

A Clinical Study of Oral Tongue Cancer

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TATEDA, M., SHIGA, K., SALJO, S. and YOKOYAMA, J. *A Clinical Study of Oral Tongue Cancer.* Tohoku J. Exp. Med., 2000, **192** (1), 49–59 — Thirty-nine previously untreated patients with squamous cell carcinoma of the oral tongue treated with curative intent in our hospital from 1993 through 1998 are reviewed. Of these patients, those in the early stage (stages I and II) constituted 64%. The over all 5-year survival rate of all the patients was 60%. The 5-year survival rate of the patients with early stage cancers was unsatisfactory (stage I: 73%; II: 56%). This was thought to be related to the absence of elective neck dissection and the administration of chemotherapy in the patients with early stage cancer. We concluded that elective neck dissection for levels I, II and III is the first choice of treatment strategy for patients with stage II cancer. Our data indicate that chemotherapy in patients with early stage cancer was not beneficial and might have increased the risk of late lymph node metastasis in the clinically N0 patients without neck dissection. There were 9 patients younger than 40 years of age and their survival rate at 5 years was 80%, which was better than that of the older patients. The treatment strategy for patients younger than 40 years of age was similar to that of older patients. ——— tongue cancer; elective neck dissection; young adult © 2000 Tohoku University Medical Press

Although oral tongue cancer is a relatively common type of head and neck cancer, its treatment strategy has not been standardized. Especially in early stage cancer, there are many problems such as late cervical lymph node metastasis, distant metastasis, choice of therapy including brachytherapy and surgery, elective neck dissection, indications of pull-through methods and treatment of young adults. In our institution, oral tongue cancer has been mainly treated by surgery, and additional therapy has been conducted in the patients with advanced cancer. We analysed the problem in our treatment for patients with tongue cancer retrospectively, and here in discuss appropriate treatment strategies for such patients.

Received July 4, 2000; revision accepted for publication August 29, 2000.

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SUBJECTS AND METHODS

Thirty-nine patients with squamous cell carcinoma of the oral tongue treated with curative intent at our hospital for the first time from March 1993 through April 1998 were reviewed. We analysed the treatment method, results of treatment and survival rate. The stage of each patient was classified according to the Union International Control Cancer system (UICC 1987). Staging classification was mainly based on the histological findings (pTN). Patients who were diagnosed as having no lymph node involvement by physiological and radiological examination and who underwent no elective neck dissection were temporarily evaluated as pN0.

Details of the patients' characteristics are listed in Table 1. The patients consisted of 25 males and 14 females. The age of the patients ranged from 23 to 76 years with a mean age of 53.3 years. There were 9 adult patients younger than 40 years of age (23%). The primary site was located on the right side of the tongue in 19 patients and on the left side in 20 patients. Surgical specimens of all patients were confirmed as squamous cell carcinoma of the oral tongue by histological examination. Of these, 27 were well differentiated, 8 moderately differentiated, and 1 poorly differentiated; no definite confirmation of the grade of differentiation could be made in 3. Nine, 16, 8 and 6 patients were classified as stage I, stage II, stage III and stage IV, respectively. Patients in the early stage, i.e., stage I and stage II, constituted 64%. The pT classification was pT1 for 9 patients (23%), pT2 for 19 (49%), pT3 for 9 (23%), and pT4 for 2 (5%). The pN classification was pN0 for 29 (74%) patients, pN1 for 4 (10%), pN2a for 1 (3%), and pN2b for 5 (13%).

All patients underwent surgical resection of their primary tumors. Patients evaluated as N1 clinically underwent selective neck dissection, and patients clinically evaluated as worse than N2 underwent modified or radical neck dissection. Patients evaluated worse than pN2 were treated by postoperative irradiation. Chemotherapy was used for advanced cancers and a part of early cancers. Details of the treatment are shown in Table 2.

Survival time was measured from the initiation of treatment. Actual survival probabilities were calculated using the method of Kaplan-Meier, and comparisons of survival curves between all different subgroups were performed using the log-rank test and Wilcoxon's test. Statistical analysis was performed by the chi-square test.

