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Clinical Research Paper

Survival analysis of 229 patients with advanced squamous cell carcinoma of the oral tongue

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Key words: oral carcinoma, squamous cell carcinoma, tongue, survival analysis, prognosis

Background and Objective: Patients with advanced squamous cell carcinoma (SCC) of the oral tongue have poor prognosis. This study analyzes the most important factors affecting the prognosis of the patients with advanced (stage III and IV) SCC of the oral tongue. Methods: Complete clinical and follow-up data of 229 patients with pathologically confirmed advanced SCC of the oral tongue, initially treated at Sun Yat-sen University Cancer Center were retrospectively analyzed. Survival analysis was performed using the Kaplan-Meier analysis, comparisons among groups were analyzed using a log-rank test, and multivariate analysis was conducted using the Cox proportional hazard model. Independent risk factors were deducted. The risk function was established and evaluated. Results: The mean survival time of the 229 patients was 80.33 months, with the two- and five-year survival rates at 50.66% and 37.99%, respectively. Univariate analysis showed that age, tongue base invasion, cervical lymphatic metastasis, stage, surgical treatment, recurrence and residual tumor were risk factors affecting prognosis ($p < 0.05$). Multivariate analysis indicated that tumor invasion across the midline, cervical lymphatic metastases, surgical treatment, recurrence and residual tumors were independent factors for prognosis. Moreover, the risk function effectively predicted the prognosis. Conclusions: The prognosis of patients with advanced SCC of the oral tongue is poor. Tumor invasion across the midline, cervical lymphatic metastasis, surgical treatment, recurrence and residual tumor are independent factors affecting the prognosis.

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As compared to early stage carcinoma of tongue, the therapy for late stage carcinoma of tongue lacks standardization and the recurrence rate in local region is higher, resulting in poorer prognosis.[1-5] Currently, in terms of factors influencing the prognosis of late stage carcinoma of tongue, there are few reports. This research aims at investigating the most related clinical and pathological factors in influencing prognosis of the squamous cell carcinoma of tongue at late stage. This study will hopefully provide evidence for individualized therapy and prognostic assessment for patients with late stage squamous cell carcinoma of the tongue.

Patients and Methods

Studied subjects and selection criteria. Research subjects were the initially treated in our hospital from January 1985 to December 1999 and they were all diagnosed as squamous cell carcinoma. The selection criteria for this research was that patients were in stage III and IV. The staging was based on the TNM Staging Standard for Oral Carcinoma established by UICC in 2002. Patients who primarily received surgical treatment were classified accordingly to pathological staging, while those without surgical treatment were verified as having infiltrative locations of primary lesions and lymphatic metastases by imaging examinations (CT or MRI). Afterward, they were combined with pathological biopsies for final staging; (1) for patient with primary lesions at the active part of tongue; if the carcinoma was at the root of tongue, he or she would not be included in the study; (2) all patients would receive imaging examinations (ultrasound, CT or MRI) to verify the locations of primary lesions and the status of lymphatic metastases; (3) no sign of remote metastasis was discovered in any of the cases at the time of admission and during therapy; (4) all cases had complete clinical and pathological data, including sex, age, staging, status of treatment, therapeutic effect and recurrent state. The follow-up period for all patients was more than five years.

Clinical data. The age of onset for the 229 patients in the group were between 23 and 86 years old, with a medium value

of 54 years, 160 cases were male (69.87%) and 69 were female (30.13%). Tumors were all single incidence. Clinical manifestation showed as a hard mass in tongue. One hundred seven cases had violated the medial line and 74 cases had infiltration to the root of tongue. One hundred four infiltrated the bottom of the oral cavity, while 73 experienced limitation to motion of tongue. For the clinical staging, the following were included: 120 cases in stage III, 109 cases in stage IV; 129 cases in stage T1, 29 cases in stage T2, one case in stage T3, 70 cases in stage T4; 70 cases in stage N0, 129 cases in stage N1, 29 cases in stage N2 and one case in stage N3. For pathological classification there were 168 cases in stage I, 51 cases in stage II and 10 cases in stage III.

