Postoperative Recurrence-related Factors of 125 Patients with cT1-2N0 Squamous Cell Carcinoma of the Oral Tongue

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[ABSTRACT] **BACKGROUND & OBJECTIVE:** The treatment pattern for cT1-2N0 squamous cell carcinoma (SCC) of the oral tongue is controversial; the postoperative recurrence rate of the disease is high and the salvage effect is poor. This study was to explore the postoperative recurrence-related factors of cT1-2N0 SCC of the oral tongue, to analyze their effects on the survival, and to seek more reasonable therapeutic modality. **METHODS:** Clinical data of 125 patients with cT1-2N0 SCC of the oral tongue, treated in Cancer Center of Sun Yat-sen University from Jan. 1992 to Dec. 2000, were reviewed. Of the 125 patients, 58 were at stage T1, 67 were at stage T2; 17 (13.6%) were treated with local operation alone, 53 (42.4%) were treated with both local operation and selective neck dissection, and 55 (44.0%) were treated with operation and chemotherapy and/or radiotherapy. The correlations of disease duration, tumor growth pattern, clinical TNM stage, pathologic grade, occult cervical lymphatic metastasis, tumor invasion depth, treatment methods and neck management to tumor recurrence and prognosis were analyzed. **RESULTS:** Forty-one (32.8%) patients had recurrence; the overall 5-year survival rate was 62.59%. The 5-year survival rate was significantly lower in recurrent group than in non-recurrent group (38.74% vs. 74.69%, log-rank=19.27, $P<0.001$). Disease duration (χ^2 test, $P=0.002$), tumor growth pattern (χ^2 test, $P<0.001$), neck management (χ^2 test, $P<0.001$) and occult cervical lymphatic metastasis (Cox regression, $P=0.001$) were significantly related to the recurrence of cT1-2N0 SCC of the oral tongue. Tumor invasion depth (Cox regression, $P=0.005$) and the site of recurrent tumor (Cox regression, $P<0.001$) were significantly related to the prognosis of cT1-2N0 SCC of the oral tongue. **CONCLUSION:** Disease duration, tumor growth pattern, neck management, and occult cervical lymphatic metastasis are main recurrent factors of cT1-2N0 SCC of the oral tongue; tumor invasion depth and the site of recurrent tumor are important prognostic factors.

KEYWORDS: Tongue neoplasm; Squamous cell carcinoma; Tumor recurrence; Multivariate analysis

1. Introduction

Treatment of cT1-2N0 squamous cell carcinoma of the oral tongue is still controversial. The postoperative recurrence rate is high, while the salvage effect is poor. Recurrence is the major factor influencing the prognosis of the carcinoma. By retrospectively analyzing the clinical data of 125 cases with cT1-2N0 squamous cell carcinoma of the oral tongue between Jan. 1992 and Dec. 2000, we aimed to analyze the postoperative recurrence-related factors of cT1-2N0 squamous cell carcinoma

of the oral tongue, compare the influences of various factors, and investigate more reasonable therapeutic measures.

2. Materials and Methods

2.1 Study subjects and inclusion criteria

In total 125 patients initially treated in Tumor Center of Sun Yat-sen University, from Jan. 1st, 1992 to Dec. 31st, 2000 were enrolled. All the patients were pathologically diagnosed as squamous cell carcinoma of the tongue, and the inclusion criteria were as follows: (1) Patients of stage cT1-2N0 (TNM staging adopted the UICC staging method in 2002). (2) The primary focus was located in the oral tongue (including the lateral tongue margin, the tongue tip, the dorsum of the tongue or the ventral part of the tongue). (3) All were initially treated patients, whose primary focuses were radically dissected. (4) All patients had complete clinical data, and the follow up period was more than 5 years.

2.2 Judgment of the tongue carcinoma with negative cervical lymphatic metastasis

According to the standard reported [1], the following conditions were considered as cN0: (1) No enlarged lymph node was touched in the cervical region, or the patient had movable enlarged lymph nodes or soft lymph nodes, or lymph nodes with a diameter<1.0cm. (2) Imaging examination (CT, MRI, ultrasonic B) did not find enlarged lymph nodes, or found the lymph node with the maximal diameter <1.0cm, or the maximal diameter of the lymph node was<1.5cm, but without central necrosis, without marginal strengthening, or without disappearance of the fat space around the lymph nodes, and so on. (3) Judgment should be made based on palpitation if no imaging data were available.

