Original

An Analysis of Distant Metastases in Oral Squamous Cell Carcinoma

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(Received for publication, March 10, 2010)

Abstract: Metastases to distant organs are well known to be factors influencing prognosis in patients with oral cancer. Therefore, it is very important to detect the metastasis of cancer as early as possible and to investigate the factors associated with the mechanism of metastasis. This study evaluated the risk of distant metastasis by the degree of histological malignancy among 59 patients with oral squamous cell carcinoma (SCC) who were treated at our department during the past five years. The degree of histological malignancy of initial biopsy specimens was evaluated by Anneroth’s classification and its relationship with metastasis was analyzed. Distant metastasis occurred in 7 of 59 patients (11.9%) and was located predominantly in the lung and bone. There was a significant correlation between the degree of histological malignancy and distant metastasis (P<0.05); however, there was no significant difference between T classification and metastasis in the distant organs. It is considered that histological malignancy is useful for predicting the prognosis and deciding additional treatments for oral SCC. When a total score on histological malignancy grading exceeds 14, metastasis in the distant organs should be carefully considered.

Key words: Oral region, Squamous cell carcinoma, Distant metastasis, Histological malignancy grading

Introduction

Since not only the suppression of primary lesion but also the presence or absence of metastasis in the distant organs may greatly influence the outcome of oral cancer, suppression of metastasis has become an important subject1). However, the therapeutic regimen has been selected mainly based on the stage of clinical progression in most cases. Therefore, metastasis may occur even in T1 and T2 cases and it is often difficult to suppress distant metastasis due to insufficient prediction, with rather unfavorable therapeutic results. Thus, an adequate therapeutic regimen needs to be established by clarifying possible factors involved in distant metastasis in individual cases. In the present study, we clinically evaluated the relationship between T classification and the distant metastasis in patients with oral squamous cell carcinoma (SCC) encountered during the past five years in our department. Moreover we histopathologically observed the biopsy specimens of primary lesion and evaluated the relationship between the degree of histological malignancy based on Anneroth’s classification2) and metastasis in the distant organs.

Patients and Methods

Patients

Fifty-nine from 65 patients with primary oral SCC who were admitted and underwent treatment in our department during the past five years, and who were conducted at least ten-year follow-up, were selected as subjects for this study. Regarding the treatment method, treatment with a combination of surgery, chemotherapy and radiotherapy was applied to 24 cases, surgery alone to 13 cases, treatment combined with surgery and chemotherapy to 12 cases, treatment combined with chemotherapy and radiotherapy to 9 cases, and treatment combined with surgery and radiotherapy to 1 case. The primary SCC sites of these patients were the tongue in 23 cases, mandibular gingiva in 15 cases, floor of the mouth in 8 cases, buccal mucosa in 7 cases and maxillary gingiva in 6 cases.

Procedures

In relation to metastasis, T classification was examined clinically, while the degree of histological malignancy of biopsy specimens of primary lesion was evaluated according to Anneroth’s classification3). A total of 6 parameters were evaluated: namely, 3 parameters including the degree of keratinization,
nuclear polymorphism and number of mitoses as factors for tumor cell population, and 3 parameters including pattern of invasion, stage of invasion and degree of lymphoplasmocytic infiltration as factors for tumor-host relationship. Biopsy specimens of the primary lesion were stained by Hematoxylin-Eosin (HE).

**Statistical analysis**

Each value of histological malignancy was expressed as mean ± standard deviation (SD). Relationships between metastasis and histological malignancy were tested using the Mann-Whitney U-test. P<0.05 was considered statistically significant. Statistical analyses were performed using Stat View (Abacus Concepts Inc., Berkeley, CA, USA, 1998).

## Results

### Metastatic rate and the affected site

Metastases were noted in 7 out of 59 cases (11.9%), counting 4 cases of solitary metastasis and 3 cases of multiple metastases in 7 cases, with 12 sites of metastases in total. The metastases were located predominantly in the lung and bone (Tables 1, 2).

