The role of surgical therapy in the management of intravenous bisphosphonates-related osteonecrosis of the jaw

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Objectives. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) seems resistant to conventional treatment approaches. We report a study with a surgical concept characterized by resection of the necrotic bone followed by sufficient wound closure.

Study design. In a clinical study of 24 patients with 33 sites of BRONJ, the surgical basis of the treatment was as follows: (1) conservative treatment with antimicrobiological rinsing, (2) resection of the entire necrotic bone and smoothening of any sharp bone edges, and (3) coverage of the remaining bone by use of a bilayered wound closure.

Results. In 88% of cases, BRONJ could be treated with success by use of this surgical therapy. Median follow-up was 60 weeks. There was no statistically significant difference between treatment results irrespective of whether or not bisphosphonate treatment was continued.

Conclusion. Because of the high success rate of this surgical technique it seems that patients with BRONJ may benefit from this approach. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:153-163)

In 2003, Marx 1 first described an association of exposed necrotic bone of the jaw with long-term application of bisphosphonates (BPh). Since then, an increasing number of cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) have been documented. On the basis of current knowledge, the most important mechanism in the pathogenesis of BRONJ seems to be inhibition of osteoclast function by BPh. 2-4 This causes a decrease of bone remodeling and an increase in bone density. As a result, the bone becomes over-aged, and self-healing capacity is reduced. BRONJ usually occurs after minor dento-alveolar surgery or injuries of the mucosa, or is related to ill-fitting dentures. In addition to the clinical appearance of nonhealing exposed necrotic bone, concomitant local infection is often observed with BRONJ. The grade of infection ranges from asymptomatic to acute deep purulent infection of the bone and surrounding soft tissue with abscess and fistula formation.

BRONJ seems resistant to customary dental antiinfective treatment; for example, antimicrobiological rinsing (e.g., chlorhexidine, peroxide), curettage of the exposed bone followed by simple closure of the mucosa, or open wound management with regular changing of a gauze wick. In many cases the severity and stage of the BRONJ is even worsened by these procedures. Several articles in the recent literature deal with the question of the most effective treatment of BRONJ (Table I). Current concepts vary from conservative approaches with antimicrobiological rinsing and oral antibiotics to radical surgery, depending on the stage and severity of the BRONJ. 5-7,9-12,15,16 There are, however, still few results from studies of the success of surgical treatment of BRONJ. We therefore present a study of a surgical concept characterized by resection of the entire necrotic bone followed by conscientious smoothening of sharp bone edges then bilayered wound closure.
METHODS

Twenty-four patients (12 female and 12 male) with median follow-up of 66 weeks and a total of 33 sites of BRONJ were included in a retrospective study. Nineteen sites were in the mandible and 14 in the maxilla. The observation period for the study started in July 2006 and ended in December 2009. Operations were performed from July 2006 to August 2008. The patients’ characteristics are listed in Table II. For inclusion, the patients had to undergo surgical treatment. All patients were informed that the therapy should be regarded as an individual attempt at healing, and consented. In addition, surgery was performed on patients only when their general health status allowed the surgical procedure with insurable risks and their estimated life expectancy was longer than 1 year. Life expectancy was estimated on the basis of the state of the primary disease and the stability of metastasis, and after consulting the treating oncologist. For assessment of general health status before surgery, the Physical Status Classification System of the American Association of Anesthesiology was used.\(^\text{17}\) The operation was performed only when the patients were classified from ASA I to ASA III. 

BRONJ was diagnosed clinically first. Clinical signs were pain, swelling, halitosis, nonhealing, exposed necrotic bone, and fistulas with connection to the bone. The site of BRONJ must have existed for minimum of 8 weeks. Three-dimensional radiological imaging was used to visualize the extent of BRONJ underneath the mucosa.\(^\text{18,19}\) Cone-beam computed tomography (CBCT) with a volume of 3 to 6 cm\(^3\) (J. Morita MFG Corp, Kyoto, Japan) was used to examine the affected sites. Instead of CBCT, in 2 cases multislice CT (MSCT) scans were available from another department for this purpose. The radiological signs of BRONJ in the CBCT are equivalent to the signs in the MSCT and are, according to Bianchi et al.,\(^\text{18}\) (1) erosion of the cortical bone, (2) osteosclerosis, (3) sequestration, and (4) formation of periostal new bone (Fig. 2, b).