2.3 Clinical data

The onset ages of 125 cases were 21-87 years old, with a median age of 52 years. There were 72 males (57.6%) and 53 females (42.4%); 58 cases of stage T1N0, and 67 cases of T2N0. There were 22 cases (17.6%) of exophytic type, 34 cases (27.2%) of ulcerative type, 29 cases (23.2%) of infiltrating type, and 40 cases (32.0%) of mixed type (ulcerative and infiltrating types).

2.4 Treating method

(1) The primary focus was treated with semi-tongue dissection. The carcinoma was dissected from 1cm away from the focus judged by naked eyes, and wedge resection was performed if the carcinoma was located in the tongue tip. (2) Supraomohyoid neck dissection (dissection of lymph nodes in area Ⅰ-Ⅲ) and complete cervical lymph node dissection (lymph nodes in area Ⅰ-Ⅴ) were performed. The latter dissection included the functional cervical dissection and typical cervical dissection. Lateral cervical dissection was performed to patients with the primary focus located along the tongue margin, and cervical lymph nodes of both sides should be dissected if the primary focus was involved in the middle line.

Seventeen cases (13.6%) were performed with semi-tongue dissection, 27 cases (21.6%) with semi-tongue dissection plus supraomohyoid lymph node dissection, 11 cases (8.8%) with semi-tongue dissection plus functional cervical dissection, and 15 cases (12.0%) with semi-tongue dissection plus classic cervical dissection. In addition, 55 cases received the comprehensive treatment. Among these patients, 30 cases had preoperative chemotherapy, 5 cases had postoperative chemotherapy, 14 cases had postoperative radiotherapy, and 6 cases had preoperative induction chemotherapy and postoperative supplementary radiotherapy. ^{60}Co or accelerator linear was used in radiotherapy. The dose was 40-70 Gy for the primary focus and the cervical region, 60-70 Gy for the primary focus of patients with positive incision margins, and 40-60 Gy for the cervical region of patients with occult lymphatic metastasis. The chemotherapy scheme was a single drug treatment of pingyangmycin (a total dose of 160-240mg) or fluorouracil plus cis-platinum, pingyangmycin (or bleomycin) for 1-3 therapeutic courses. Five cases were performed wedge resection in the tongue tip, which were included in the semi-tongue dissection group due to the limited number. All the patients were performed lymph node dissection on one side.

2.5 Statistical analysis

SPSS10.0 software was used to perform statistical analysis. Survival rate was calculated by using the longevity table. Log-rank test of Kaplan-Meier method was used to compare survival rates. Chi square test was used for single factor analysis, and Cox model for multiple factors analysis. $P<0.05$ was set as the

statistical significance level.

3. Results

3.1 Recurrence and survival

Of 125 cases, 41 cases had recurrent carcinomas, and the total recurrent rate was 32.8%. There were 12 cases (9.6%) with a single recurrent carcinoma in the tongue tip, 26 cases (20.6%) in the neck, three cases (2.4%) in the neck and the tongue. The results of single factor analysis are shown in Table 1. In total 47 patients died. Among them, 35 died of tongue carcinoma, 8 died of other diseases, and 4 cases died of the second primary carcinoma. The total 3- and 5-year survival rates were 69.67% and 62.59%. The survival curve is shown in Figure 1. The 3- and 5-year survival rates were 43.90% and 38.74%, respectively in the recurrent group, 82.72% and 74.69% in the non-recurrent group (P<0.001).

