Short Communication

Clinical study of treatment methods and associated factors in mandibular osteoradionecrosis

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Abstract: This study aimed to determine the appropriate treatment methods and evaluate associated factors by comparing nonoperative treatment alone with a combination of both nonoperative and surgical treatment in 34 patients with mandibular osteoradionecrosis (mORN). The associated cure factors were analyzed by Cox regression. Propensity scores were calculated from factors that were not significant in the univariate analysis and used as covariates in the multivariate analysis. The cure rate among patients who received nonoperative and surgical treatment was higher than that observed with nonoperative treatment alone. Only the treatment method was associated with cure in both univariate and multivariate analyses.

Keywords: cure factor, mandibular osteoradionecrosis, propensity score, retrospective study

Introduction

Mandibular osteoradionecrosis (mORN) is one of the delayed adverse effects of radiation therapy [1]. It is defined as the partial exposure and necrosis of bone after radiation. It may progress irreversibly once it develops and reduces the quality of life of the patient to a great extent.

The incidence of ORN has declined over the past few decades due to the identification of risk factors and widespread use of intensity-modulated radiotherapy (IMRT) [2]. However, the pathogenesis of this disease remains unclear, and therapeutic management of ORN is still subject to debate.

Nonoperative or surgical treatment methods are selected depending on the pathology of the disease. The treatment goals are to remove necrotic bone, relieve symptoms, and restore both esthetics and functionality. Representative nonoperative treatments include antimicrobials, irrigation, and also hyperbaric oxygen therapy (HBO). HBO is often used as nonoperative treatment for mORN because it can stimulate fibroblast proliferation and angiogenesis [3]. In recent years, however, reports have suggested that the effectiveness of nonoperative treatment for mORN should be reconsidered and surgical treatment provided [4,5]. Thus, additional studies are required to determine the optimal treatment for mORN.

The objective of this study was to determine appropriate treatment methods and associated factors by comparing a group of patients who received nonoperative treatment alone with a group of patients who received both nonoperative and surgical treatment.

Materials and Methods

Patients

Forty patients who were diagnosed with mORN at the Department of Oral Medicine, Hokkaido University Hospital between January 2007 and December 2018 were recruited. Subsequently, 34 patients whose medical records had thorough information regarding their treatment were enrolled in this study. The definition of mORN used in this study is based on that used by Jin et al. [6] and is as follows: an irradiated jaw becoming devitalized and exposed without healing for a period of 3-6 months. All patients received nonoperative therapy; surgical therapy was administered depending on the change in symptoms. This retrospective study was conducted with the approval of the Hokkaido University Hospital Independent Clinical Research Review Committee (Approval No. 2020-0109). All the study procedures were carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. This article does not disclose identifiable information on any of the participants in any form. Hence, consent to publication is not applicable here.

Treatment algorithm

Early stage mORN patients are initially followed up with nonoperative treatment. If symptoms continue to worsen despite nonoperative treatment, surgical treatment is scheduled. However, sequestrectomy or marginal mandibulectomy should be performed in early stage mORN patients who receive surgical treatment. In severe cases, such as those with a cutaneous fistula, segmental mandibulectomy is scheduled as early as possible and nonoperative treatment is performed until surgery.

Study variables

Various factors, such as patient characteristics (age, sex, smoking habits, alcohol consumption, and diabetes mellitus [DM]) and clinical parameters (primary site, radiation method, radiotherapy dose, time from radiotherapy to onset of mORN, pathological classification of mORN, treatment information, overall mean duration of treatment, mean time to cure, and mean time from diagnosis to surgical intervention) were retrospectively examined. The time from the start of radiotherapy to the onset of mORN was defined as the time from the start of radiotherapy to the diagnosis of mORN by oral surgeons.

Classification of mORN

Pathological classification of mORN was based on imaging and clinical findings and classified according to Notani’s classification [7], as follows: Grade I is “ORN confined to alveolar bone,” Grade II is “ORN limited to alveolar bone and/or mandible above the level of the inferior alveolar canal,” and Grade III is “ORN involving the mandible below the level of the inferior alveolar canal and ORN with a skin fistula and/or pathological fracture.”

Treatment

Nonoperative treatment included local cleansing and the use of antibiotics and HBO, whereas surgical treatment consisted of sequestrectomy, marginal mandibulectomy, and segmental mandibulectomy, which were performed under general anesthesia.