Depending on the severity of the BRONJ, every site was grouped according to the clinical staging system published by Wilde et al. (Table III).\(^\text{20}\) Diagnosis of BRONJ was confirmed histologically by use of specimens taken during surgical treatment. The following treatment procedure was applied in all cases without consideration of the stage of BRONJ:

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommended treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruigerro et al., 2006(^\text{5})</td>
<td>Treatment strategy depends on the stage of BRONJ. Conservative treatment in low-stage BRONJ with antimicrobial rinses, analgesia, and antimicrobial therapy in cases with pain and infection. Surgical debridement of necrotic bone in combination with antimicrobial therapy, analgesia, and antimicrobial rinses in high-stage BRONJ.</td>
</tr>
<tr>
<td>AAOMS, 2007 and 2009(^\text{6,7})</td>
<td>Treatment strategy depends on the stage of BRONJ. Conservative treatment in low-stage BRONJ with antimicrobial rinses, analgesia, and antimicrobial therapy in cases with pain and infection. Surgical treatment in the form of debridement of necrotic bone in combination with antibiotic therapy as long-term palliation in high-stage BRONJ.</td>
</tr>
<tr>
<td>DGMKG, 2007(^\text{8})</td>
<td>Surgical procedure with resection of the necrotic bone and safe wound closure.</td>
</tr>
<tr>
<td>Marx, 2007(^\text{4})</td>
<td>Treatment strategy depends on the stage of BRONJ. Conservative treatment in low-stage BRONJ with antimicrobial rinses, analgesia, and antimicrobial therapy in cases with pain and infection. Surgical treatment in the form of radical resection of the necrotic bone in high-stage BRONJ.</td>
</tr>
<tr>
<td>Montebagioni et al., 2007(^\text{9})</td>
<td>Conservative treatment with long-term administration of antibiotics to control the symptoms of BRONJ</td>
</tr>
<tr>
<td>Kahn et al., 2008 and 2009(^\text{10,11})</td>
<td>Treatment strategy depends on the stage of BRONJ. Conservative treatment in low-stage BRONJ with antimicrobial rinses, analgesia, and antimicrobial therapy in cases with pain and infection. Surgical treatment in the form of debridement of the necrotic bone in high-stage BRONJ. Segmental resection to remove large portions of bone or fractured bone. Aggressive debridement is contraindicated, however.</td>
</tr>
<tr>
<td>Wutzel et al. 2008(^\text{12})</td>
<td>Surgical treatment characterized by minimum resection of the necrotic bone and soft tissue closure with a local flap procedure.</td>
</tr>
<tr>
<td>Abu-Id et al. 2008(^\text{13})</td>
<td>Surgical treatment with radical resection of the necrotic bone is the only curative approach.</td>
</tr>
<tr>
<td>Pautke et al. 2009(^\text{14})</td>
<td>Surgical treatment with fluorescence-guided bone resection and wound closure.</td>
</tr>
<tr>
<td>Carlson et al. 2009(^\text{15})</td>
<td>Surgical treatment with resection of BRONJ permits acceptable healing and a high degree of success is realized.</td>
</tr>
<tr>
<td>Stockmann et al. 2009(^\text{16})</td>
<td>Surgical treatment with macroscopic removal of the altered bone and primary wound closure.</td>
</tr>
</tbody>
</table>
Conservative treatment with a daily antimicrobial rinse, using 1% to 3% peroxide, was started after the first appointment. In cases with symptoms of acute infection (e.g., swelling, pain, halitosis, or discharge of pus), oral antibiotics were applied immediately (e.g., amoxicillin with sulbactam or penicillin in combination with metronidazol or clindamycin in cases of allergy against beta-lactam antibiotics). The duration of the conservative treatment was not limited to a defined outcome but instead depended on personal factors, for example additional therapy (e.g., chemotherapy), compliance, or a suitable appointment for surgery depending on the general health status of the patient.

Surgery consisted of resection of all the infected and necrotic bone (Fig. 1, b, Fig. 2, e and f, Fig. 3, c and d, and Fig. 4, c and d). Resection margins were determined by the clinical appearance of bleeding bone. Depending on the severity of the BRONJ, an extraoral approach was chosen. For stage IV BRONJs in the mandible, continuous resection was used. For primary reconstruction of the mandible, a 2.4 titanium reconstruction plate was used (Fig. 2, f).