Table 1 Univariate analysis of postoperative recurrence-related factors for the 125 patients with cT1-2N0 squamous cell carcinoma of the oral tongue

Variable	Cases	Recurrence [cases(%)]	P value
Disease duration			
≤6 months	86	20(23.3)	
>6 months	39	21(53.8)	<0.001
Tumor growth pattern			
Growth out	22	2 (9.1)	
Ulcered	34	9(26.5)	
Infiltrative	29	19(65.5)	
Ulcered and infiltrative	40	11(27.5)	<0.001
T stage			
T1	58	18(31.0)	
T2	67	23(34.3)	0.696
Differentiation grade			
Well	90	25(27.8)	
Moderate	30	14(46.7)	
Poor	5	2(40.0)	0.067
Occult cervical lymphatic metastasis			
Positive	14	6(42.9)	
Negative	111	35(31.5)	0.040
Lingualis infiltration			
Yes	89	31(34.8)	
No	36	10(27.8)	0.112
Treatment pattern			
Only surgery	70	22(31.4)	
Combined	55	19(34.5)	0.713
Neck management			
Observation	17	10(58.8)	
SOHND	27	8(29.6)	
FND	11	2(18.2)	
RND	15	2(13.3)	<0.001

SOHND, supraomohyoid neck dissection; FND, functional neck dissection; RND, radical neck dissection.

3.2 Influence of occult cervical lymph node metastasis on recurrence

Fourteen cases (2 cases of T1 and 12 cases of T2) found lymph node metastases were confirmed by pathological examination after operation. The metastatic sites were all limited to area Ⅰ-Ⅲ of the neck on the same side, without metastasis to the cross side. The metastatic rate of the occult lymph nodes was 11.2% (14/125). The metastatic rate was 3.5% (2/58) for the occult lymph node in T1 patients, and 17.9% (12/67) in T2 patients (P<0.01). During the follow up, among the 14 cases with occult lymph node metastasis, six cases had recurrence in the cervical lymph node (6/14). The 5-year survival rates of the patients with or without lymph node metastasis were significantly different (P=0.032) (Figure 2).

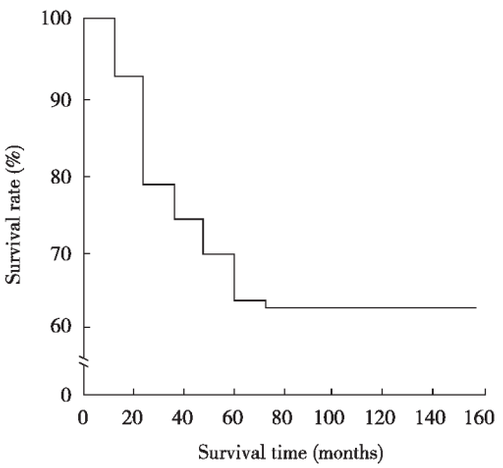

Figure 1 Overall survival curve of the 125 patients with stage cT1-2N0 squamous cell carcinoma of the oral tongue

3.3 Influence of tumor invasion depth on recurrence

Pathological examination after operation indicated that, the recurrence rate was 34.8% (31/89) and 27.8% (10/36) for patients with or without myometrial invasion (P<0.05). The 5-year survival rates of patients in the two groups were 85.29% and 54.55% ($log\text{-}rank$=9.13, P=0.002) (Figure 3).

3.4 Relevant factors affecting the prognosis of

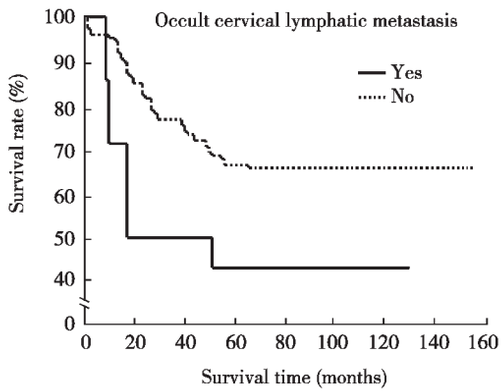

Figure 2 Survival curves of the patients with or without occult cervical lymphatic metastasis

