Influence of Prior Hyperbaric Oxygen Therapy in Complications Following Microvascular Reconstruction for Advanced Osteoradionecrosis

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Objective: To review surgical outcomes in the management of advanced mandibular osteoradionecrosis (ORN) with aggressive debridement and microvascular reconstruction.

Design: Retrospective cohort study.

Setting: Tertiary care referral center.

Patients: Thirty patients with Marx stage III ORN of the mandible who underwent debridement with microvascular reconstruction. Two types of patients with stage III disease were included: those who had not received prior hyperbaric oxygen (HBO) therapy but who presented with a pathologic fracture, orocutaneous fistula, or bony resorption of the inferior border of the mandible (group 1, n=9), and those who were classified as having stage III disease as a result of failure of previous debridement and HBO therapy (group 2, n=21).

Main Outcome Measure: Clinical resolution of ORN as well as surgical perioperative complications.

Interventions: Debridement and primary free flap reconstruction in all patients; Perioperative HBO therapy in 3 patients.

Results: The overall complication rate was 43%, but 29 (97%) of 30 patients had clinical resolution of their ORN. There were no flap failures. After smoking status and use of perioperative HBO were adjusted for, patients with Marx stage III disease who had received prior HBO therapy (group 2) were significantly more likely to have postoperative wound infection (P=.01) and overall surgical complications (P=.04) than were patients with stage III disease who had never been treated with HBO (group 1). Perioperative HBO therapy was provided too infrequently to comment on its effectiveness.

Conclusions: Microvascular reconstruction is effective in the treatment of patients with mandibular ORN. Management of mandibular ORN can be successfully achieved without the use of perioperative HBO therapy. Because only 3 patients received perioperative HBO therapy, we are unable to comment on its potential benefit. Patients in whom prior HBO therapy has failed are significantly more likely to have surgical complications than are other patients with Marx stage III disease, and further study is required to improve outcomes in this subgroup of patients.

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OSTEORADIONECROSIS (ORN) is a potentially devastating complication of radiation therapy for head and neck cancer. It is defined as exposed irradiated bone that fails to heal over a period of 3 months. While incidence rates vary, most reports cite an incidence between 5% and 15% in patients who have undergone irradiation.2 It is the result of both the short- and the long-term effects of radiation therapy on bone and the surrounding soft tissue. Controversies regarding the management of ORN are a reflection of the variability of the disease. Early lesions may respond to conservative measures such as improved oral hygiene and/or transoral debridement. Hyperbaric oxygen (HBO) therapy has proved useful in the treatment of patients with ORN. It has been shown to enhance wound healing through increased oxygen tension, resulting in vascular proliferation.3 Despite these measures, there is a subset of patients who progress to more extensive disease. Similarly, patients may present initially with more extensive disease, including pathologic fracture, orocutaneous fistula, and extensive bone necrosis.

Patients who present with extensive ORN or in whom less invasive therapy has failed often require aggressive resection, necessitating some form of reconstruction. Aggressive debridement and microvascular reconstruction in the manage-
ment of ORN has been found to be successful in a number of series. It allows restoration of bone continuity, with good functional and cosmetic results. It also introduces tissue with a nonirradiated blood supply into the region, further improving the chance for wound healing and bone viability.

In 1983, Marx presented a protocol for the systematic management of ORN of the mandible (Figure). The protocol consisted of 3 stages of therapy through which patients were advanced until they achieved resolution of their ORN. Stage I consisted of primary HBO therapy, regardless of prior treatment. Nonresponders were advanced to stage II, which involved transoral debridement and additional HBO therapy. Nonresponders at this stage were advanced to stage III, which involved more extensive resection, with additional HBO therapy and secondary delayed reconstruction. Patients who presented with a pathologic fracture, orocutaneous fistula, or radiographic evidence of bony resorption of the inferior border of the mandible were also classified as having stage III disease. These patients underwent stage III resection with perioperative HBO therapy, without stage I and II treatment.

Patient outcomes were determined by the stage at which patients achieved resolution of their ORN. As a result, Marx staging is often used to classify patients based on extent of disease. The stage at which patients responded to therapy was reflective of the severity of disease. We point out that there are 2 distinct types of patients that are classified as having stage III ORN. The first group consists of patients who present initially with advanced evidence of ORN (ie, pathologic fracture, orocutaneous fistula, or resorption of the inferior mandible) without previous HBO therapy. The second group consists of patients with similar or less advanced disease who are classified as having stage III disease on the basis of poor response to prior HBO therapy and debridement (stage I and II therapy).