Table II. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Primary disease</th>
<th>Kind of BPh holiday</th>
<th>Location of BRONJ (FDI-system)</th>
<th>Staging of BRONJ</th>
<th>Cause for BRONJ</th>
<th>Treatment result</th>
<th>&quot;Period with healed BRONJ&quot; (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>†1</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>44-47</td>
<td>II</td>
<td>i.f.d.</td>
<td>+</td>
<td>55</td>
</tr>
<tr>
<td>†2</td>
<td>♀</td>
<td>BCa</td>
<td>Z+B</td>
<td>35-37</td>
<td>III</td>
<td>EX</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>†3</td>
<td>♂</td>
<td>MM</td>
<td>Z+P</td>
<td>33</td>
<td>II</td>
<td>EX</td>
<td>+</td>
<td>22</td>
</tr>
<tr>
<td>†4</td>
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<td>Z+B</td>
<td>15-17</td>
<td>II</td>
<td>EX</td>
<td>+</td>
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<tr>
<td>†5</td>
<td>♀</td>
<td>BCa</td>
<td>Z+P+B</td>
<td>44-46</td>
<td>I</td>
<td>i.f.d.</td>
<td>+</td>
<td>117</td>
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<td></td>
</tr>
<tr>
<td>†6</td>
<td>♀</td>
<td>BCa</td>
<td>Z+P+B</td>
<td>12-14</td>
<td>III</td>
<td>EX</td>
<td>+</td>
<td>59</td>
</tr>
<tr>
<td>†7</td>
<td>♂</td>
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<td>Z+P+B</td>
<td>47-44</td>
<td>IV</td>
<td>Inc</td>
<td>+</td>
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<tr>
<td>†8</td>
<td>♀</td>
<td>NHL</td>
<td>Z</td>
<td>33-45</td>
<td>IV</td>
<td>i.f.d.</td>
<td>+</td>
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<tr>
<td>†9</td>
<td>♀</td>
<td>MM</td>
<td>Z</td>
<td>38</td>
<td>II</td>
<td>i.f.d.</td>
<td>+</td>
<td>77</td>
</tr>
<tr>
<td>†10</td>
<td>♂</td>
<td>MM</td>
<td>Z</td>
<td>38</td>
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<td>+</td>
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<tr>
<td>†11</td>
<td>♂</td>
<td>PCa</td>
<td>Z+P</td>
<td>15-17</td>
<td>IV</td>
<td>EX</td>
<td>+</td>
<td>24</td>
</tr>
<tr>
<td>†12</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>15-14</td>
<td>II</td>
<td>Ex</td>
<td>+</td>
<td>67</td>
</tr>
<tr>
<td>†13</td>
<td>♀</td>
<td>BCa</td>
<td>Z</td>
<td>17</td>
<td>I</td>
<td>Ex</td>
<td>+</td>
<td>58</td>
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<td></td>
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</tr>
<tr>
<td>†14</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>33-31</td>
<td>III</td>
<td>i.f.d.</td>
<td>+</td>
<td>22</td>
</tr>
<tr>
<td>15</td>
<td>♂</td>
<td>ThCa</td>
<td>Z</td>
<td>23-26</td>
<td>III</td>
<td>EX</td>
<td>–</td>
<td>49</td>
</tr>
<tr>
<td>16</td>
<td>♂</td>
<td>KCa</td>
<td>Z+P+B</td>
<td>38-32</td>
<td>III</td>
<td>EX</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>♂</td>
<td>MM</td>
<td>Z</td>
<td>37-36</td>
<td>III</td>
<td>PARO</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>32-42</td>
<td>III</td>
<td>Ex</td>
<td>+</td>
<td>89</td>
</tr>
<tr>
<td>19</td>
<td>♀</td>
<td>MM</td>
<td>Z</td>
<td>23-25</td>
<td>III</td>
<td>APOS</td>
<td>+</td>
<td>96</td>
</tr>
<tr>
<td>20</td>
<td>♀</td>
<td>BCa</td>
<td>Z</td>
<td>13-25</td>
<td>III</td>
<td>Ex</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>21</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>34-35</td>
<td>II</td>
<td>Ex</td>
<td>+</td>
<td>59</td>
</tr>
<tr>
<td>22</td>
<td>♂</td>
<td>PCa</td>
<td>Z</td>
<td>17-18</td>
<td>III</td>
<td>Ex</td>
<td>+</td>
<td>51</td>
</tr>
<tr>
<td>23</td>
<td>♀</td>
<td>BCa</td>
<td>Z+B</td>
<td>15-17</td>
<td>III</td>
<td>Ex</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>♀</td>
<td>MM</td>
<td>Z+P</td>
<td>25-28</td>
<td>IV</td>
<td>Ex</td>
<td>+</td>
<td>71</td>
</tr>
</tbody>
</table>

