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Examination of Factors Predicting Occult Metastasis of the Cervical Lymph Nodes in T1 and T2 Tongue Carcinoma

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Occult metastasis of the cervical lymph nodes was examined as a prognostic factor for T1 and T2 tongue carcinoma. The T classification and thickness of tongue carcinoma as well as histological malignancy were assessed respectively as clinical and histopathological factors related to metastasis. Sixty-eight patients who had undergone partial glossectomy for the treatment of T1 or T2 tongue carcinoma were studied. Occult metastasis of the cervical lymph nodes occurred in 15 out of 68 patients (22.1 %). It occurred in 18.4 % of T1 patients and 26.7 % of T2 patients. Although the incidence of metastasis was higher in patients with larger tumors, a significant difference was not observed. Examination of the thickness of the tongue tumors revealed a mean value of 3.5 mm in patients without metastasis versus 5.5 mm in patients with metastasis, which was a significant difference. Examination of histological malignancy showed a significant correlation between the pattern of invasion and the incidence of occult metastasis to the cervical lymph nodes. There was a significant difference between the total score of the group without occult metastasis (12.8 points) and that of the group with metastasis (14.4 points). Improvement of the prognosis might be possible through elective neck dissection if occult metastasis to the cervical lymph nodes could be predicted.

Key words : T1 and T2 Tongue carcinoma, Occult metastasis, Prognostic factor, Thickness of tongue carcinoma, Histological malignancy

OBJECTIVE

Occult metastasis to the cervical lymph nodes is the most important prognostic factor for T1 and T2 tongue carcinoma [1]. Occult metastasis to the cervical nodes signifies metastasis only detected after surgery. If metastasis could be recognized in advance, improvement of the prognosis might be possible through elective neck dissection.

In the present study, the clinical T classification and thickness of tongue carcinoma, as well as histological malignancy, were investigated as predictive factors for cervical node metastasis.

SUBJECTS

Among patients who had received treatment for T1 or T2 tongue carcinoma at our department during a seven-year period from January 1994 to December 2000, 68 patients who met the following criteria were selected as subjects for the study.

1) Diagnosis of N0 disease prior to surgery.
2) Only surgical resection of the primary tumor was performed.
3) Local recurrence was not noted during the clinical course.

The subjects consisted of 38 men and 30 women whose ages ranged from 28 to 76 years (mean: 59 years). There were 38 cases of T1 disease and 30 cases of T2 disease (Table 1).

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Table 1 Patients profiles and T stage

Number	68
Age	28–76 years (mean 59)
Male/Female	38/30
Stage T1	38
T2	30

METHODS

1. Incidence of occult metastasis to cervical lymph nodes based on the T classification.
2. Incidence of occult metastasis to cervical lymph nodes based on the thickness of the tongue tumor.

After fixing in 10 % formalin, resected tissues were all cut into slices approximately 2 mm thick in the frontal plane in preparation for H-E(Hematoxylin Eosin staining) sections. A preparation that displayed the deepest extent of the tumor was used when the thickness of the tongue carcinoma was measured. The method of Brown *et al.* was employed [2], and the thickness of the protruding tumor was expressed as length A, while the depth from the surface of the normal mucosa was measured as length B in ulcerative carcinomas (Fig. 1).

Tumor thickness was compared between patients with or without occult metastasis to the cervical lymph nodes.

3. Incidence of occult metastasis to cervical lymph nodes based on histological malignancy.

Anneroth's classification [3] was used for the evaluation of the tumor's histological malignancy (Table 2). The extent of keratinization, nuclear polymorphism, and the number of mitoses were assessed as tumor cell factors, while the pattern of invasion, stage (depth of invasion), and lymphocyte/plasma cell infiltration were assessed to evaluate the tumor-host relationship. Each parameter was given a score of 0 to 4 points, and the final score for each parameter as well as the total score for all six parameters (maximum: 24 points) were used to examine the relationship with occult metastasis to the cervical lymph nodes.

Statistical analysis of data was performed by the t-test and the χ^2-test, and significant differences were defined as $p < 0.05$.

RESULTS

1. Occult metastasis to the cervical lymph nodes was observed in 15 out of 68 patients (22.1 %), including seven of the 38 patients with T1 disease (18.4 %) and eight of the 30 patients with T2 disease (26.7 %). Although the incidence of occult metastasis to cervical lymph nodes seemed to increase with the size of the tumor, a significant relationship was not noted (Fig. 2).
2. The mean thickness of the tongue tumor was 3.5 mm in patients without occult metastasis to the cervical nodes. On the other hand, the mean thickness of the tongue tumor was 5.5 mm in patients with occult metastasis to the cervical nodes, being larger than in the non-metastasis group. A significant difference was observed between the two groups (Fig. 3).
3. The histological malignancy grade was a significant difference between the average total score of the group without occult metastasis to the cervical nodes (12.8 points) and that of the group with occult metastasis (14.4 points) (Fig. 4). In each parameters, the incidence of occult metastasis to the cervical nodes tended to increase with the score for the pattern of invasion, and a statistically significant difference was noted. On the other hand, other parameters did not show any specific relationship with the incidence of occult metastasis to the cervical nodes.

