3 \pm 7.8 Group 2: 14.7 \pm 7.1 Group 3: 7.9 \pm 6.4	Group 1: superficial debridement (4) Group 2: sequesterotomy (3) Group 3: antibiotic therapy (9)	Decrease of exposed bone area for all groups
		Z (10) comb (5)				
		P (0)				
Vescovi et al. 2007	19	P (0)	ns	Range 4–9	Group 1: medical therapy (antibiotics and chlorhexidine mouth rinse) Group 2: medical therapy and sequesterotomy and bone curettage Group 3: Nd:YAG laser and medical therapy Group 4: sequesterotomy and bone curettage and ND:YAG laser and medical therapy	Affected bone covered by mucosa: Group 1: 1 in 3 patients Group 2: 4 in 7 patients Group 3: 2 in 2 patients Group 4: 6 in 7 patients
		Z (10)				
		A (2)				
		P+Z (7)				
Vescovi et al. 2008	28	Z (15) A+Z (2)	ns	Range 4–7	Group 1: sequesterotomy, medical therapy and Nd:YAG laser biostimulation (8) Group 2: medical therapy and Nd:YAG laser biostimulation (6) Group 3: sequesterotomy and medical therapy (6) Group 4: medical therapy (8)	Complete mucosal healing Group 1: 6 in 8 patients Group 2: 3 in 6 patients Group 3: 4 in 6 patients Group 4: 1 in 3 patients
		P+Z (10)				
		? (1)				
Wutzl et al. 2008	41 out of 58 underwent surgery	P (8)	Patients with exposed, necrotic bone in the maxillofacial region that had persisted for more than 8 weeks after bisphosphonate therapy. Confirmation of osteonecrosis by biopsy. "Typical pattern" of bone morphology on CT. No history of radiation therapy to the jaws	189 \pm 23 days	Sequesterotomy and decortication (29) with soft tissue closure or flap procedure (12) in combination with antibiotics and chlorhexidine mouth rinse	24 in 41 patients had intact mucosa 7 in 41 patients exposed necrotic bone 4 in 41 patients had signs of inflammation 2 in 41 patients had fistulas 3 in 41 had fractures 1 in 41 had abscesses
		Z (29)				
		A (1)				
		I (2) Z+R (2) comb (11)				

Table 1 (continued)

Author	No. of patients (<i>n</i>)	BIS (<i>n</i>)	Definition of BONJ	Mean follow-up period (months \pm SD)	Treatment concept (<i>n</i>)	Outcome at the end of follow-up
Boonyapakorn et al. 2008	22 out of 80 patients develop BONJ	P (3) Z (14) P+Z (4) Z (14)	Exposed or necrotic bone of maxilla or mandible with or without pain, evidence of regional soft tissue inflammatory swelling or infection, exposed bone with pathological fracture with pain, swelling or extraoral fistula	6	Group 1: sequestrectomy (12) Group 2: sequestrotomy (1) Group 3: surgical wound debridement(2) Group 4: wound debridement without surgery (3) Group 5: antibiotics i.v/oral (3) Group 6: no therapy (1)	Group 1: 7 in 12 patients had recurrence 3 in 12 patients had satisfactory wound healing Group 2: 0 in 1 patient had recurrence 1 in 1 patient satisfactory wound healing Group 3: 2 in 2 patients had recurrence Group 4: 2 in 3 patients had recurrence 1 in 3 patients stabilised necrosis without pain Group 5: 1 in 3 patients satisfactory wound healing 2 in 3 patients had stabilised necrosis without pain Group 6: Lost to follow-up

BIS bisphosphonate, SD standard deviation, Z zoledronic acid, P pamidronate, A alendronate, I ibandronate, R risedronate, comb combination of medication, *n* number of patients, *ns* not specified

three times a day until day 10 after surgery. In cases of allergy to amoxicillin with clavulanate, clindamycin was administered every 8 h in successive doses of 300, 300 and 600 mg. Dosages of antibiotics were chosen according to the established guidelines of the DGZMK [11]. Before surgery, in all patients, standard parameters for blood coagulation (partial thromboplastin time, thrombin time, international normalised ratio and platelet counts) were determined. When patients were on anticoagulation with phenprocoumon, this therapy was stopped. When an INR value >2.0 was reached, subcutaneous injections of nadroparin (0.01 ml/kg) two times daily were given. When patients received acetylsalicylic acid, the anticoagulation was stopped in accordance with their general practitioner 10 days before until 7 days after surgery.