The FDI tooth-numbering system is used for description of the location of BRONJ. For staging of BRONJ, the staging system according to Wilde et al. was used (Table II).

BPh, bisphosphonates; BRONJ, bisphosphonate-related osteonecrosis of the jaw; †, deceased; ♂, male; ♀, female; Z, zolendronate; B, bondronate; P, pamidronate; MM, multiple myeloma; BCa, breast cancer; PCa, prostate cancer; ThCa, thyroid cancer; KCa, kidney cancer; HL, Hodgkin’s lymphoma; NHL, non-Hodgkin’s lymphoma; Ex, tooth extraction; i.f.d., ill-fitting dentures; Inc, incision after abscess formation; PARO, periodontal disease; root, remaining root of a tooth; excision, condition after an excision unknown, reason unknown; +, successful treatment; –, unsuccessful treatment.
relation to the BRONJ with an insecure prognosis for preservation for the next half year because of periodontal disease or caries were removed during the same operation. Perioperative antibiotic therapy was administered intravenously.

(3) Conscientious smoothening of all sharp bone edges was performed using a rotating bur (Fig. 1, b, Fig. 3, c).

(4) Intraoral closure was achieved by bilayered wound closure with absorbable suture material. The suturing technique was characterized by mobilization of a muco-periostal flap. The periosteum was slit and a connective tissue flap as thick as possible and with a large basis was mobilized from the vestibulum to ensure sufficient vascularization of the flap (Fig. 1, c, Fig. 3, e). In the posterior maxillary region it can be useful to dissect a buccal fat pad flap for this purpose (Fig. 4, e), especially when the maxillary sinus is opened during resection of the bone necrosis. In the mandible, the lingual connective tissue was also dissected. After suture of the connective tissue flap over the bone (Fig. 1, d, Fig. 3, e, and Fig. 4, f), the mucosa flap was sutured over the connective tissue flap with deep mattress knots followed by single knots to adapt the mucosal edges (Fig. 1, e, Fig. 3, f, and Fig. 4, g). The result was a seal suture free from tension.

(5) Removal of visible sutures was not performed earlier than 14 days after the operation.

(6) Patients were not allowed to wear dentures for the first 4 postoperative weeks.

(7) After surgery, the patients were seen weekly for the first month, once a month in the following 3 months, every 3 months up to 1 year, and every 6 months thereafter. The patients were always examined with regard to the clinical signs of BRONJ mentioned earlier: (1) pain, (2) swelling, (3) nonhealing exposed necrotic bone, and/or (4) fistulas with connection to the bone.

The outcome of the therapy was evaluated on the basis of treatment success. Only complete healing of

Fig. 1. Principal of bilayered suturing technique. a, BRONJ with exposed necrotic bone. b, Dissection of a muco-periostal flap, resection of the entire infected and necrotic bone and conscientious smoothening of all sharp bone edges with a rotating bur. c, Slitting of the periosteum and mobilization of the flap. d, Dissection of a connective tissue flap and suturing the flap over the bone. e, Suturing of the mucosa flap over the connective tissue flap with deep mattress knots followed by single knots to adapt the mucosal edges.
Of the 33 sites treated, 20 were located in the mandible and 13 in the maxilla. Two of the 4 treatment failures occurred in the mandible, the other 2 in the maxilla ($P = .64$).

In only 2 of the 33 sites, continuity resections of the mandible had to be performed (Table II, Patients 7 and 8). These 2 patients experienced anesthesia of the right side of the lower lip after the operation. In the other 31 sites, peripheral resections were sufficient. In 1 case of these, a 2.4 reconstruction plate was implanted to prevent a pathologic fracture of the mandible after peripheral resection (Table II, Patient 2). This patient showed paresthesia of the left side of the lower lip after surgery. In only one other patient of the peripheral resection group paresthesia of one side of the lower lip occurred after surgery (Table II, Patient 21). There was neither anesthesia nor paresthesia observed in the tongue nor in the innervation area of the infraorbital nerve.