But the incidence of occult metastasis to the cervical nodes showed a tendency of becoming high by the increase in points in number of mitosis and stage of invasion (Fig. 5).

DISCUSSION

It is said that tongue carcinoma is more likely to metastasis to the cervical lymph nodes than other oral cancers [4]. In particular, the incidence rises in patients with advanced tumors, for which neck dissection

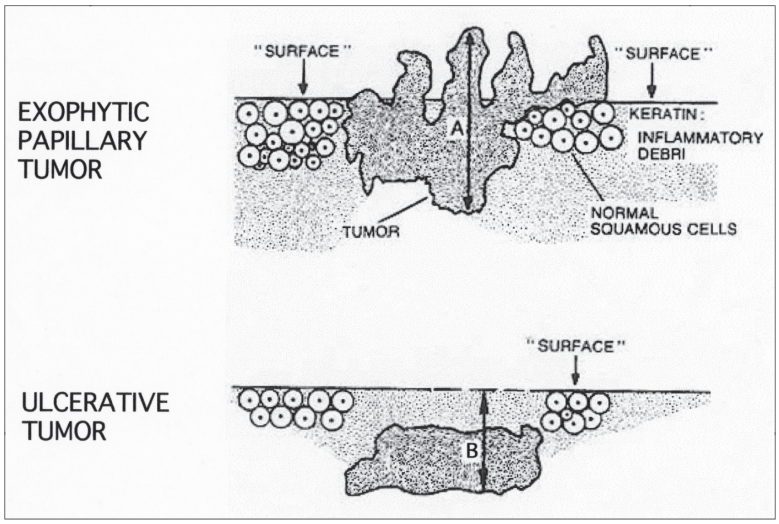

Fig. 1 Diagram of methods of measurement of tumor thickness

Table 2 Malignancy grading system of oral squamous cell carcinoma

Histologic grading of malignancy of tumor cell population				
Morphologic parameter	Points			
	1	2	3	4
Degree of keratinization	Highly keratinized ($>$ 50 % of the cells)	Moderately keratinized (20–50 % of the cells)	Minimal keratinization (5–20 % of the cells)	No keratinization (0–5 % of the cells)
Nuclear polymorphism	Little nuclear polymorphism ($>$ 75 % mature cells)	Moderately abundant nuclear polymorphism (50–75 % mature cells)	Abundant nuclear polymorphism (25–50 % mature cells)	Extreme nuclear polymorphism (0–25 % mature cells)
Number of mitoses/HPF *	0–1	2–3	4–5	$>$ 5
Histologic grading of malignancy of tumor-host relationship				
Morphologic parameter	Points			
	1	2	3	4
Pattern of invasion	Pushing, well-delineated infiltrating borders	Infiltrating, solid cords, bands and/or strands	Small groups or cords of infiltrating cells ($\eta > 15$)	Marked and widespread cellular dissociation in small groups of cells ($\eta < 15$) and/or in single cells
Stage of invasion (depth)	Carcinoma in situ and/or questionable invasion	Distinct invasion, but involving lamina propria only	Invasion below lamina propria adjacent to muscles, salivary gland tissues and periosteum	Extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone
Lympho-plasmocystic infiltration	Marked	Moderate	Slight	None

* HPF = high power field.