Surgical procedure

All patients were treated under general anaesthesia. In each case, a smear was taken from the exposed bone for microbiological examination. Bacterial cultures were done in order to investigate the antibiogram profiles.

Subsequently, a mucoperiosteal flap was raised in the region of the exposed bone. An osteotomy was carried out that only left behind bone that did not show an altered colour and was bleeding from the surfaces as criteria for sound bone. Sharp edges of bone that can potentially traumatise surrounding soft tissue were removed. Biopsies of bone were sent out for pathological examination to exclude malignancy. Primary wound closure was carried out without tension on the mucoperiosteal flap after the incision of the periosteum. Interrupted sutures were made with resorbable suture material (Vicryl 5-0, Ethicon, Norderstedt, Germany).

In-patient period

After surgery, the patients were fed using a gastric tube according to the established guidelines of the DGZMK [11]. Oral food intake was not allowed for 10 days. Antiseptic mouth rinses [Hexetidín, 5-Amino-1,3-bis(2-ethylhexyl)hexahydro-5-methylpyrimidin, Pfizer Pharma GmbH, Karlsruhe, Germany] had to be performed three times a day. Ibuprofen 600 mg was administered three times daily as analgesic. The wounds were checked daily for signs of infection and wound breakdown. In cases of wound breakdown, a new wound closure was performed. Sutures and gastric tube were removed at day 10 after surgery, and subsequently, the patients were discharged. The patients were reexamined on a bimonthly basis for 12 months. The former operation area was checked for intactness of the mucosal layer. When recurrence of BONJ or new regions of BONJ were found, osteotomy and primary wound closure under general anaesthesia was

carried out again (Fig. 1). It was documented if patients died during the follow-up period.

Statistics

For statistical analysis, group means and standard deviations were calculated for each parameter using the SPSS software (version 16; SPSS Inc., Chicago, USA). Data were compared using the Mann–Whitney *U* test. A *p* value <0.05 was considered statistically significant.

Results

Patients

Twenty-six female (mean age, 66 ± 10.8 years) and 24 male patients (mean age, 71 ± 9.8 years) were included in the study. Nine patients received pamidronate and 39 patients zoledronic acid. One patient in succession got a combination of both and one patient received ibandronate after zoledronic acid. The mean duration of bisphosphonate therapy was 31 ± 17 months before surgery was carried out (Table 2). None of the patients developed BONJ before 12 months of administration of bisphosphonates.