### Relationship between T classification and metastasis

According to T classification, there were 17 cases of T1, 26 cases of T2, 11 cases of T3 and 5 cases of T4. The metastatic rate in T1 cases was 5.9% and that of T2 cases was 3.8%, while the rate in T3 cases was as high as 36.4% and that of T4 cases was 20%. However, there was no significant difference. Regarding
the site of primary lesion, the metastatic rate was 3/23 (13.0%) in the tongue, 1/15 (6.7%) in the mandibular gingiva, 1/8 (12.5%) in the oral floor, 0/7 (0%) in the buccal mucosa and 2/6 (33.3%) in the maxillary gingiva. Although no metastasis was observed in T1 cases of primary lesion in the tongue, mandibular gingiva and buccal mucosa, metastasis was observed in T1 cases of primary lesion in the oral floor. The relationship between T classification and the degree of histological malignancy was examined: the degree of histological malignancy in T1, T2, T3 and T4 cases was 11.53 ± 2.40, 12.58 ± 2.10, 14.09 ± 3.11, and 15.20 ± 3.27, respectively. Thus, the larger T classification, the higher the histological malignancy observed (Tables 1–3).

**Relationship between degree of histological malignancy and metastasis**

Regarding the relationship between the degree of histological malignancy and metastasis, both total and mean scores were significantly higher in the cases with metastasis (16.86 ± 2.78) than in the cases without metastasis (12.21 ± 2.17) (P<0.05). In the former cases, mean values for all 6 parameters were higher.

<table>
<thead>
<tr>
<th>Histological malignancy</th>
<th>Metastasis (7 cases)</th>
<th>No metastasis (52 cases)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total scores</td>
<td>16.86 ± 2.78</td>
<td>12.21 ± 2.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Degree of keratinization</td>
<td>2.43 ± 0.79</td>
<td>1.83 ± 0.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nuclear polymorphism</td>
<td>3.00 ± 0.58</td>
<td>1.96 ± 0.63</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Number of mitoses</td>
<td>2.00 ± 0.82</td>
<td>1.15 ± 0.42</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pattern of invasion</td>
<td>3.14 ± 0.69</td>
<td>2.40 ± 0.72</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stage of invasion</td>
<td>3.86 ± 0.39</td>
<td>2.75 ± 1.33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lymphoplasmocytic infiltration</td>
<td>2.43 ± 0.98</td>
<td>2.12 ± 0.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean scores</td>
<td>2.81 ± 0.47</td>
<td>2.04 ± 0.36</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± standard deviation.

Figure 1. Sixty-year-old man with carcinoma of the tongue in case No.2. (A) Left side of tongue tumor at first visit. (B) Macroscopic findings of autopsy. (C) Initial biopsy shows well differentiated SCC. Total score of Anneroth’s histological malignancy was 14 points, and each score of 6 parameters was as follows: keratinization 2, nuclear polymorphism 2, number of mitoses 1, pattern of invasion 2, stage of invasion 4, lymphoplasmocytic infiltration 3 (HE×200). (D) Histopathological findings of autopsy specimen of metastasis tumor in lung (HE×200). Bars: 100µm
than those in the latter. Among the 6 parameters, a significant difference was observed in the degree of keratinization \((P<0.05)\), nuclear polymorphism \((P<0.05)\), number of mitoses \((P<0.05)\), pattern of invasion \((P<0.05)\), and stage of invasion \((P<0.05)\). No distant metastasis was observed in the patients whose total score on histological malignancy grading was lower than 13, while distant metastasis was observed in 7 of the 26 patients (26.9%), whose total score was higher than 14 (Table 4, Fig. 1).

Discussion

In cases of oral SCC, metastasis may occur even in T1 or T2 cases of primary tumor, which is a problem when establishing a therapeutic regimen. However, predictive factors for metastasis of oral SCC have not been established. In the present study, metastasis was examined clinically and histopathologically in patients with oral cancer in order to elucidate the factors involved in the mechanism of metastasis. The metastatic rate was reported to be from 7.5 to 57% in patients with oral SCC\(^3\)\(^-\)\(^8\). Metastasis in the mechanism of metastasis. The metastatic rate was reported in patients with oral cancer in order to elucidate the factors involved in the mechanism of metastasis. The metastatic rate was reported to be from 7.5 to 57% in patients with oral SCC\(^3\)\(^-\)\(^8\). Metastasis was detected in 11.9% as a whole in this study, which was lower than the results reported by other authors. As for the metastatic rate by different sites of primary lesion, no metastasis was observed in the buccal mucosa. This may be explained by the fact that the primary tumor was confined to the buccal mucosa region and did not extend to the gingiva in this study.

The most common organ of distant metastasis of oral SCC was lung and this tendency corresponded to other reports\(^3\)\(^-\)\(^10\). The second most frequent organ of metastases was reported to be liver\(^4\)\(^-\)\(^9\). Merino et al.\(^7\) reported that 33 metastases in liver were found in 546 cases with SCC of the head and neck region but only one case was found in 116 oral SCC cases. The frequency of liver metastases from oral SCC appears to be limited and no metastasis was found in this study.