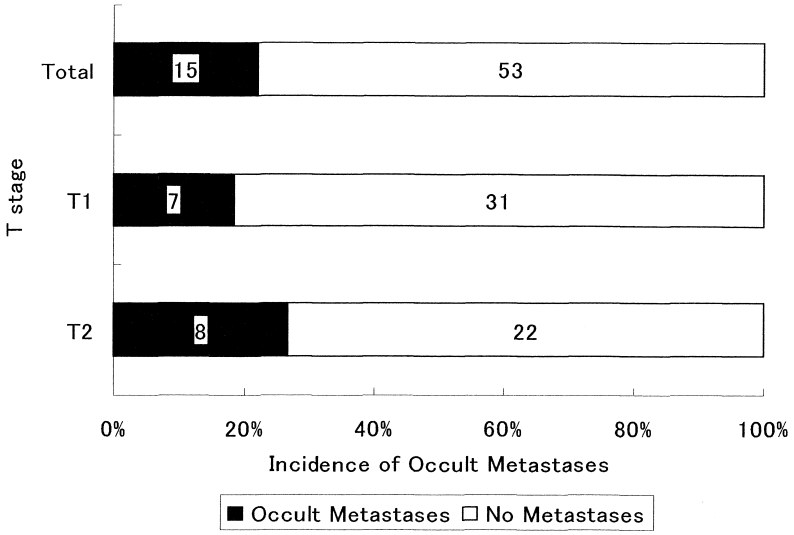

Fig. 2 Incidence of occult cervical node metastases in T1, T2 tongue cancer

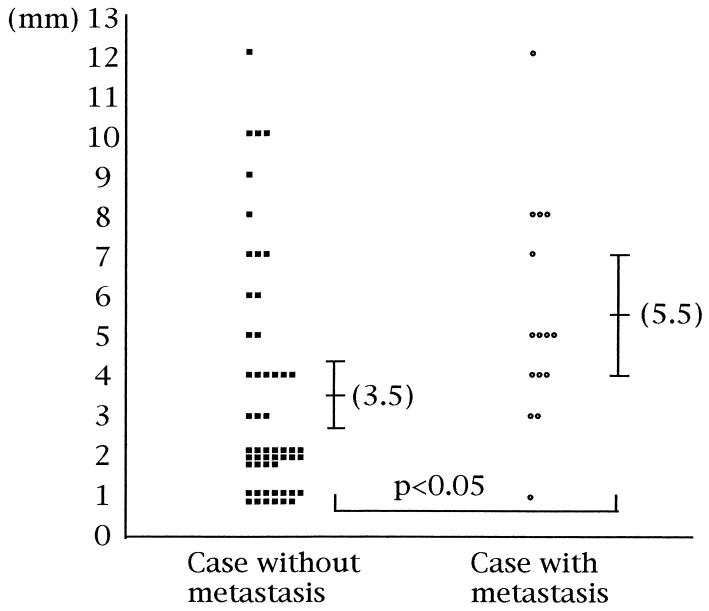

Fig. 3 Tumor thickness in relation to metastatic status

and irradiation are generally combined with resection of the primary lesion. However, when the tumor is diagnosed as N0 at the time of first treatment and occult metastasis to the cervical lymph nodes are found after surgery, it is not uncommon for the prognosis to be poor due to inadequate treatment. Conventionally, neck dissection has been performed after occult metastasis is discovered. However, the response is poor, with a salvage rate of only 10 to 50 % [5]. Such a poor response has been attributed to the high incidence of extra capsular invasion by occult metastases to the cervical nodes, involvement of multiple lymph nodes, recurrence at a different location following salvage surgery, and distant metastasis. In particular, in the case of T1 and T2 tongue carcinoma, only the primary tumor is treated in many patients, leaving the potential for occult metastasis to the cervical lymph nodes to determine the prognosis. The incidence of