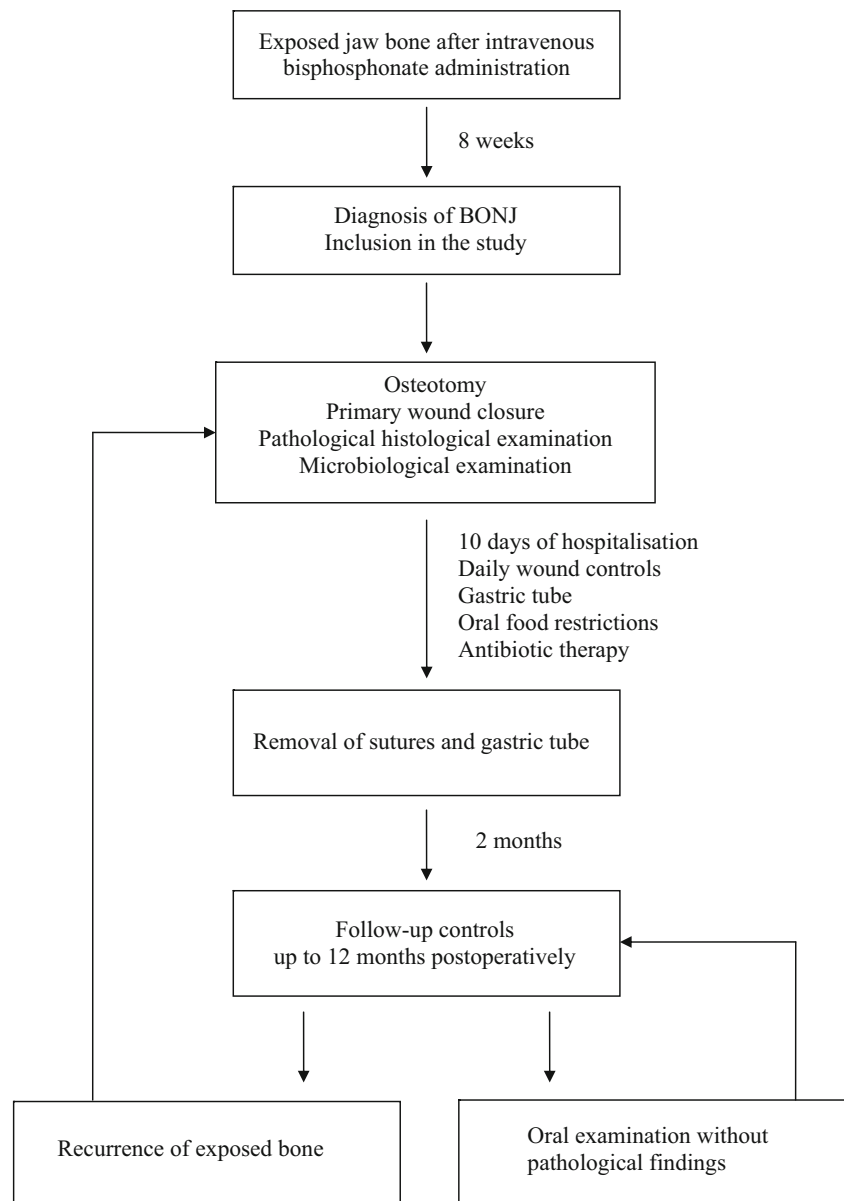
Twenty-one patients received bisphosphonates due to metastatic breast cancer, 12 because of multiple myeloma, 15 patients because of metastatic prostate cancer and one patient because of cancer of unknown primary and one patient on grounds of severe osteoporosis.

In 36 patients, the lesions occurred in the mandible, in 13 patients in the maxilla and in one patient in the maxilla and mandible simultaneously. Six patients were fully dentate, 40 patients partially dentate and four patients edentulous. BONJ was related to dental surgical interventions in 25 patients, and in 25 patients, BONJ occurred without preceding trauma. In ten patients, BONJ was found in a region that was loaded by the basis of the prosthesis. BONJ was documented in 19 patients adjacent to teeth and in 15 patients in edentulous areas of the alveolus loaded with a removable prosthesis and in six patients in the retromolar region. In the computed tomography (CT) images of none of the patients could additional lesions be found that hinted at BONJ or bony metastases besides the sites of BONJ that were the indication for the CT scans.

According to the classification of the AAOMS of BONJ, 13 patients suffered from stage I, 23 patients from stage II and 14 patients from stage III.

In-patient period

There were five patients on oral anticoagulant therapy (Table 3). Three patients received phenprocoumon. In these

Fig. 1 Design of the study

patients, anticoagulation therapy has been stopped prior to surgery and changed to nadroparin. Two patients received acetylsalicylic acid 100 mg daily. The coagulation parameters before surgery showed an appropriate coagulation status and platelet count at the day before surgery in all patients.

Eight of stage III patients showed osteonecrosis of the mandible in combination with extraoral fistulas. In these cases, osteotomy of necrotic bone and excision of fistula was carried out. In seven patients, the mandible had to be stabilised by a reconstruction plate because the risk of fracture was anticipated. In one additional patient, a mandibulectomy had to be carried out and also required a reconstruction plate.