There were no plate fractures, plate exposures, or plate or screw loosenings during the observation period. Malocclusion was not observed during the study.

In 5 sites that were located in the maxilla, a buccal fat pad flap was used for wound closure after bone resection (Table II, Patients 2, 11, 22, 23, and 24).

In 10 of 24 patients with 15 sites of BRONJ, BPh therapy was discontinued by the oncologist after diagnosis of BRONJ. No treatment failure was found in these patients. The 4 unsuccessful treatment results occurred in the 14 patients who had 18 sites of BRONJ and in which BPh therapy was continued with the same dosage. There was, however, no significant dependence of treatment results on whether the BPh therapy was continued or discontinued ($P = .51$).

Of 33 sites of BRONJ, 6 were classified as stage I BRONJ, 12 as stage II BRONJ, 11 as stage III BRONJ, and 4 as stage IV BRONJ. The 4 treatment failures were all in stage III BRONJ sites. The statistical analysis showed a significant dependence of treatment result on the severity of the BRONJ ($P = .028$).

Seven patients died during the observation period. In all 7 patients a successful treatment result was recorded until their death (Table II, Patients 1, 2, 3, 5, 11, 12, and 13). Patient 1 died after surgery had been performed on 2 different sites, 13 and 8 months earlier. Patient 2 died 14 months after the operation. Patient 3 died 6 and 3 months after surgical treatment of 2 different sites. Patient 5 died 117, 108, and 90 months after successful treatment of 3 different sites. Patient 11 committed suicide 6 months postoperatively. The death of patients 12 and 13 were recorded 16.0 months and 13.4 months after surgery.

Two other patients (Table II, Patients 14 and 20) did not return for their regular recall appointments, so the postoperative follow-up without any signs of recurrence of BRONJ was shorter than 1 year.

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**Table III. Clinical staging of bisphosphonate-related osteonecrosis of the jaw according to Wilde et al$^{20}$**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical and radiological signs in patients with a history of bisphosphonate therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No exposed, necrotic bone</td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic exposed, necrotic bone or single intraoral fistula</td>
</tr>
<tr>
<td>II</td>
<td>Exposed, necrotic bone associated with pain and infection</td>
</tr>
<tr>
<td>III</td>
<td>Exposed, necrotic bone associated with pain, infection with swelling and abscesses, multiple intraoral fistulas, and extended osteolyses in the radiological findings</td>
</tr>
<tr>
<td>IV</td>
<td>Exposed, necrotic bone associated with pain, infection with swelling and abscesses, pathological fracture, naso-oral fistula, extraoral fistula, or osteolyses extending to the inferior border</td>
</tr>
</tbody>
</table>

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BRONJ, with no exposed necrotic bone, no residual mucosal defect, no fistulas, and the absence of swelling and pain was assessed as successful treatment. Unsuccessful treatment was documented when nonhealing sites or recurrence of clinical signs of BRONJ (exposed bone, mucosal defect, fistulas, swelling, pain) were seen at any time during the follow-up period.

To evaluate long-term success we defined the “period with healed BRONJ” as the period of time after surgery until final monitoring of the patient during the observation period with clinical appearance of complete healing of BRONJ (no signs of exposed necrotic bone, no residual mucosal defect, no fistulas, absence of swelling and pain).

The chi-square test was used for the statistical analysis of proportions across levels of categorical variables. Statistical analysis was performed using SPSS for Windows (SPSS, Chicago, IL). Differences were considered statistically highly significant if the $P$ value was less than .005 and statistically significant if the $P$ value was less than .05.

**RESULTS**

Of the 33 sites, 29 (88%) were treated successfully with a median “period with healed BRONJ” of 60 weeks. In 4 sites (12%), an unsuccessful result had to be acknowledged. In 3 of the 4 unsuccessfully treated sites the failure was recognized as early suture dehiscence 2, 8, and 12 weeks after surgery (Table II, Patients 16, 17, 23). In the fourth site (Table II, Patient 15), the failure was diagnosed after a “period with healed BRONJ” of 49 weeks after surgery during a routine recall appointment.