At the time Marx presented his protocol, the primary modality of reconstruction was nonvascularized free bone graft. For advanced (stage III) ORN, he recommended not only delayed reconstruction but also additional HBO therapy at the time of surgery. Given the success of vascularized bone grafts in the management of ORN, as well as in the setting of previous radiation in general, it has been our institutional experience to proceed with debridement and free flap reconstruction without adjunctive HBO therapy. We sought to investigate the effectiveness of vascularized free bone graft in the treatment of patients with stage III ORN. Of secondary interest was the effectiveness of prior and/or adjunctive perioperative HBO therapy in patients undergoing these reconstructions.

**METHODS**

A retrospective chart review was performed to examine complication rates and outcomes in the management of advanced ORN with microvascular reconstruction at the University of Washington Medical Center, Seattle. Between November 1995 and February 2002, a total of 30 patients were identified who underwent aggressive debridement with immediate microvascular reconstruction for advanced osteoradionecrosis of the mandible. All patients had biopsy-confirmed ORN and met the criteria for Marx stage III classification.

Demographic information was recorded on patient age, sex, and current smoking status. We documented initial tumor site, stage, and previous oncologic surgery when applicable. Details about radiation therapy included whether it represented primary, preoperative, or postoperative treatment, and the type of radiation delivered (ie, brachytherapy or electron, neutron, or photon therapy). Because most patients were referred from distant sites, often many years after undergoing radiation therapy, accurate information regarding radiation dosage was frequently unavailable. The time from the completion of radiation therapy to the initial development of ORN, as well as the time from radiation to resection with microvascular reconstruction, was also recorded. Finally, the dates and amounts of prior HBO therapy were recorded when applicable.

There were 2 subgroups of patients with Marx stage III ORN. Group 1 (n = 9) consisted of patients with a pathologic fracture, an orocutaneous fistula, or radiographic evidence of bony resorption of the inferior border of the mandible, but who had never been previously treated with HBO therapy. Group 2 (n = 21) consisted of patients who had persistent ORN despite previous HBO therapy and/or debridement, with or without the presence of the clinical entities that defined group 1.

All patients underwent aggressive resection of necrotic bone until healthy bleeding bone was encountered. The type of free flap used was determined by the presence and length of the segmental mandibular defect or by the need for additional soft tissue coverage. The decision to use perioperative HBO therapy was dictated by arrangements made by the referring institution, and was adjusted for in the analysis. Three patients in group 1 received perioperative HBO therapy around the time of their resection and microvascular reconstruction.
Complications were defined as the development of any of the following in the postoperative period: (1) wound infection, (2) orocutaneous fistula, (3) plate exposure, (4) flap failure, (5) hematoma, or (6) medical complications such as pneumonia, myocardial infarction, or venous thrombosis. Given the relative infrequency of any one of these complications, and to account for the presence of multiple complications in the same patient, a categorical variable denoting the occurrence of a surgical complication of any type was created. Clinical resolution of ORN was defined as complete restoration of mucosal and/or cutaneous bone coverage, as well as mandibular continuity.

The 2 groups were compared for differences in the incidence of complications using the χ² statistic. Multiple regression analysis was performed across groups to control for potential confounding variables and additional predictors of outcome. Analyses of ORN rates across groups were performed using the log-rank statistic. Statistical analysis was performed using commercially available software (Stata Corp, College Station, Tex).

Table 1. Demographic Data for Patients With Marx Stage III Disease

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 9)</th>
<th>Group 2 (n = 21)</th>
<th>Total (N = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (67)</td>
<td>9 (43)</td>
<td>15 (50)</td>
<td>.23</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>69.7 ± 11.2</td>
<td>60.2 ± 7.6</td>
<td>63.1 ± 9.7</td>
<td>.02</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1 (11)</td>
<td>3 (14)</td>
<td>4 (13)</td>
<td>.82</td>
</tr>
<tr>
<td>Cancer surgery</td>
<td>7 (78)</td>
<td>17 (81)</td>
<td>24 (80)</td>
<td>.84</td>
</tr>
<tr>
<td>Bone resection for carcinoma</td>
<td>3 (33)</td>
<td>2 (10)</td>
<td>3 (10)</td>
<td>.40</td>
</tr>
<tr>
<td>Primary radiation therapy</td>
<td>2 (22)</td>
<td>1 (4.8)</td>
<td>3 (10)</td>
<td>.84</td>
</tr>
<tr>
<td>Postoperative radiation therapy</td>
<td>7 (78)</td>
<td>2 (10)</td>
<td>9 (30)</td>
<td>.045</td>
</tr>
<tr>
<td>Perioperative HBO</td>
<td>5 (56)</td>
<td>3 (33)</td>
<td>8 (26)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Group 1 includes patients who had not received previous hyperbaric oxygen (HBO) therapy. Group 2 includes patients in whom previous HBO failed. All values are expressed as number (percentage) unless otherwise noted.