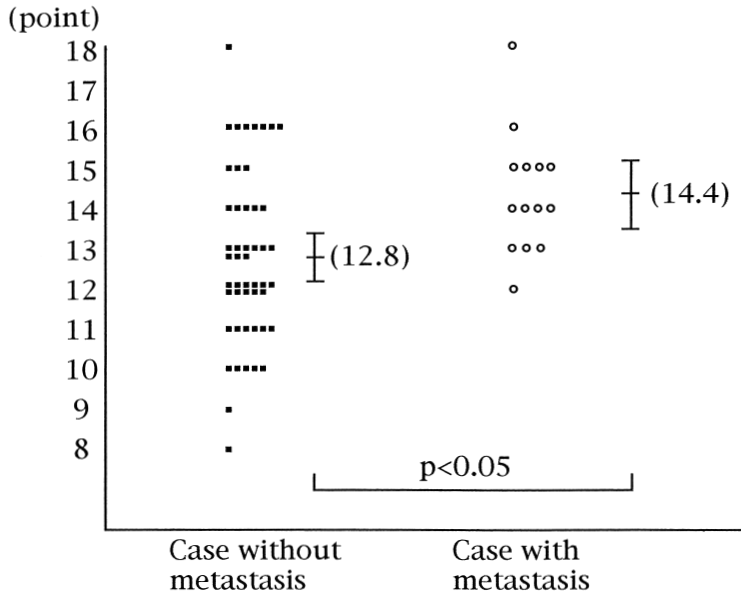

Fig. 4 Total histologic malignancy score in relation to metastatic status

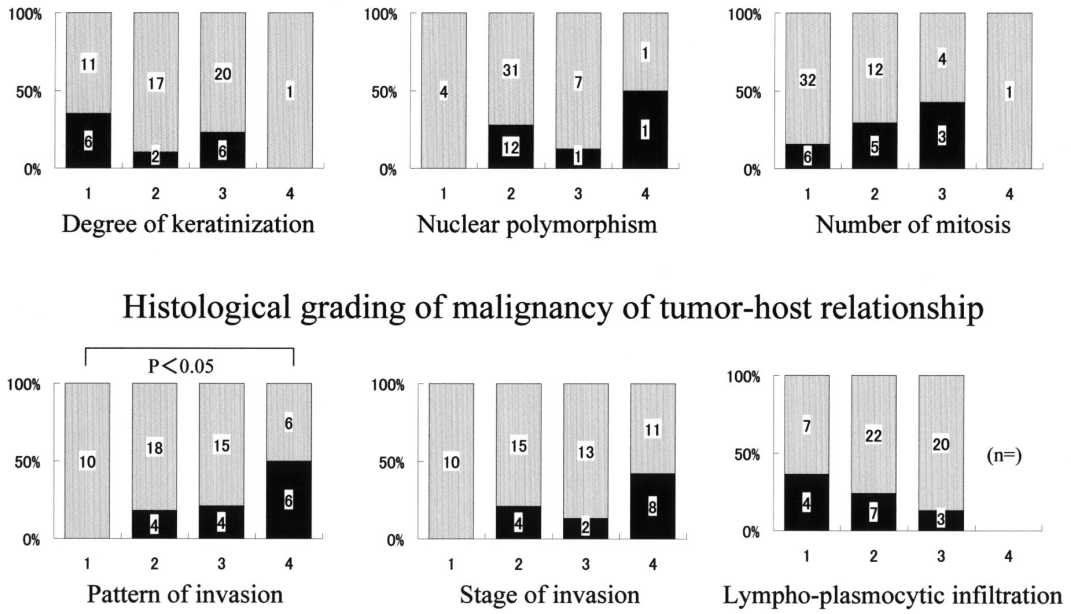

Fig. 5 Histological grading of malignancy of tumor cell population

occult metastasis to cervical nodes has been commonly reported as 20 to 30 % [5, 6]. At our department, the incidence was 22.1 %, falling within the range found by various authors.

For this reason, a number of authors have reported an improved response through elective neck dissection of N0 cases [7]. However, since all patients are equally indicated for such surgery at present, it is essential to determine those who are likely to develop occult metastasis to the cervical lymph nodes.

The present study showed a tendency for occult metastasis to the cervical nodes to increase in relation to the T classification and

the thickness of the tongue tumor. However, since a significant association was only observed for the thickness of the tongue tumor, this was considered to be a more reliable factor than the T classification. A study on the incidence of occult metastasis to cervical lymph nodes in 100 patients with T1T2N0 tongue carcinoma by Fakih *et al.* [8] showed that there was a significant difference in the incidence of occult metastasis between tumors with a thickness of 4 mm or more and those with a thickness of less than 4 mm. There are also other reports of a difference in the incidence of occult metastasis to the cervical lymph nodes when the subjects were divided at 4 mm [9]. In the present study, the upper limit of the thickness of the tongue tumor on a standard normal distribution with a 95 % confidence interval of the mean values was 4.3 mm in patients without metastasis.

On the other hand, the lower limit of the standard normal distribution was 4.0 mm in patients with occult metastasis to the cervical nodes. Comparison of tumors measuring 4 mm or less with those greater than 4 mm revealed that the incidences of occult metastasis to the cervical nodes was 13 % and 41 %, respectively, showing a significant difference.

In 1987, Anneroth *et al.* [3] presented an original method for evaluating histological malignancy based upon a review of various reports. One feature of this method is the fact that it allows more objective evaluation through quantification of parameters for the tumor cell factors, anatomical assessment of factors in the tumor-host relationship such as the pattern and depth of invasion, and clear definition of tumor cell counts. However, the pattern of invasion was the only parameter that was significantly correlated with the incidence of occult metastasis to the cervical lymph nodes in the present study. There have been few reports on histological malignancy and the prognosis that indicated all of the factors as reflecting the prognosis [10]. Rather, most reports have indicated that keratinization, nuclear polymorphism, and the number of mitoses do not serve as prognostic factors [11–13]. On the other hand, many authors have concluded that the pattern of invasion is a useful prognostic factor [14–16] Yamamoto *et al.* [15] divided type 4 (diffuse invasion) of Jacobsson's [17] classification into 4C (cord-like) and 4D (diffuse), and reported that this classification may be useful for predicting occult metastasis to the cervical nodes.

In the present study, the thickness of the tongue tumor and the pattern of invasion were found to be useful for predicting occult metastasis of T1 and T2 tongue carcinoma to the cervical lymph nodes, in addition to the T classification. In particular, the incidence of occult metastasis to the cervical nodes was 50 % when the thickness of the tongue tumor exceeded 4 mm and the pattern of invasion was scored as 4 points, suggesting the necessity of additional measures for these patients such as elective neck dissection.

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