Osteotomy and primary wound closure could be carried out in all patients successfully according to the defined

clinical criteria. Gastric tubes were well tolerated for 10 days by all patients.

Two patients who suffered from plasmocytoma developed major bleeding complications in the region of the floor of the mouth that required tracheostomy, surgical revision and monitoring vital signs in an intensive care unit. These two patients did not show an increased risk for bleeding in the standard coagulation tests that were done before surgery (Table 3).

Early postoperatively wound breakdown occurred in one patient at day 3 after surgery. A new wound closure without revision of the bone was performed. Subsequently, wound healing was uneventful. In three patients, the inferior alveolar nerve had to be exposed during osteotomy. These patients suffered from numbness of the skin in the

Table 2 Basic patient data

Pat. no.	Gender	Age (years)	Dg	IV BP	ASA score	Death during follow-up of 12months	Duration of BP administration before onset of BONJ	Affected jaw	BONJ related to dental surgery	Recurrence during follow-up of 12months	AAOMS stage	Pain related to BONJ
1	F	67	Bc	Z	2	No	48	Max	No	No	2	No
2	M	62	Mm	Z	3	Yes	24	Max	No	No	2	No
3	M	78	Mm	P	3	No	32	Mand	No	No	1	No
4	M	71	Pc	Z	2	Yes	36	Mand	No	No	2	Yes
5	F	75	Bc	Z	2	No	24	Mand	No	No	3	Yes
6	M	76	Mm	Z	3	Yes	96	Mand	No	No	3	No
7	F	46	Bc	Z	2	No	12	Max	No	No	3	Yes
8	M	81	Pc	P	2	Yes	24	Max	Yes	No	2	Yes
9	F	61	Mm	Z	2	No	24	Max	Yes	No	3	Yes
10	F	69	Bc	P; Z	2	No	32	Mand	No	No	1	No
11	F	65	Bc	Z	2	No	12	Mand	Yes	No	3	No
12	F	70	Bc	Z	3	No	36	Max	Yes	Yes	3	Yes
13	F	57	Bc	Z	2	No	12	Mand	No	No	2	Yes
14	M	72	Pc	Z	3	No	32	Max	Yes	No	1	No
15	M	62	Pc	Z	2	No	12	Mand	Yes	No	2	No
16	F	72	Bc	Z	2	No	34	Mand	No	Yes	1	Yes
17	F	83	Bc	P	3	Yes	20	Mand	Yes	No	1	Yes
18	M	64	Pc	P	3	No	60	Max	Yes	No	1	No
19	F	56	Bc	P	3	No	12	Mand	Yes	No	2	No
20	M	92	Pc	Z	3	No	23	Max	Yes	No	2	No
21	F	76	Bc	P	2	No	24	Mand	No	Yes	3	No
22	F	71	Bc	Z	1	No	20	Mand	Yes	No	2	Yes
23	M	78	Pc	Z	3	No	14	Mand	Yes	No	3	Yes
24	M	62	Op	Z	3	No	44	Mand	No	No	1	No
25	M	81	Pc	Z	3	No	32	Mand	Yes	No	2	No
26	F	50	Bc	Z	3	No	32	Mand	Yes	No	1	No
27	F	69	Mm	Z	2	No	30	Mand	Yes	No	2	No
28	F	76	Bc	Z	2	No	40	Mand	No	No	1	No
29	M	60	Lc	Z	3	No	36	Mand	Yes	No	3	No
30	M	68	Mm	Z	2	No	20	Max	Yes	No	2	Yes
31	F	62	Bc	Z	2	No	32	Max	No	No	2	No
32	F	78	Bc	Z	3	No	27	Mand	Yes	No	2	Yes
33	F	72	Bc	Z	3	No	38	Mand	No	Yes	1	No
34	M	63	Mm	P	3	No	22	Mand	No	No	2	No
35	M	71	Pc	Z	3	No	30	Max	No	No	3	No
36	M	63	Pc	Z	3	No	13	Mand	No	No	2	Yes
37	F	61	Bc	P	3	No	34	Mand	Yes	Yes	2	Yes
38	M	75	Pc	Z	3	No	33	Mand	Yes	No	2	No
39	F	67	Bc	Z	3	No	30	Mand	Yes	No	1	No
40	M	87	Pc	Z	3	No	25	Mand	Yes	No	2	No
41	F	82	Mm	P	2	No	12	Max	Yes	No	3	No
42	M	70	Mm	Z	3	No	30	Mand	No	No	2	Yes
43	F	75	Mm	Z	2	Yes	12	Mand	No	No	3	No
44	M	81	Pc	Z	3	No	36	Mand	No	No	3	No
45	F	56	Bc	Z	2	No	48	Mand	No	No	1	No
46	M	71	Mm	Z	3	No	24	Mand	No	No	2	Yes
47	M	72	Pc	Z	3	No	36	Mand	No	No	2	No
48	M	62	CUP	Z	2	No	36	Mand, Max	No	No	3	No