There was no significant dependence of treatment results on location of BRONJ in the upper or lower jaw. Of the 33 sites treated, 20 were located in the mandible and 13 in the maxilla. Two of the 4 treatment failures occurred in the mandible, the other 2 in the maxilla ($P = .64$).

In only 2 of the 33 sites, continuity resections of the mandible had to be performed (Table II, Patients 7 and 8). These 2 patients experienced anesthesia of the right side of the lower lip after the operation. In the other 31 sites, peripheral resections were sufficient. In 1 case of these, a 2.4 reconstruction plate was implanted to prevent a pathologic fracture of the mandible after peripheral resection (Table II, Patient 2). This patient showed paresthesia of the left side of the lower lip after surgery. In only one other patient of the peripheral resection group paresthesia of one side of the lower lip occurred after surgery (Table II, Patient 21). There was neither anesthesia nor paresthesia observed in the tongue nor in the innervation area of the infraorbital nerve.

There were no plate fractures, plate exposures, or plate or screw loosenings during the observation period. Malocclusion was not observed during the study.

In 5 sites that were located in the maxilla, a buccal fat pad flap was used for wound closure after bone resection (Table II, Patients 2, 11, 22, 23, and 24).

In 10 of 24 patients with 15 sites of BRONJ, BPh therapy was discontinued by the oncologist after diagnosis of BRONJ. No treatment failure was found in these patients. The 4 unsuccessful treatment results occurred in the 14 patients who had 18 sites of BRONJ and in which BPh therapy was continued with the same dosage. There was, however, no significant dependence of treatment results on whether the BPh therapy was continued or discontinued ($P = .51$).

Of 33 sites of BRONJ, 6 were classified as stage I BRONJ, 12 as stage II BRONJ, 11 as stage III BRONJ, and 4 as stage IV BRONJ. The 4 treatment failures were all in stage III BRONJ sites. The statistical analysis showed a significant dependence of treatment result on the severity of the BRONJ ($P = .028$).

Seven patients died during the observation period. In all 7 patients a successful treatment result was recorded until their death (Table II, Patients 1, 2, 3, 5, 11, 12, and 13). Patient 1 died after surgery had been performed on 2 different sites, 13 and 8 months earlier. Patient 2 died 14 months after the operation. Patient 3 died 6 and 3 months after surgical treatment of 2 different sites. Patient 5 died 117, 108, and 90 months after successful treatment of 3 different sites. Patient 11 committed suicide 6 months postoperatively. The death of patients 12 and 13 were recorded 16.0 months and 13.4 months after surgery.

Two other patients (Table II, Patients 14 and 20) did not return for their regular recall appointments, so the postoperative follow-up without any signs of recurrence of BRONJ was shorter than 1 year.
Fig. 2. Clinical example of a mandible continuity resection. 

a, Dental panoramic radiograph at the time of the initial diagnosis of BRONJ with slight signs of osteolyses (white arrow). Radiographic findings correspond to the clinical picture of Fig. 2, c. 
b, Cone beam computed tomography (J. Morita MFG Corp) with extensive osteolyses up to the inferior border of the mandible (white arrows) after several treatments with rim osteotomy without wound closure. Radiographic findings correspond to the clinical picture of Fig. 2, b. 
c, Clinical picture at initial diagnosis of BRONJ with exposed necrotic bone in the mandible (corresponding to Fig. 2, a). 
d, Clinical picture after treatment with rim osteotomy without wound closure. Multiple intraoral fistulas (white arrows) and abscess formation (corresponding to Fig. 2, b). The clinical picture does not show the real extent of BRONJ beneath the mucosa. 
e, Intraoperative picture after dissection of the mandible using an extraoral approach with pathologic fracture (white arrow) and reactive periostal reaction (black arrows) (corresponding to Fig. 2, b and d). 
f, Intraoperative picture after resection of the mandible and reconstruction with a 2.4 titanium reconstruction plate. 
g, Postoperative intraoral picture with no signs of BRONJ. 
h, Panoramic radiograph 1 year postoperative with slight periostal bone regeneration along the implanted reconstruction plate (white arrow).
DISCUSSION

The results of this study demonstrate that in many cases BRONJ can be healed by using the surgical treatment concept described previously.