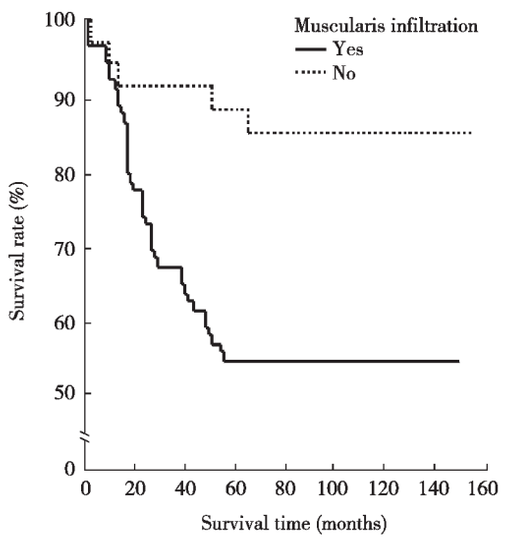

Figure 3 Survival curves of the patients with or without muscularis infiltration

patients with cT1-2N0 squamous carcinoma of oral tongue

The recurrence sites included the primary focus, the cervical lymph node, the primary focus and the lymph node. Invasion depth and the recurrence site could affect the prognosis (Table 2).

4. Discussion

The recurrence rate was high for patients with the disease of more than 6 months, or patients having myometrial invasion or occult cervical lymph node metastasis, or patients who received pure semi-tongue dissection. The recurrence rate was not related to T stages, differentiation degrees and therapeutic schemes. Currently, the therapy of cT1-2N0 tongue squamous cell carcinoma is controversial.

4.1 Relationship between occult cervical lymph node metastasis and carcinoma recurrence

It was reported that, the occult lymphatic metastasis rate of cT1-2N0 tongue squamous cell was 10%-40%; and the metastatic rate of T1 was higher than that of T2 [2-4]. In this study, the occult lymphatic metastasis rate was 11.2% (14/125). The recurrence rate was 42.9% and 31.5% in the groups with or without occult lymphatic metastasis (P=0.040); and the 5-year survival rates between the two groups were different (P=0.032); there were significant differences in occult lymphatic metastasis rates between T1 and T2 patients (P<0.001). The survival rate of the patients was significantly affected by the occult lymphatic metastasis, therefore we believe that it is necessary to perform cervical dissection for T2 patients.

Studies have demonstrated that for patients with occult lymphatic metastasis, the recurrence rate could be decreased and the survival rate could be improved when patients were administrated with auxiliary post-operative radiotherapy [3-6]. Indications of post-radiotherapy include the following conditions: (1) more than two metastatic lymph nodes are confirmed in post-operative pathological examination, (2) having two or

Table 2 Multivariate Cox regression analysis of postoperative recurrence-related factors in the 125 patients with cT1-2N0 squamous cell carcinoma of the oral tongue

Variable	B	SE	Wald	*P*	Exp(B)	95% CI
Sex	−0.179	0.329	0.297	0.586	0.836	0.439−1.592
Disease duration	−0.578	0.449	1.656	0.198	0.561	0.233−1.353
Tumor growth pattern	0.220	0.170	1.681	0.195	1.247	0.893−1.740
Site	0.229	0.244	0.881	0.348	1.257	0.780−2.028
T stage	0.312	0.334	0.877	0.349	1.367	0.711−2.627
Treatment pattern	−0.009	0.105	0.008	0.929	0.991	0.807−1.216
Differentiation	0.298	0.297	1.006	0.316	1.347	0.753−2.410
Tumor invasion	1.412	0.499	8.009	0.005	4.104	1.543−10.910
Occult cervical lymphatic metastasis	0.766	0.422	3.293	0.070	2.151	0.941−4.920
Site of recurrence	0.588	0.167	12.479	0.000	1.801	1.299−2.496

more than two metastatic areas, (3) with vascular invasion. It was also reported that, for patients with occult lymphatic metastasis in the cervical area, the death risk was still not lowered although auxiliary radiotherapy was performed after operation [2]. Our data showed that, among the four cases who received auxiliary radiotherapy after operation, three cases had recurrent carcinoma; while among the 10 cases received no auxiliary radiotherapy, three of them had recurrent carcinoma. Patients with recurrent carcinoma all died, and the survival rate was not improved. Therefore, parallel radiotherapy and chemotherapy might improve prognosis of patients who have post-operative radiotherapy indications.