Table 2 (continued)

Pat. no.	Gender	Age (years)	Dg	IV BP	ASA score	Death during follow-up of 12months	Duration of BP administration before onset of BONJ	Affected jaw	BONJ related to dental surgery	Recurrence during follow-up of 12months	AAOMS stage	Pain related to BONJ
49	F	69	Mm	Z; I	2	No	96	Mand	No	No	2	Yes
50	F	69	Bc	Z	2	No	36	Mand	Yes	No	1	No
Σ	26 F 24 M	69.5±9.2	21 Bc 12 Mm 15 Pc 1 Op 1 CUP	9 P 39 Z 1 Z;I 1 P;Z	1 ASA1 22 ASA 2 27 ASA 3	6 Yes 44 No	31±17 months	13 Max 36 Mand 1 both	25 Yes 25 No	5 Yes 45 No	13 Stage I 23 Stage II 14 Stage III	18 Yes 42 No

AAOMS American Association of Oral and Maxillofacial Surgeons, *ASA* American Society of Anesthesiologists, *BONJ* bisphosphonate-associated osteonecrosis of jaws, *BP* bisphosphonate, *CUP* cancer of unknown primary, *Dg* diagnosis, *F* female, *I* ibandronate, *IV* intravenous acid, *M* male, *Mand* mandible, *Max* maxilla, *MC* breast cancer, *MM* multiple myeloma/plasmocytoma, *OP* osteoporosis, *P* pamidronate, *Pat. no.* number of patients, *PC* prostate cancer, *Z* zoledronic

innervation area of the inferior alveolar nerve, which had resolved after 12 months completely in two patients, whilst it remained for longer than 12 months in the third patient.

Histopathologic and microbiological examination

In all cases, the histological pathological assessment showed signs of necrotic bone or chronic osteomyelitis, and in two cases, metastases of plasmocytoma were apparent.

The histological images showed a combination of necrotic bone with areas of acute osteomyelitis. Colonies of actinomyces were seen in 33 samples.

The microbiological examination could identify actinomyces in 27 smears. Furthermore, the antibiogram showed that the determined microbial spectrum was sensitive to the administered antibiotics amoxicillin in combination with clavulanate. In six cases, the antibiotic medication with clindamycin was ineffective and had to be replaced.

Follow-up examinations

Forty-four patients could be followed up for 12 months after surgery. During the observation period, three patients suffering from plasmacytoma, two patients suffering from prostate cancer and one patient suffering from breast cancer died as the cause of their underlying disease. During the follow-up period, BONJ recurred in five patients. All recurrences occurred in the region of primary lesions. No additional new BONJ lesions were found during follow-up. In these cases, osteotomy and primary wound closure were carried out again. During the remaining follow-up period, no additional recurrence occurred. There was no statistically significant difference between the different stages of BONJ and the number of recurrences (Table 4).