Evaluation criteria of therapeutic effects

A cured case was defined as one in which there was an improvement in mORN status after treatment, and no obvious recurrent findings, such as drainage, pain, or bone exposure in the oral cavity, were observed during follow-up.

Statistical analysis

Statistical analyses were performed using JMP pro for windows (Version 14.0, SAS Institute, Cary, NC, USA) and included Fisher’s exact test, Cox regression, and log-rank test. The cumulative incidence of the cure rate of mORN and the time of surgical intervention were calculated using the
intervention was 8 months (median, 5 months; range, 2-31 months).

months; range, 4-52 months), and the mean time from diagnosis to surgical intervention was 8 months (median, 5 months; range, 2-31 months).

Table 1 lists the characteristics of the 34 patients included in this study.

### Table 1: Patient and treatment characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category (reference)</th>
<th>N (n = 13)</th>
<th>N and S (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≥65 (≤65)</td>
<td>6 (7)</td>
<td>11 (10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex</td>
<td>male (female)</td>
<td>10 (3)</td>
<td>18 (3)</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoke</td>
<td>no (yes)</td>
<td>4 (9)</td>
<td>16 (5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>yes (no)</td>
<td>7 (6)</td>
<td>13 (8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>yes (no)</td>
<td>3 (10)</td>
<td>7 (14)</td>
<td>0.70</td>
</tr>
<tr>
<td>Primary site</td>
<td>oropharynx (OC)</td>
<td>8 (5)</td>
<td>11 (10)</td>
<td>0.73</td>
</tr>
<tr>
<td>RT technique</td>
<td>3D-CRT (IMRT)</td>
<td>7 (6)</td>
<td>18 (1)</td>
<td>N/A</td>
</tr>
<tr>
<td>RT dose (Gy)</td>
<td>≥70 (&lt;70)</td>
<td>8 (5)</td>
<td>12 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from irradiation to onset of mORN (months)</td>
<td>≥55 (&lt;55)</td>
<td>6 (7)</td>
<td>12 (9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Notani’s classification</td>
<td>Grade 3 (Grades 1,2)</td>
<td>1 (12)</td>
<td>11 (10)</td>
<td>0.01</td>
</tr>
<tr>
<td>HBO (times)</td>
<td>≥10 (&lt;10)</td>
<td>5 (8)</td>
<td>13 (8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dosing period of antimicrobial medicine (months)</td>
<td>≥4 (&lt;4)</td>
<td>4 (9)</td>
<td>13 (8)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

| Treatment method        | N and S (N)          | 2 (11)     | 12 (9)          | 0.03    |

On the basis of Fisher’s exact test. N, nonoperative treatment; N and S, nonoperative treatment and surgical treatment; OC, oral cavity; N/A, not applicable; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; HBO, hyperbaric oxygen therapy; mORN, mandibular osteoradionecrosis.

### Results

Table 1 lists the characteristics of the 34 patients included in this study. A total of 13 patients received nonoperative treatment and 21 underwent nonoperative and surgical treatment; among them, 2 and 12 patients were cured by nonoperative and surgical treatment, respectively. The following items demonstrated statistically significant differences between the two groups in this study: smoking habits, radiotherapy (RT) technique, Notani’s classification, and treatment outcome. The number of patients who received surgical treatment was as follows: 9 for sequestrectomy, 1 for marginal mandibulectomy, and 11 for segmental mandibulectomy. The overall mean duration of treatment was 57 months (median, 51.5 months; range, 12-125 months). The mean time to cure was 22 months (median, 21 months; range, 4-52 months), and the mean time from diagnosis to surgical intervention was 8 months (median, 5 months; range, 2-31 months).

Kaplan-Meier curves were created based on the treatment method and time to cure (Fig. 1A) and the surgical treatment group and time of surgical intervention (Fig. 1B). Although the cure group showed relatively early surgical interventions, no statistically significant difference was observed between the timing of surgical intervention and the surgical group. The cure rate in the nonoperative and surgical treatment group was significantly higher than that in the nonoperative treatment alone group (P = 0.03).