Treatment. Group—surgical treatment. The treatment for the primary lesion included the following: the tumor was removed with 1 to 2 cm of extra normal tissues around the lesion site under naked eyes; while partial, hemi- or total glossectomy (depending on the local status) was conducted on the diseased lateral tongue. The treatment for the neck region included the following: patients with negativity in lymph nodes were recommended for elective lateral neck dissection, with a range from, at minimum, region I to region III of the unilateral side. Patients with positive lymph nodes should receive radical lateral neck dissection, inclusive of region I to IV of the unilateral side. Before surgery, radiotherapy with dosage of 40 to 60 Gy should be used for patients who wished to save the function of tongue. After surgery, postoperative radiotherapy with dosage of 40 to 60 Gy should also be used for patients with nearly positive or positive lymph nodes metastases. The procedure could be either surgery at two weeks after radiotherapy or radiotherapy two weeks after surgery. Inductive radiotherapy was also used for patients who wished to save the function of tongue or patients who had difficulties with tumor resection, and the DBF proposal was primarily used. After drug administration, observation continued. If the tumor was discovered to shrink in size, then one more course of radiotherapy was performed before surgery. If the tumor showed no change or became malignant, immediate surgery would be performed instead.

In this study, there were 51 patients with simple surgical treatment and there were 120 patients who received comprehensive treatment with surgery as primary method. This included: 24 cases of surgery and radiotherapy; 39 cases of chemotherapy, surgery, and radiotherapy; and 57 cases of chemotherapy and surgery. According to the classification of surgical modalities, 171 cases underwent surgical resection of the primary lesion and neck dissection, which further involved 62 cases with neck dissection in selected regions (50 dissections in region I to III and 12 dissections in region I to IV) and 109 cases with complete neck dissection (including region I to IV). In the complete neck dissection, 45 cases were functional neck dissection and 64 cases were classical neck dissection. In all cases of neck dissection, 146 were unilateral neck dissection, while 25 were bilateral neck dissection.

Group—non-surgical treatment. For late stage patients who could not undergo surgery, based on the range of tumors as well as the bodily status and will of the patient, simple radiotherapy, simple chemotherapy, or comprehensive therapy with radiotherapy and chemotherapy could be given. There were 58 patients in this non-surgical treatment group, including four cases of simple radiotherapy, 23 cases of simple chemotherapy and 24 cases of comprehensive therapy with radiotherapy and chemotherapy. Seven patients refused treatment.

Treatment for recurrence of tumor. For cases of partial recurrence in the neck or recurrence of the primary lesion site, curative treatment was given, including resection of the primary lesion site, the neck dissection, palliative radiotherapy or chemotherapy.

Follow-up time and method. Follow-up information came from telephone interviews and re-examinations in the outpatient department. The follow-up time started on the date of confirmed diagnosis and ended in June 2006.

Statistical analysis. SPSS 10.0 software was used for statistical analysis. Chi-square test was used for nominal data. The Kaplan-Meier method and logrank test were respectively used for survival rate and single-factorial survival analysis. Cox regression analysis was performed for multi-variance analysis. Statistical significance was indicated by $p < 0.05$.

Results

Results of follow-ups. Until the last follow-up in June 2006, 64 patients survived and 158 died, while six were lost to follow-up. The follow-up time lasted from 60 to 198 months, with a medium time of 109 months. In the 158 cases of death, 152 patients died of disease related to tumor. As for the six patients lost to follow-up, the follow-up times were over five years.

Survival rate. In this study, the overall average survival time for patients with advanced squamous cell carcinoma of tongue was 80.33 months. For the survival statuses of these 229 patients with advanced squamous cell carcinoma of tongue (Fig. 1). The two year and five year survival rates were respectively 50.66% (116/229) and 37.99% (87/229). The two year and five year survival rates for the patients in stage III were significantly higher than those of the patients in stage IV ($x^2 = 4.982$, $p = 0.026$). (Table 1 and Fig. 2).