In the two patients where plasmocytoma was found in the bone biopsies, the healing of the surgical site was uneventful. These patients were referred to the oncologist for restaging and further treatment. A local radiation therapy was started 4 weeks after surgery with a final dose of 30 Gy.

Discussion

Since the first report of BONJ in 2003, numerous papers have been published on the topic. However, there is still controversy on how to treat the affected patients. Especially the relevance of radical surgical treatment of BONJ has been questioned by some authors [9, 20, 38]. It has been reported that surgery is ineffective in stopping the pathological process [7, 19] and may worsen the clinical situation [20]. Therefore, it is not surprising that current therapeutic strategies only aim at control of the symptoms of BONJ, whilst radical removal of necrotic bone is limited to severe cases [35]. There is an expert recommendation that osteotomy only should be carried out in stage three as classified by the American Association of Oral and Maxillofacial Surgeons [1]. The rationale for these treatment concepts is that the effect of bisphosphonates affects the complete jaw, and as a consequence, long-term healing cannot be expected [30]. To date, there is only a limited number of prospective studies available concerning the different treatment concepts of BONJ (Table 1). Currently published prospective studies underline the important contribution of surgical treatment of BONJ, but primary outcome variables are not clearly specified and surgical concepts were applied heterogeneously [4, 6, 23, 36, 39] (Table 1). Furthermore, there is imprecision concerning the standard definition of BONJ, which already exists since the

Table 3 Coagulation parameters assessed before surgery

Patient no.	Dg	Excessive bleeding	anticoagulation therapy before surgery	Coagulation parameter the day before surgery				
				Quick (%)	INR	PTT (s)	TT (s)	Thrombocytes ($10^6/\mu\text{l}$)
1	Bc	No	No	98	1.02	31.0	10.3	283
2	Mm	No	No	80	1.12	28.3	11.3	236
3	Mm	No	No	92	1.07	28.3	10.7	176
4	Pc	No	No	85	1.08	30.2	10.5	416
5	Bc	No	No	93	1.03	25.8	11.5	331
6	Mm	No	Yes (1)	56	1.34	37.6	10.0	182
7	Bc	No	No	79	1.13	32.2	9.7	328
8	Pc	No	No	93	1.04	36.4	10.7	147
9	Mm	No	No	>100	0.86	27.1	10.5	265
10	Bc	No	No	91	1.05	29.7	11.2	243
11	Bc	No	No	>100	1.00	27.9	10.3	361
12	Bc	No	No	88	10.70	28.4	10.0	239
13	Bc	No	No	93	1.03	28.3	9.9	375
14	Pc	No	No	>100	0.95	28.0	10.1	251
15	Pc	No	No	>100	0.96	27.3	10.3	253
16	Bc	No	No	>100	0.96	28.5	10.1	324
17	Bc	No	No	81	1.12	33.5	9.8	329
18	Pc	No	Yes (1)	85	1.07	27.9	11.0	235
19	Bc	No	No	>100	0.89	26.2	10.1	253
20	Pc	No	No	93	1.00	29.3	10.2	238
21	Bc	No	No	100	0.99	27.7	10.9	283
22	Bc	No	No	94	1.03	33.3	10.2	229
23	Pc	No	Yes (2)	94	1.03	32.3	10.1	323
24	Op	No	No	>100	0.97	28.1	10.3	225
25	Pc	No	No	93	1.04	28.1	11.1	316
26	Bc	No	No	91	1.05	26.8	10.4	167
27	Mm	Yes	No	90	1.05	28.0	10.4	294
28	Bc	No	No	>100	0.93	25.7	10.6	362
29	Lc	No	No	>100	0.92	38.5	10.1	233
30	Mm	No	No	>100	0.98	33.4	10.1	320
31	Bc	No	No	92	1.05	30.1	10.2	220
32	Bc	No	No	>100	0.97	29.1	11.1	338
33	Bc	No	No	94	1.06	28.4	10.2	481
34	Mm	Yes	No	>100	0.96	31.1	10.5	234
35	Pc	No	No	95	0.99	33.2	9.6	435
36	Pc	No	No	93	1.04	32.4	10.6	271
37	Bc	No	No	81	1.06	32.9	11.1	249
38	Pc	No	No	>100	0.98	25.8	9.8	295
39	Bc	No	No	>100	1.00	32.0	10.9	200
40	Pc	No	No	>100	1.02	30.3	10.1	241
41	Mm	No	No	>100	0.97	27.8	10.1	274
42	Mm	No	No	>100	1.00	32.9	9.3	191
43	Mm	No	Yes (1)	83	1.13	38.3	16.8	170
44	Pc	No	No	>100	0.96	26.6	11.5	195
45	Bc	No	No	94	1.03	28.8	10.1	382
46	Mm	No	No	>100	0.96	24.8	8.9	380