Thirty patients underwent aggressive bony and soft tissue debridement with microvascular free flap reconstruction during the study period. Twenty-six (87%) of the 30 patients were treated for squamous cell carcinoma of the head and neck. The remaining patients received postoperative radiation therapy for an adenocarcinoma and a liposarcoma of the tongue base, an adenoid cystic carcinoma of the submandibular gland, and a parotid carcinoma of unknown type. All patients had biopsy-confirmed ORN of the mandible.

Demographic information is presented in Table 1. The mean age for the cohort was 63.1 years at the time of surgery. Fifteen patients (50%) were male. Twenty-four patients (80%) received postoperative radiation therapy, while the remaining patients were treated with primary external beam therapy. Two patients were treated with neutron beam therapy.

There were no flap failures. Twenty-nine of the 30 patients achieved resolution of their ORN. The overall complication rate was 43% (13/30). The distribution of complications across flap types is listed in Table 2. Ten of the 13 complications occurred in patients receiving fibula flaps; however, this did not reach statistical significance (P = .19) when compared with complication rates in other flaps. This is not surprising given the overall number of fibula flaps used and the substantial defects for which they were required. The association of bone flaps with overall surgical complication rates was not statistically significant (P = .15). Three patients with fibula flaps subsequently required pectoralis major flaps for fistula closure. The 1 patient with unresolved ORN was a heavy smoker and was noncompliant with follow-up. He developed a fistula with a pathologic fracture of his native mandible 5 months after surgery. He refused further treatment.

The distribution of reconstructive techniques that were used in the present study is presented in Table 3. Twenty-four patients required segmental mandibular resection to achieve healthy bone margins. The flap of choice for this purpose was the fibula osteocutaneous flap, which was used to reconstruct 19 (79%) of the 24 segmental defects. Iliac crest osteomyocutaneous flaps were used in patients who had either abnormal preoperative lower extremity vascular study results or previous fibula flaps for oncologic reconstruction. When successful debridement to healthy bone was achieved without segmental resection or destabilization of mandibular continuity, soft tissue coverage with a radial forearm fasciocutaneous flap was used. No comparisons could be made between patients with and without perioperative treatment with HBO.
since so few patients (n = 3) received perioperative HBO therapy.

No statistically significant baseline differences were observed between the 2 subgroups of patients with Marx stage III ORN with respect to sex, prior oncologic surgery, prior chemotherapy, or type of radiation therapy. Differences were noted with respect to average age (P = .02), perioperative HBO (P = .053), and smoking status (P = .045); therefore, we adjusted for these variables in the comparisons of Marx III subgroups. The mean ± SD duration of hospital stay for the resection and reconstruction, performed simultaneously, was 9.0 ± 4.8 days and did not differ significantly between subgroups.

We noted significantly different complication rates in the Marx stage III subgroups. Overall surgical complications occurred in 52% (11/21) of patients in whom prior HBO therapy had failed (group 2), compared with 22% (2/9) of patients who had not been treated with HBO previously (group 1, Table 4). After active smoking status and use of perioperative HBO therapy were adjusted for, this difference was found to be statistically significant (P = .04). There was also a significant association between failure of previous HBO therapy and development of postoperative wound infection (P = .01). Age, sex, tumor site, tumor stage, type of radiation, and type of flap were not found to be significant predictors of complications in multiple regression modeling (P = .80). Log-rank test demonstrated no significant differences across subgroups with respect to the time course for the development of ORN from the end of radiation therapy (P = .87).

Table 3. Distribution of Reconstructive Techniques*

<table>
<thead>
<tr>
<th>Flap Type</th>
<th>Group 1 (n = 9)</th>
<th>Group 2 (n = 21)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac crest</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Fibula</td>
<td>5</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Radial forearm</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
</tbody>
</table>

*See footnote to Table 1 for explanation of groups.

Table 4. Distribution of Complications Across Osteoradionecrosis Status in Marx Stage III Disease*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=11)</th>
<th>Group 2 (n=21)</th>
<th>Adjusted P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical complications</td>
<td>2 (20)</td>
<td>11 (52)</td>
<td>.04</td>
</tr>
<tr>
<td>Fistula</td>
<td>1 (11)</td>
<td>9 (43)</td>
<td>.01</td>
</tr>
<tr>
<td>Plate exposure</td>
<td>1 (11)</td>
<td>5 (24)</td>
<td>.62</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>.26</td>
</tr>
<tr>
<td>Medical complications</td>
<td>1 (11)</td>
<td>2 (10)</td>
<td>.85</td>
</tr>
</tbody>
</table>

*See footnote to Table 1.
†Adjustment in regression analysis for smoking status and perioperative HBO therapy.