The two year survival rates of the patients who received the following, surgery + radiotherapy, chemotherapy + surgery + radiotherapy, chemotherapy + surgery, and simple surgery, were 56.86%, 71.93%, 50.00% and 51.28%, respectively. There was no statistical significance in the differences ($x^2 = 3.998$, $p = 0.263$).

Single factorial analysis. Possible factors influencing the prognosis of advanced squamous cell carcinoma of tongue include sex, age, infiltration to medial line, infiltration to the root of tongue, infiltration to the bottom of oral cavity, lymphatic metastasis, pathological type, staging, pathological classification, surgical treatment, recurrence or residual tumor and the year of case. Single-factorial analysis was performed for these factors. Kaplan-Meier analysis and log-rank test were used. Variable factors with statistical significance included the following: age, infiltration to the root of the tongue, lymphatic metastasis, staging, surgical treatment, recurrence or residual tumor. For the complete detailed results of single factorial analysis (Table 2 and Figs. 3–5).

Multi-variance analysis. Using variable factors with statistical significance obtained from single factorial analysis and other possible clinically influencing factors, all were included in the

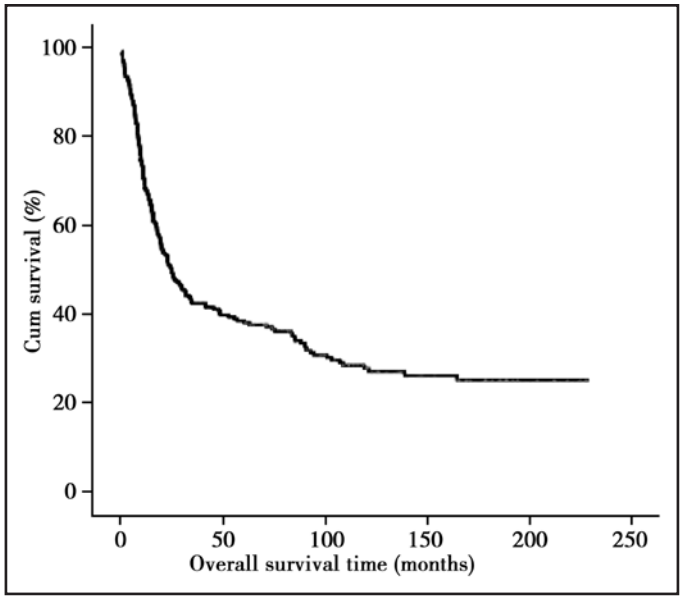

Figure 1. The survival curve of 229 patients with advanced squamous cell carcinoma of the oral tongue.

Table 1 **The 1-, 2-, 3- and 5-year survival rate of stage III and IV squamous cell carcinoma of the oral tongue**

Stage	Survival rate (%)			
	1-year	2-year	3-year	5-year
Ⅲ	70.83[a]	55.83[a]	50.83[a]	45.83[a]
Ⅳ	65.14	44.95	33.03	30.28
Total	68.12	50.66	42.36	37.99

[a]$p < 0.05$, vs. stage III.

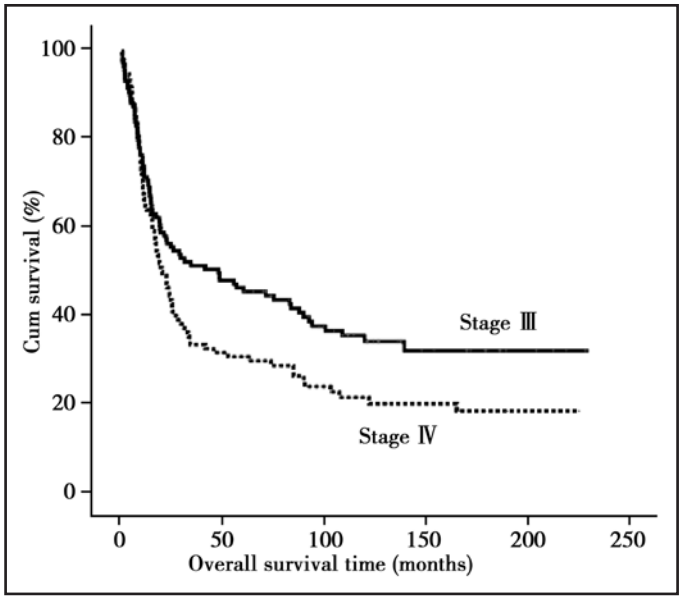

Figure 2. Survival curves of patients with stage III or stage IV squamous cell carcinoma of the oral tongue.