As shown in Table 2, the results of the univariate analysis showed a significant difference only in the treatment method (hazard ratio [HR], 4.65; 95% confidence interval [CI], 1.26-29.90). Based on these results, a propensity score was calculated from items other than the treatment method in the univariate analysis (C-statistic = 0.82). A significant association was found for the treatment method (HR, 6.90; 95% CI, 1.52-49.20) when the propensity score was used as a covariate along with the treatment method in the multivariate analysis (Table 3).

### Discussion

A propensity score is an aggregate of multiple covariates into a single number, which is used to adjust for confounders. This is the first study to use propensity score to evaluate the treatment effects of mORN, taking into account various factors, such as age, sex, smoking habits, alcohol consumption, radiotherapy dose, DM, Notani’s classification, hyperbaric oxygen therapy.
Oxygen therapy, and use of antimicrobial drugs. The confounding effects of these factors were adjusted using propensity scores and multivariate analysis was used to evaluate the relationship of these factors with the treatment method that showed significant results in the univariate analysis; however, only the treatment method was associated with cure in the present study. In this study, the cure rate with nonoperative and surgical treatment was higher than that with nonoperative treatment alone. The nonoperative and surgery group demonstrated signs of cure at relatively any time point; however, no further cure was observed after 60 months. On the contrary, no signs of a cure were observed in patients who received nonoperative treatment even after 20 months.

Nonoperative treatments such as antibiotics, irrigation, and HBO often precede by surgical treatment [8]. This may be due to the patient’s resistance to surgery. Recently, the efficacy of pentoxifylline-tocopherol-clodronate (PENTOCLO) treatment for ORN as nonoperative treatment has been reported [9]. Although no patients were treated with it in this study, its effects are attracting attention, and this treatment is expected to aid in avoiding excessive surgery. However, if the effect of this nonoperative treatment is not sufficient and the patient continues to deteriorate, surgical treatment may have to be considered. In order to make this decision, it is important to decide whether to continue the nonoperative treatment. Notani et al. [7] proposed that the efficacy of nonoperative treatment should be evaluated within 36 months after irradiation. In this study, nonoperative treatment alone did not result in cure even after more than 20 months of treatment. In light of this result, it seems that nonoperative treatment should be judged on its effectiveness over a shorter period of time. The use of HBO and antibiotics for ORN is currently under review [4,10]. Both antimicrobials and HBO were not associated with cure in the present study. Therefore, long-term nonoperative treatment as the main treatment for mORN may not contribute to any improvement, and the disease can progress with time.

Furthermore, it is important to decide when surgical treatment should be performed. Bettoni et al. [5] proposed that early surgical treatment is preferred because most mORNs are progressive and irreversible. Notani et al. [7] suggested that radiation-induced bone damage is not expected to change over time and early surgery is preferable. On the other hand, some reports recommend avoiding early surgical treatment and providing nonoperative treatment first [8]. Among the cases that demonstrated signs of cure in the present study, surgical intervention was performed within 15 months of diagnosis. Although patients who underwent surgical intervention relatively early tended to be cured, some of the cases that were not cured were treated by surgery at an early stage. While the results of this study do not necessarily suggest that early surgical intervention is desirable, surgery may be considered at an early stage if no change is observed with nonoperative treatment.

One of the limitations of this study is the limited number of overall cases and the few factors associated with cure. In addition, this study used the propensity score as an adjustment for confounders. However, this score may change if the other factors that are not investigated in this study are included as confounders, such as pre-RT dental procedures and dental status. Additional studies using an increased number of cases and items to be investigated are warranted.

In summary, the results of this study suggest that long-term nonoperative treatment should be avoided for mORN and surgical treatment should be considered in addition to nonoperative treatment.

Conflict of interest
None declared.

References

Table 3 Factors associated with cure of mandibular osteoradionecrosis in the multivariate Cox regression model when propensity scores were entered as covariate

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category (reference)</th>
<th>Hazard ratio</th>
<th>95% CI for difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment method</td>
<td>N and S (N)</td>
<td>6.90</td>
<td>1.52-49.20</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Propensity scores were calculated from the following items: age, sex, smoking habits, alcohol consumption, radiotherapy dose, diabetes mellitus, Notani’s classification, hyperbaric oxygen therapy, and dosing period of antimicrobial medicine. CI, confidence interval; N and S, nonoperative treatment and surgical treatment; N, nonoperative treatment.