Although the metastatic rate was higher in T3 (36.4%) and T4 cases (20.0%) as compared to T1 and T2 cases (4 to 6%), no significant difference was noted among them. This suggested misprediction of metastasis can be induced when considering T classification alone as a predictive factor for metastasis. Some authors found a significant correlation between local extension of tumor and risk of distant metastases\(^3\)\(^-\)\(^10\), whereas others did not find this\(^11\)\(^,\)\(^12\). Thus, a systematic assessment, including other factors, appears to be necessary.

A possible relation of the degree of malignancy judged by histopathological findings to prognosis of oral SCC has been investigated since Broders\(^13\) reported the degree of keratinization of cancer cells in relation to prognosis of oral cancer in 1920. In 1966, Arthur and Fenner\(^14\) reported a significant correlation between prognosis of tongue cancer and histological parameters such as the keratinization, mitosis, hyperchromatism, and cell irregularity. Their report led to the tendency in research to establish the systematic assessment of multiple factors for prognosis prediction. Jakobsson et al.\(^15\) evaluated 8 parameters in total: 4 parameters including structure, keratinization tendency, nuclear aberrations and number of mitoses as factors for tumor cell population, and 4 parameters including mode of invasion, stage of invasion, vascular invasion and degree of lymphoplasmocytic infiltration as factors for tumor-host relationship, which indicated a distinct relation between the degree of histological malignancy and recurrence or survival rate in patients with carcinoma of the larynx. In 1975, however, Willen et al.\(^16\) evaluated 6 of the 8 parameters by excluding the structure because of resemblance to the mode of invasion and the vascular invasion because of its difficulty in judging induced by possible individual differences in the vascular distribution. Thereafter, they reported that a relation existed between metastasis and prognosis in SCC of the gingiva. Lund et al.\(^17\) and Holm et al.\(^18\) reported a relation of histological malignancy evaluated by multiple factors to the prognosis in SCC of the tongue. Further, Yamamoto et al.\(^19\) focused on the mode of invasion for the parameter and subdivided Grade 4 proposed by Jakobsson et al.\(^15\) into Grade 4C and 4D. They subsequently reported a possible relation between metastasis in the cervical lymph nodes and histological malignancy evaluated by multiple factors\(^19\). In 1987, Anneroth et al.\(^20\) reviewed these reports published after Broders’s study\(^13\), and a total of 6 parameters (3 parameters including degree of keratinization, nuclear polymorphism and number of mitoses as factors for tumor cell population, and 3 parameters including pattern of invasion, stage of invasion and degree of lymphoplasmocytic infiltration as factors for tumor-host relationship) were assessed in 4 grades from 1 to 4 points each and the total number of points was used as a predictor for the degree of histological malignancy. As compared with conventional reports on assessment, the border between various score results can be depicted clearly in simplified figures and tables with distinctly indicated number of cancer cells and mitoses as well as the clarified degree of depth achieved by anatomical evaluation, all of which enable us to evaluate the degree of histological malignancy in a simpler and more objective way. Therefore, among various assessment methods, the method of evaluating the degree of histological malignancy according to the classification proposed by Anneroth et al.\(^21\) was used in the present study. A significant correlation was found between the degree of histological malignancy and metastasis, indicating that histological malignancy could serve as a predictor for metastasis.

The therapeutic regimen should be judged by the factors of not only T classification but also the evaluation of the degree of histological malignancy. Anneroth et al.\(^21\) reported that the SCC cases of the floor of the mouth were histopathologically divided into two groups with low malignancies (mean points ranging from
1.0 to 2.5) and high malignancies (mean points ranging from 2.6 to 4.0) and they showed a statistical significance between clinical stage and mean of malignancy score. In this study, the degree of histological malignancy of the cases with metastasis was $16.86 \pm 2.78$ (14.08–19.64), and that of the cases without metastasis was $12.21 \pm 2.17$ (10.04–14.38). The total score of histological malignancy of the metastatic group was significantly higher than that of the non-metastatic group. These results suggested that 14 points is the critical score in judging histological malignancy and that metastasis should be carefully considered when the degree of histological malignancy exceeds a total score of 14. Nevertheless, further investigation of predictive factors for metastasis of oral SCC is required.

References