Table 2 **Univariate analysis of survival of 229 patients with advanced squamous cell carcinoma of the oral tongue**

Variable	Cases	Survival rate (%)		*P* value (log-rank)
		2-year	5-year	
Gender				0.457
Female	160	48.75	38.13	
Male	69	55.07	39.13	
Age (years)				0.036
<40	43	55.81	48.84	
≥40	186	49.46	36.02	
Invasion across the midline of the tongue				0.232
No	152	55.14	43.93	
Yes	72	46.72	33.61	
Tongue base invasion				0.010
No	155	55.48	42.58	
Yes	74	40.54	29.73	
Invasion of mouth floor				0.855
No	180	51.11	37.78	
Yes	49	48.98	40.82	
Mandibular invasion				0.331
No	217	50.69	38.71	
Yes	12	50.00	33.33	
Lymphatic metastasis				0.014
No	70	62.86	52.86	
Yes	159	45.28	28.95	
Extent of the tumor				0.065
T1–2N1	34	55.88	41.18	
T1–2N2, T1–2N3, T3–4N2, T3–4N3	32	31.25	25.00	
T3–4N0	163	53.37	41.92	
Stage				0.026
Ⅲ	120	55.83	45.83	
Ⅳ	109	44.95	30.28	
Histology				0.323
G1	168	52.98	40.48	
G2 or G3	61	44.26	32.79	
Surgical treatment				0.000
No	58	24.14	15.52	
Yes	171	59.65	45.61	
Recurrence or residual tumor				0.000
No recurrence or residual tumor	65	76.47	62.75	
Recurrence	104	21.67	16.67	
Residual tumor at the first treatment	60	37.31	20.90	
Treatment time				0.089
1985 Jan.–1989 Dec.	85	47.06	37.65	
1990 Jan.–1994 Dec.	67	62.69	49.25	
1995 Jan.–1999 Dec.	77	49.16	39.87	

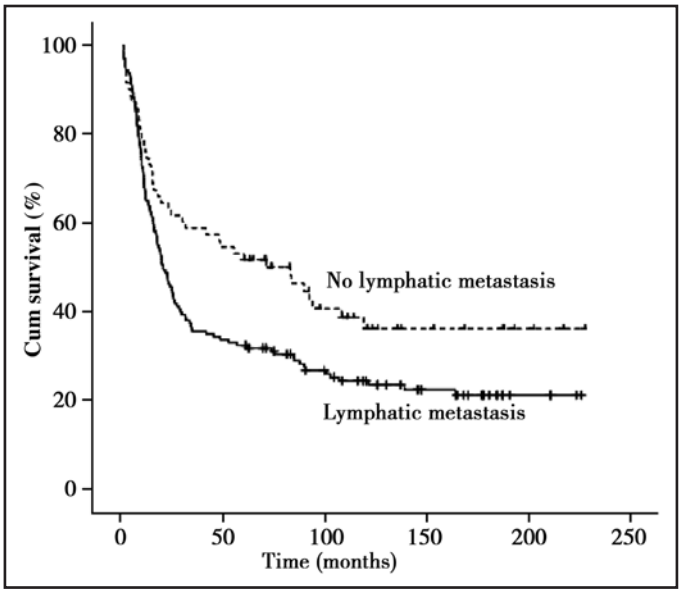

Figure 3. Overall survival curves of patients with advanced squamous cell carcinoma of the oral tongue with or without lymphatic metastasis.