Table 3 (continued)

Patient no.	Dg	Excessive bleeding	anticoagulation therapy before surgery	Coagulation parameter the day before surgery				
				Quick (%)	INR	PTT (s)	TT (s)	Thrombocytes ($10^6/\mu\text{l}$)
47	Pc	No	No	93	1.03	29.1	9.7	218
48	CUP	No	No	>100	1.02	31.5	10.7	275
49	Mm	No	No	>100	1.00	30.3	10.7	225
50	Bc	No	Yes (2)	86	1.10	29.6	10.5	313
			1. phenprocoumon therapy 2. acetylsalicylic acid 100 mg/day	Normal > 70	Normal ratio 26–38	Normal ratio 8–13	Normal ratio 140–400	

Dg diagnosis, INR international normalised ratio, no. number of patients, PTT partial thromboplastin time, TT thrombin time

year 2007. It was published by the task force of the American Society for Bone and Mineral Research [15] and the AAOMS [1].

Therefore, it has been the aim of the present study to follow up patients after osteotomy and primary wound closure of BONJ for 12 months and to report the success rate of this specific treatment concept.

An important aspect for the decision to perform an osteotomy was that this allowed sending out a bone sample for pathological histological examination. In the present study, two cases of metastases of plasmocytoma could be identified within the osteonecrosis. It seems that independent of the approach adopted for the treatment of osteonecrosis, the harvest of bone biopsies is mandatory to exclude metastases of the underlying disease.

If metastases are detected, treatment options have to be discussed with the attending oncologist. In the two cases of metastases of plasmocytoma in the present study, it was decided to irradiate the affected region of the jaw. During the follow-up period, there was no recurrence of exposed bone in the irradiated bone regions.

Osteotomy was associated with sensitivity disorders of the area innervated by the mental nerve in three patients. In one patient, the sensitivity disorders were still apparent at the end of the follow-up interval. It has to be assumed that sensitivity disorders that last longer than 1 year have to be considered permanent [24]. Patients have to be informed about this possible compli-

cation that has to be accepted when the complete removal of necrotic bone is the priority.

It seems that patients suffering from plasmocytoma are at special risk when it comes to complications arising from osteotomy. In the present study, two patients with plasmocytoma as underlying disease developed major bleeding complications in the postoperative course. Tracheostomy was required, as well as monitoring of vital signs on an intensive care unit.

When hypercoagulability is encountered in patients suffering from plasmocytoma, anticoagulation therapy is necessary. However, in rare cases, paraproteinemia can lead to bleeding complications. This specific risk of bleeding cannot be identified by assessing the standard coagulation parameters. In the two plasmocytoma patients with bleeding complications, the problem was caused by paraproteins that inhibit factor XIII, leading to a decreased fibrin formation similar to von Willebrand's syndrome [16, 17]. The lesson learned from the bleeding complications was to assess the bleeding time in all patients suffering from plasmocytoma before surgery in the future.

As a consequence of the underlying disease, the risk of life-threatening bleeding complications is always present in plasmocytoma patients. Extensive osteotomy of jaw regions affected by BONJ should only be performed if there is access to an intensive care unit. Plasmocytoma patients have to be informed about their additional risks in detail. The follow-up data show that the success rate for radical osteotomy in plasmocytoma patients does not differ from that of other patients.