Conservative treatment options with antimicrobial rinses and additional antibiosis can reduce the acute symptoms of the concomitant infection; for example, swelling, discharge of pus, and pain. It seems, however, that complete resection of all infected and necrotic bone is needed to create the necessary conditions for reliable primary wound healing.

Adequate surgical planning is therefore essential. Because the clinical picture usually does not show the real extent and severity of BRONJ or its proximity to

Fig. 3. Clinical example of a peripheral bone resection. a, Clinical photograph on initial diagnosis of BRONJ with exposed necrotic bone (white arrow) in the mandible. b, Radiographic findings corresponding to the clinical photograph of Fig. 3, a. c, Intraoperative picture after dissection of BRONJ using an intraoral approach. d, Intraoperative picture after resection of the necrotic and infected bone and smoothening of the sharp bone edges (black arrows). e, Bi-layered wound closure: connective tissue is sutured over the bone (black arrows). f, Mucosa flap is sutured over the connective tissue flap with deep mattress knots (white arrow) followed by single knots to adapt the mucosa edges (black arrows). g, Postoperative intraoral picture with no signs of BRONJ. h, Panoramic radiograph 1 year postoperative showing the bone defect after peripheral resection (white arrow).
important anatomical structures, for example, the alveolar nerve or the maxillary sinus, the authors believe that 3-dimensional radiological imaging is mandatory before the surgical procedure. The possibility and efficiency of visualization of BRONJ by use of MSCT or CBCT was shown in previous studies. In this study, CBCT was preferred to MSCT to reduce radiological exposure. The resection margins were determined by the clinical appearance of bleeding bone. This is not always easy to achieve, however, because bleeding bone is sometimes not clearly apparent. Therefore, a high degree of experience is needed, especially in cases with advanced bone sclerosis, which can often be found in the mandible. For this purpose the technique of fluorescence-guided bone resection described by Pautke

Fig. 4. Clinical example of maxillary resection and a buccal fat pad flap. a, Clinical photograph on initial diagnosis of BRONJ with exposed necrotic bone in the maxilla (white arrow). b, Intraoperative photograph after dissection of BRONJ. c, BRONJ specimen after resection. d, After resection of the necrotic and infected bone with a wide opening of the maxillary sinus (black arrow). e, Mobilization of a buccal fat pad flap. f, Bilayered wound closure: covering of the bone and the sinus with the buccal fat pad flap (black arrows). g, Suturing of the mucosa over the fat pad flap with deep mattress knots (black arrows) followed by single knots to adapt the mucosa edges (white arrows). h, Postoperative intraoral photograph with no signs of BRONJ.
et al.\textsuperscript{14} might be helpful, but this must be proved for a larger number of cases. The significantly high failure rate in stage III BRONJ sites in this study might also be caused by the problem of the determination of the necessary resection margins. Probably in these sites nonsufficient resection of the bone was performed because the surgeons wanted to save some bone, for example to preserve the continuity of the mandible or to avoid a hemimaxillectomy. In stage I to stage II BRONJ sites this problem might be less serious, as a secure resection of the entire necrotic bone can be achieved mostly without injuring important anatomical structures. In contrast, in stage IV BRONJ sites the necessity of a huge resection was obvious and was planned beforehand. In these cases damage of peripheral nerves may be expected. Particularly anesthesia or paresthesia of the mandibular nerve can be observed after huge peripheral or continuity resections of the mandible. However, the risk for nerve damage of the lingual or even the infraorbital nerve seems to be very low. Other complications, which can be seen after tumor surgery, like plate fractures, plate exposures, plate or screw loosening, or malocclusion may be possible, but could not be observed in our patients; however, we had only 3 cases where an osteosynthesis plate had to be implanted.

Because of reduced remodeling of bisphosphonate-affected bone, inhibited resorption of the alveolar crest can be seen after dento-alveolar surgery. The authors believe that strict smoothening of all sharp bone edges is of major importance to minimize the risk of secondary perforation of the thin mucosa by sharp bone edges.

The bilayered wound closure provides safe coverage of the bone with soft tissue. This technique reduces the risk of recurrent infection of the bone and creates a strong scar after complete healing that is resistant to traumatic injuries of the mucosa.