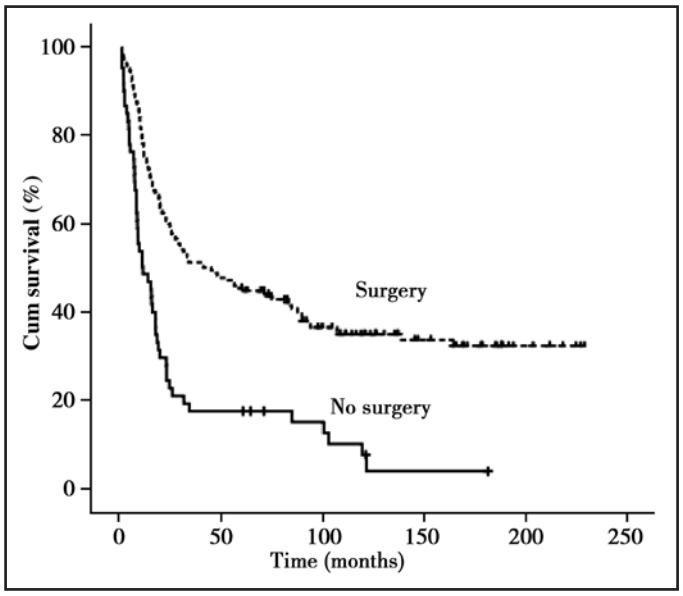

Figure 4. Overall survival curves of patients with advanced squamous cell carcinoma of the oral tongue treated by different modes.

multi-variance analysis—Cox regression analysis. For the results, please see Table 3. The p-values for the four factors, infiltration to medial line, lymphatic metastasis, surgical treatment and residual tumor or recurrence, were 0.012, 0.044, 0.003 and 0.000, respectively. Also, the p-value of the factor—infiltration to the root of tongue, was 0.086, closer to 0.05.

The prognostic risk-predictive function and reliability analysis. The prediction model of postoperative survival in case of advanced carcinoma of the tongue was established as $h\ (t,x) = h0\ (t)$ exp $(0.297X_1 + 0.439X_2 + 0.411X_3 - 0.562X_4 + 1.013X_5)$ and this model was verified by systemic ROC testing (Area = 0.726, p = 0.000). This model could be regarded with statistical significance. According to the established prognostic predictive model for cases of advanced carcinoma of tongue, the equation for acquired prognostic index (PI) was PI = $0.297X_1 + 0.439X_2 + 0.411X_3 - 0.562X_4 + 1.013X_5$, where PI < 0 was classified as low-risk group, 0–1.3 was the medium-risk group and PI > 1.3 was the high-risk group. For each patient, his or her PI-value was calculated and based on the results, the 229 patients were placed into three groups. The survival rates of the groups were calculated. The five year survival rates of the three groups were 69.4%, 35.0% and 19.5%, respectively. By logrank test, there was statistical significance among the survival rates of the three groups ($x^2 = 38.308$, p = 0.001). For the functional curve of risk for each group, please see Figure 6.

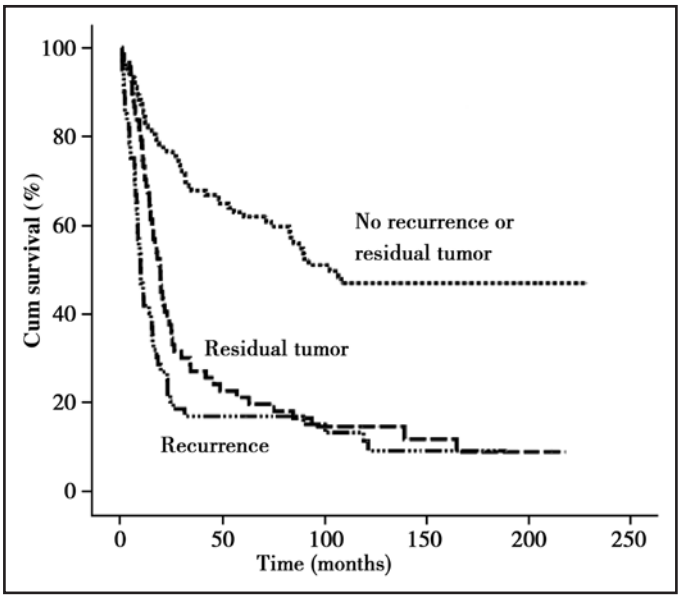

Figure 5. Overall survival curves of patients with advanced squamous cell carcinoma of the oral tongue with or without residual tumor or recurrence in the first treatment.