4.2 Relationship between the operative method and recurrence

At present, the treatment of patients with cT1-2N0 tongue squamous carcinoma is controversial. There are mainly two theories, one of which is that selective cervical dissection or selective radiotherapy in the cervical area should be performed [2, 7, 8]; the other one is that the cervical area should be observed, and salvage therapy should be performed when cervical lymphatic metastasis is observed [5]. In our study, 26 cases were performed classic cervical dissection and two of them had recurrent carcinoma, all of which were recurrence of the primary focus; 17 cases were performed functional cervical dissection and two of them had recurrent carcinoma, all of which were recurrent cervical nodes; 43 cases were performed supraomohyoid neck dissection and 8 cases had recurrent carcinoma, 7 of which had recurrent cervical lymph node, and 1 had recurrence of the primary focus. The recurrence rates of the pure semi-tongue dissection group and semi-tongue dissection plus cervical dissection group were 58.9% (10/17) and 22.6% (12/53) (P =0.005); but there was no significant difference in the survival rate (P>0.05). Among the patients with recurrent carcinoma, 24 cases underwent cervical dissection and (or) cervical radiotherapy and only 8 cases were saved, a successful rate of 33%. The recurrence of the regional lymph node was the most common reason for the failure of operation. The successful rate of salvage treatment was low when cervical lymphatic metastasis occurred. But selective cervical dissection could obviously lower the recurrence rate of the regional lymph node and the subsequent death, thus to improve the total survival rate [6, 7]. Therefore, we advocate that selective cervical dissection should be performed on patients with cT1-2N0 tongue squamous cell carcinoma, thus to improve the control rate over the cervical site. There was no significant difference among the squamous cervical dissection group, the functional cervical dissection group and the classical cervical dissection group (P>0.05). Therefore, we believe that the selective cervical dissection area should be area Ⅰ-Ⅲ, and the operation is supraomohyoid neck dissection.

4.3 Relationship of myometrial invasion and recurrence

It is believed in relevant studies that, the tumor free survival rate of patients with the depth of tumor invasion less than 4mm is obviously superior to that of the patients with the depth of tumor invasion more than 4mm. At the same time, if the occult lymphatic metastasis is also low, selective cervical dissection could significantly improve the survival rate of patients with the depth of tumor invasion more than 4mm [2, 4, 5, 9]. Yamamoto *et al.* [10] proposed that, when the tumor had a distinctive border, the host may have a stronger resistance to the tumor cells; and the tumor resistance was weak when the tumor grew diffusedly. Especially for the small mass or single cellular carcinoma, the front growing cells could enter the lymphatic system more easily to form a metastatic focus. Our study indicated that, whether the muscular layer was invaded or not would not affect the recurrence rate significantly. Though we did not accurately measure the invasion depths of the carcinoma, there was significant difference in the 5-year survival rate between the two groups (P=0.002). Therefore, we believe that selective cervical dissection should be performed on patients with myometrial invasion; and the time to perform selective cervical dissection is 8-12 weeks after operation on the primary focus [5].

4.4 Recurrent time

Yuen *et al.* [11] reported that, the average recurrent time for patients with tongue squamous cell carcinoma of the early phase was 6 months; and 90% of the patients had recurrent carcinoma within 20 months. In our study, the average recurrent time was within 21 months (1-141 months) and 28 cases (68%) had recurrent carcinoma within 20 months, suggesting that 2 years after operation on tongue squamous cell carcinoma is the risky period for recurrence. Therefore, we

recommend that patients with cT1-N0 tongue squamous cell carcinoma should be closely followed up within 2 years after operation.

In summary, patients with cT1No tongue squamous cell carcinoma should be closely followed up, once for every 2 months within 2 years after operation [5]. For patients with the depth of tumor invasion larger than 4mm or with myometrial invasion, selective cervical lymphatic dissection should be performed; and the range for cervical lymphatic dissection is area Ⅰ-Ⅲ, namely the supraomohyoid neck dissection.

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