In our hospitalized patients who were operated under general anesthesia, because of extended BRONJ a nasogastric tube was placed for 3 to 5 days after the operation. Whether postoperative application of a nasogastric tube has a major effect on wound healing cannot be shown scientifically, but clinical experience shows good results, not only in patients with BRONJ. It can be assumed that the least possible manipulation and irritation of the suture during the first few days after surgery is helpful for primary healing.

Stable prediction of the specific effects and optimum duration of accompanying antibiotic therapy cannot yet be made, but histological investigations have proved that BRONJ is always connected with inflammatory osteopathy.\textsuperscript{26,27} Accompanying antibiotic therapy, comparable with the therapy of osteomyelitis, seems, therefore, to be appropriate, as advised by other authors.\textsuperscript{4,8,10,11,28}

Despite the understandable wish for early prosthetic rehabilitation, the authors believe removal of the dentures to be advisable. Patients with mucosa-carried dentures should try to manage without any prostheses. If the patient cannot do without, regular monitoring is advisable, because early detection of mucosal pressure points can prevent a relapse or the development of new BRONJ.

The results of this investigation also show that BRONJ can recur weeks or months after primary healing without complications. Long-term follow-up is therefore indispensable. Whether such cases are recrudescence or new occurrence of BRONJ is open to discussion.

In this context, it is also necessary to discuss whether a drug holiday from BPh is appropriate. Marx\textsuperscript{4} describes a positive effect of a holiday from oral BPh. It has not been proved, however, that the same effect is to be expected in cases of intravenous application. Magou- poulos and colleagues, however, expect positive side effects from a drug holiday longer than 6 months, but so far there are no secure data that can confirm such a recommendation.\textsuperscript{10,29} The results of this investigation give no reason for interruption of BPh therapy when surgery is applied. There was no significant difference between the outcomes of treatment whether or not BPh therapy was continued; however, our result is based on only 24 patients with 33 sites of BRONJ. Therefore, it would be presumptuous to conclude that there is statistical evidence for interrupting BPh therapy when BRONJ is diagnosed. For this purpose, far more cases have to be documented and statistically evaluated in future studies. However, considering the high potency of intravenous BPh and the very long half-life of these drugs, a drug holiday from BPh before or during any treatment does not promise a huge positive effect.\textsuperscript{4} Taking into account that these patients normally suffer from osteolytic forms of cancer, use of BPh can secure their quality of life.\textsuperscript{30,31} In these patients, BPh prevents progression of skeletal morbidity and reduces excruciating bone pain.\textsuperscript{32} The extent to which this argument also applies to BPh treatment of osteoporosis is difficult to answer, but it has been proved that development of BRONJ under oral BPh medication is far less likely.\textsuperscript{4,33} Because intravenous application of BPh in cases of osteoporosis is increasing, it remains to be seen whether cases of BRONJ will increase.

It cannot be denied that conservative and nonsurgical treatment can reduce the symptoms and lead to downstaging of BRONJ.\textsuperscript{4,5,9,12} This was also apparent during conservative treatment of our patients. It cannot be proved by the results from this study and must be assessed in subsequent studies by use of a well-established questionnaire. It may, however, be assumed that the occurrence of BRONJ can compromise the quality
of life of affected patients as a result of halitosis, frequent consultations with the dentist or oromaxillofacial surgeon, and the repeated recurrence of acute symptoms such as pain, intraoral or extraoral fistulas, swelling, and abscess formation. Furthermore, regular treatment with antimicrobial rinses, for example peroxide or chlorhexidine, can cause discoloration of the tongue or teeth and can lead to dysgeusia. Regular administration of antibiotic drugs can also increase resistance to these antibiotics.

CONCLUSION

The results of this study lead to the conclusion that patients with BRONJ may benefit from surgical treatment, especially patients who still have a reasonable life expectancy and relatively high quality of life. Conservative treatment in terms of irrigation with antimicrobial rinses and additional antibiotics in phases of acute infection can be a therapy option for control of BRONJ symptoms, particularly if the general health status and/or the estimated life expectancy of the patient prohibit surgical treatment. Because these different factors must be taken into account, treatment possibilities must be discussed with each patient individually.

Despite progress in the treatment of BRONJ the most important issue should be prevention of the disease. Intensive cooperation among general practitioners, oncoologists, craniomaxillofacial surgeons, and dentists must therefore be established in the future.

REFERENCES


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