Discussion

In 229 cases of advanced squamous cell carcinoma of tongue, the average survival time was 80.33 months. The two-year and five-year survival rates were 50.66% and 37.99%, respectively. The two-year and five-year survival rates for carcinoma of tongue in stage III were higher than in stage IV ($p < 0.05$). In the survival curve in Figure 1, the survival curve within two years rose in a steep slope, meaning that most patients died within two years of the initial treatment. The result was in accordance to the reported.[1,2]

In the late stages of carcinoma of the tongue, the tumor can infiltrate the medial line or the root of tongue, as well as mandibular lingual membrane or cortex. The results of this study show that infiltration to the medial line was the primary factor influencing prognosis of patients with advanced carcinoma of tongue. The reason was possibly due to the fact that once the primary lesion site infiltrated the medial line, due to enlargement of tumor, the initial treatment could rarely achieve effective results without residual

Table 3 **Cox regression analysis of patients with advanced squamous cell carcinoma of the oral tongue**

Variable	B	SE	Wald	*P*	Exp(B) 95.0% CI
Tongue base invasion X1	0.297	0.173	2.957	0.086	1.346(0.959–1.889)
Invasion across the midline of the tongue X2	0.439	0.174	6.341	0.012	1.551(1.102–2.182)
Lymphatic metastasis X3	0.411	0.204	4.052	0.044	1.508(1.011–2.249)
Surgical treatment X4	−0.562	0.189	8.806	0.003	0.570(0.394–0.826)
Recurrence or residual tumor X5	1.013	0.192	27.896	0.000	2.753(1.891–4.009)

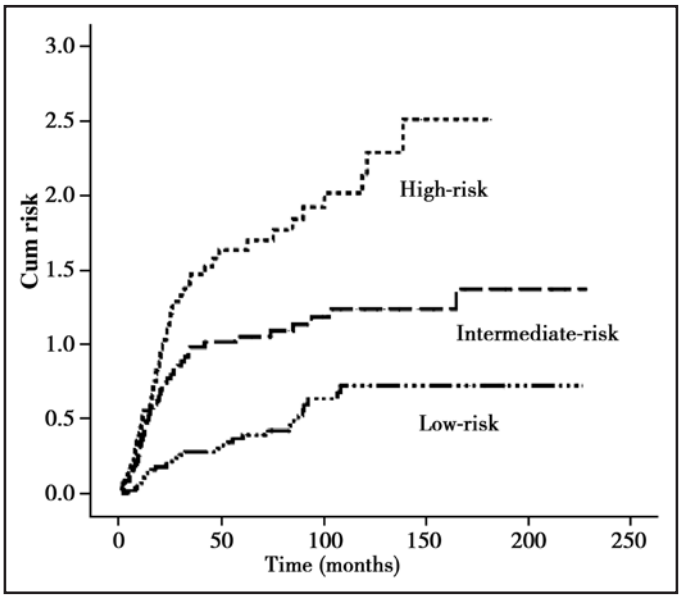

Figure 6. Curves of the risk function for patients with advanced squamous cell carcinoma of the oral tongue.

tumors. Although in the single factorial analysis, which showed the survival rate of patients with infiltration to the root of tongue by primary lesion site lower than that of the patients without such infiltration ($p < 0.05$), the p-value of such factor was revealed to be 0.086, closer to 0.05, in the multi-variance analysis. It was possibly the most important factor in influencing prognosis. The reason is when a tumor infiltrates the root of tongue, due to the limitation of anatomical prerequisites, it is more difficult to perform resection, and thus, there are more likely to be residual tumors at the edge of surgical resection. In addition, when the carcinoma infiltrates the root, the metastatic rate to lymph node also significantly rises. Therefore, the lowered survival rate in squamous cell carcinoma of tongue which infiltrates the root of tongue is possibly due to the status of sthe urgical edge and lymphatic metastasis in neck. There is research indicating that the recurrence rate is higher in patients with infiltration to the mandible or poorly differentiated tumors and these patients usually have poor prognosis as well.[1,4,5-7] However, our study concluded otherwise, which was possibly due to unbalanced mixed factors among groups.