Reconstructive techniques in the management of ORN initially involved the use of bone grafting. Given the avascular nature of this tissue, emphasis was placed on the use of HBO therapy at the time of reconstruction. Reconstruction was almost always performed on a delayed basis, usually at least 10 weeks after resolution of the ORN. By the time patients had completed reconstruction, they had often received as much as 90 to 100 hours (90 minutes per dive per day) of HBO. Both of these issues added considerable time and expense to the management of ORN, frequently in patients who had been free of cancer for many years.

One of the first reports of the use of microvascular reconstruction in the management of ORN was published by Shaha et al. At the time, only about 10% of mandibular defects due to ORN in their series were reconstructed using free flaps. More recently, Chang et al described a series of 29 patients with ORN who underwent free flap reconstruction. Although postoperative complications occurred in 6 patients (21%), and 4 patients required a second reconstructive procedure as a result of flap failure, all patients had complete resolution of their ORN.

Primary surgical therapy with microvascular reconstruction has been recommended with adjuvant HBO therapy in cases in which large areas of exposed bone, a pathologic fracture, or a fistula is present. The reported advantage of microvascular reconstruction is that it allows extensive excision of all necrotic and scarred tissue, without concern for the size of the defect. This improves the likelihood that resection of tissue back to healthy, bleeding native bone will be achieved. It also introduces tissue with a blood supply that has not been irradiated. In this setting, HBO therapy may be used as an adjuvant to increase vascular proliferation and wound healing. However, it neither revives dead bone nor resuscitates impaired bone. Thus, the margins of resection should not be reduced by the use of adjunctive HBO therapy.

In the present study, 29 of 30 patients had successful resolution of their ORN with aggressive debridement and microvascular reconstruction. Although complications occurred in 13 patients (43%) in this cohort, they were, for the most part, self-limited. Three patients required additional soft tissue coverage with myocutaneous flaps; however, none of the free flaps were lost.

An important finding of the present study is that the Marx stage III classification includes heterogeneous patients with very different prognoses. Patients in whom previous HBO therapy had failed (group 2) were found to have significantly higher rates of postoperative wound infection and overall surgical complications than patients who had not been treated with HBO. This may be because HBO-resistant ORN is more recalcitrant. In other words, patients in whom HBO therapy has failed represent a population that is self-selecting for poorer outcomes. Alternatively, prolonged periods of unsuccessful treatment may just contribute to the extent of disease. As some of these patients may have also undergone prior debridement, it is possible that they have injured tissue that has sustained the repetitive insult of debridement, resulting in more extensive disease. To our knowledge, there are no reported data to suggest that the differences in outcomes between the 2 groups can be ex-
plained by differences in oncologic treatment or by an unequal susceptibility to other complications of radiation therapy, such as hypothyroidism.

Only 3 patients received perioperative HBO therapy in conjunction with their free flap. This small sample size is inadequate to allow statistical comparison of outcomes in patients who did not undergo perioperative HBO therapy. Furthermore, the decisions to use perioperative HBO were made by outside referring physicians, which would introduce substantial bias into the comparison. The results of this cohort do demonstrate, however, that microvascular reconstruction without the use of perioperative HBO is a successful approach to the management of ORN. No conclusions from these data can be made regarding any added benefit of using perioperative HBO in the setting of microvascular reconstruction. The potential selective use of perioperative HBO in patients who are at increased risk for surgical complications needs to be refined.

It may well be that one of the subsets identified in this study may see proportionally more benefit from additional HBO therapy. There is evidence, however, that repeated HBO administration does not provide as much proportional benefit. In that case, it may be beneficial to offer HBO therapy to the patients who are most likely to benefit from additional treatment. On the other hand, if outcomes and complications rates are not significantly improved by perioperative HBO therapy, its use should be questioned given the additional time and expense involved. What can be concluded from our findings is that 27 of the 30 patients in this cohort underwent successful microvascular reconstruction without perioperative HBO therapy, and all but one had successful resolution of their ORN. This suggests that the vascularized nature of the reconstruction may offset the need for additional treatment with HBO.

**CONCLUSIONS**

Aggressive debridement and microvascular reconstruction represent an effective approach to the management of advanced ORN. Microvascular reconstruction is ultimately successful, even in the absence of perioperative HBO therapy. Patients who present with Marx stage III disease and in whom previous HBO therapy has failed are at a significantly higher risk for postoperative complications. Although these patients are ultimately able to achieve resolution of their ORN, further study of the underlying pathophysiology of radiation necrosis that places these patients at higher risk for adverse outcomes is warranted.

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**REFERENCES**