The data of the microbiological examinations revealed that there was sensitivity of the microflora to amoxicillin with clavulanate as well as clindamycin in all patients. Therefore, no sophisticated antimicrobial regimen had to be adopted.

Eighty-nine per cent of the patients who underwent osteotomy and primary wound closure because of BONJ and survived 12 months did not show any signs of recurrence of

Table 4 Statistical analysis for recurrences in the different stages of BONJ

	Stages of BONJ		
	I vs. II	I vs. III	II vs. III
Recurrence	$P=0.603$	$P=0.981$	$P=0.632$

BONJ during the follow-up period. Therefore, osteotomy and primary wound closure seemed to be an effective means of treatment of BONJ, confining the necessity of surgical treatment of the affected patients to a single session.

The use of a gastric tube to avoid oral food intake seems invasive for patients that are already compromised. However, this procedure may be one additional aspect that led to the high success rate of the treatment concept in the present study. Future clinical studies will have to show if similar success rates can be achieved in the treatment of BONJ without avoidance of oral food intake.

More conservative concepts often lead to multiple appointments for wound treatment and, therefore, are less comfortable for the patient in the long run. In the present study, only patients were included that had an estimated life expectancy of more than 12 months. This inclusion criterion was chosen to make sure that most of the patients survived the chosen follow-up period of 1 year. It could be shown that the adopted therapy concept was successful in 89% of the patients that survived 12 months. In the future, it should be discussed if the treatment concept should also be adopted in patients with shorter life expectancies as the number of appointments for the treatment of BONJ could be reduced.

In the present study, an exclusion criterion was contraindications for surgery under general anaesthesia. General anaesthesia was chosen because at the moment, it is difficult to assess the extent of the jaw region affected by BONJ precisely before surgery. Therefore, general anaesthesia was chosen to have the option to carry out mandibulectomy during surgery if it would have been necessary. In the future, when it will have become possible to assess the extent of the jaw region affected by BONJ precisely before surgery, the decision for surgery under local or general anaesthesia can be based on the extent of the jaw regions affected by BONJ.

In present study, discontinuation of bisphosphonate treatment was chosen before surgery, although at the moment, there is no scientific evidence for this concept. However, authors have recommended discontinuation [10, 22]. The aim is to promote healing of the region affected by BONJ by avoiding adverse effects of recently administered bisphosphonates on bone and soft tissue healing. However, in order not to harm the patient, discontinuation of therapy was discussed with the oncologist for every single patient in order to consider the risks and benefits of discontinuation. In the present study, there was no patient where a discontinuation of a total of 6 weeks was considered harmful to the patient by the oncologist.

Some authors have claimed that surgical debridements are not completely effective in the treatment of BONJ [20, 28, 40]. Unfortunately, the surgical techniques that were adopted by these authors are not described in detail.

Especially, it is not clear if primary wound closure was carried out. Ruggiero et al. [28] stated that it was often difficult to obtain a surgical margin with viable bleeding bone. It seems that this aspect was the major problem of previous surgical approaches. In the present study, osteotomy was carried out until bone of altered colour was removed completely and bleeding could be identified from the bony surface. In addition, a special emphasis was put on watertight primary wound closure. This surgical procedure that has not been used in previous trials may explain the high success rate of the treatment concept in the present study. However, the present study is an uncontrolled trial and only trends can be achieved. Further studies with larger numbers of patients are necessary to achieve more statistical power and to prove the effectiveness of osteotomy and primary wound closure in the treatment of BONJ.

Conclusions

Independent of the treatment concept, biopsies of the necrotic bone should be harvested to exclude tumour metastases by pathological histological examination. If patients suffering from plasmocytoma are scheduled for osteotomy and primary wound closure, bleeding time should be assessed in order to determine the risk of bleeding complications. With a success rate of 89%, osteotomy in combination with primary wound closure seems to be a viable alternative to more conservative treatment concepts.

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