Lymphatic metastasis in the neck is an important factor for influencing the prognosis of squamous cell carcinoma of the tongue. The survival rate in patients with negative lymphatic metastasis in neck was much higher than that of patients with positive results. In patients with positive lymphatic metastases, prognostic outcome was much worse in latter of stage N.[3-5] In 229 cases of advanced squamous cell carcinoma of tongue, inclusive of 70 cases of no lymphatic metastasis and 159 cases of lymphatic metastasis, the five year survival rates were 45.28% and 28.95%, respectively ($p = 0.012$). It could be assumed that lymphatic metastasis was an important influential factor for prognosis. Yang Kai et al.[6] in the research of carcinoma of tongue also believed that lymphatic metastasis was the important influential factor for prognosis because the recurrence rate was higher in patients with metastasis and they had poorer prognostic outcome. Therefore, for patients of squamous cell carcinoma of tongue with palpable lymph nodes, radical neck dissection of lymph nodes was recommended. Because current method for diagnosing the existence of lymphatic metastasis in patients of stage N0 is still difficult to confirm before surgery, there are reports that patients in stages T3 and 4N0 have higher lymphatic metastatic rate, which is approximately around 20 to 40%. They are usually recommended to undergo simultaneous elective neck dissection of lymph nodes in order to prevent recessive metastasis in the neck.[7-9]

In this group, the five-year survival rate in cases of comprehensive therapy with surgery as the primary approach is much higher than the non-surgical group (45.61% vs. 15.52%). Single factor analysis and multi-variance analysis all showed that comprehensive therapy with surgery as the primary approach was an independent factor for influencing prognosis. (During case selection in this study, because of incompleteness in the clinical and pathological data, patients with non-surgical treatment were not included, and thus, the sample size was relatively smaller.) The rate of complete remission for the initial treatment in the surgical group was 92.40% (168/171). These patients were in four surgical groups: surgery + radiotherapy, chemotherapy + surgery + radiotherapy, chemotherapy + surgery, and simple surgery. However, these survival rates had no statistical significance ($p = 0.263$). This study was not able to prove the effects of chemotherapy and radiotherapy in improving prognostic outcome.

The scope of infiltration in the group of non-surgical treatment was too large. The probability of surgical resection was remote; moreover, patients might be surgically less tolerant, where chemotherapy or/and radiotherapy might became the primary approach. The state of no residual tumor by initial treatment was only achieved in 18.96% of the cases (11/58). The rate of residual tumor after initial treatment was an important influential factor for the prognosis of patients with late stage squamous cell carcinoma of the tongue.

The existence of residual tumors and the recurrence of tumors after the initial treatment are also important factors in influencing prognosis.[10-12] In this study, the five year survival rates in cases with no residual tumor after initial treatment (the radical group) and cases with residual tumor (non-radical group) were 46.15% and 21.67%, respectively. Multi-variance analysis showed the presence of residual tumors was an independent factor influencing prognosis and most scholars support this notion.[4,9,12] Therefore, motivated treatment of the primary lesion site and the regionalized metastatic site in order to ensure no residual tumors after initial treatment is the primary treatment principle for controlling advanced squamous cell carcinoma of tongue. Comprehensive therapy with surgery as a primary approach is the essential method for doing so.

Prognostic factors, which are screened out by the Cox model, can be used to establish a PI model and has important clinical significance. It can ideally assess the risk of death and predict prognosis. In this study, when using the PI model in predicting the risk of death for patients of each group, the differences were significant and well-distributed. They have good applicational value.

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