RESULTS

The overall 5-year survival rate of all patients was 60%. Cause-specific survival rate was 64%. The overall survival rate at 5 years was 73% for patients with stage I cancer, 56% for those with stage II, 75% for those with stage III, and 25% for those with stage IV (Fig. 1). The survival rate of stage II patients was

TABLE 1. *Patients' profile and tumor characteristics*

Characteristics	Patients ($n = 39$)	
	n	%
Age (years)		
> 40	30	77
≤ 40	9	23
Sex		
Male	25	64
Female	14	36
Location		
Right	19	49
Left	20	51
Histological differentiation		
Well	27	69
Moderate	8	21
Poor	1	3
Unknown	3	8
Stage ^a		
I	9	23
II	16	41
III	8	21
IV	6	15
pT classification		
T1	9	23
T2	19	49
T3	9	23
T4	2	5
pN classification		
N0	29	74
N1	4	10
N2a	1	3
N2b	5	13

^aUICC (1987).

worse than expected. The 5-year survival rate by pT classification was 73% for patients with pT1 tumors, 59% for pT2, 55% for pT3, and 0% for pT4 (Fig. 2A). The 5-year survival rate by pN classification was 67% for patients with pN0 tumors, and 38% for patients with tumors worse than pN1. When we analysed the 5-year survival rate by the number of metastatic lymph nodes, it was 67% for the patients with no metastatic lymph nodes, 60% for those patients with one metastatic lymph node, and 0% for those with more than two metastatic lymph nodes (Fig. 2B). Disease recurred after surgical resection in 16 patients (41%)

TABLE 2. *Stage and treatment strategy*

Stage	<i>n</i>	Primary resection	Neck dissection	Chemotherapy	Radiation
I	9	9	1 ^a	1	0
II	16	16	5 ^b	8	0
III	8	8	8	7	1
IV	6	6	6	5	4

^a Clinical evaluation was T1N1.

^b Three patients were evaluated as T2N1 clinically. Two patients received elective neck dissection.

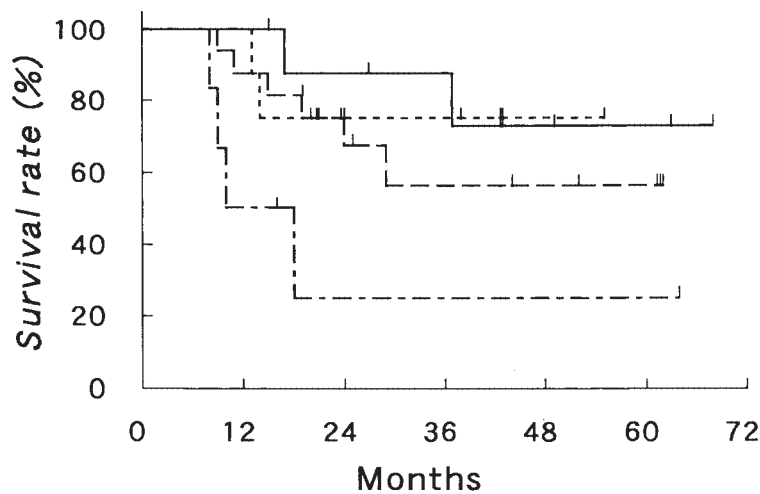


Fig. 1. Cumulative survival curves by stage classification. There was a significant difference between the 5-year survival rate of the patients evaluated as stage I and that of the patients evaluated as stage IV ($p < 0.05$).
 — stage I ($n=9$) 73%; - - - stage II ($n=16$) 56%; ···· stage III ($n=8$) 75%; - · - · stage IV ($n=6$) 25%.

between 1 and 46 months with a mean onset time of 6 months. There was local recurrence in 8 patients. Of these, 3 patients had only local recurrence, 4 suffered from both local and regional lymph node recurrence, and 1 patient experienced local recurrence, regional recurrence and distant metastasis. Regional recurrence occurred in 13 patients, alone in 8 patients (Fig. 3A). Fourteen patients died between 8 and 37 postsurgical months with a mean term of 17 months. Twelve patients died of oral tongue cancer whereas 2 patients evaluated as stage II died of other causes such as gastric cancer and sudden death (Fig. 3B). Deaths were due to local factors in 7 patients. Of these, 4 died of local factors alone, and one each died of local and regional factors, local factors and distant metastasis, and local, regional and distant metastasis, respectively. One patient died of regional factors alone. Distant metastasis occurred in 6 patients, and 4 of these died of distant metastasis alone. Three of these 4 patients were evaluated at the early stage at the time of the initial treatment. The metastatic lesions of these 6

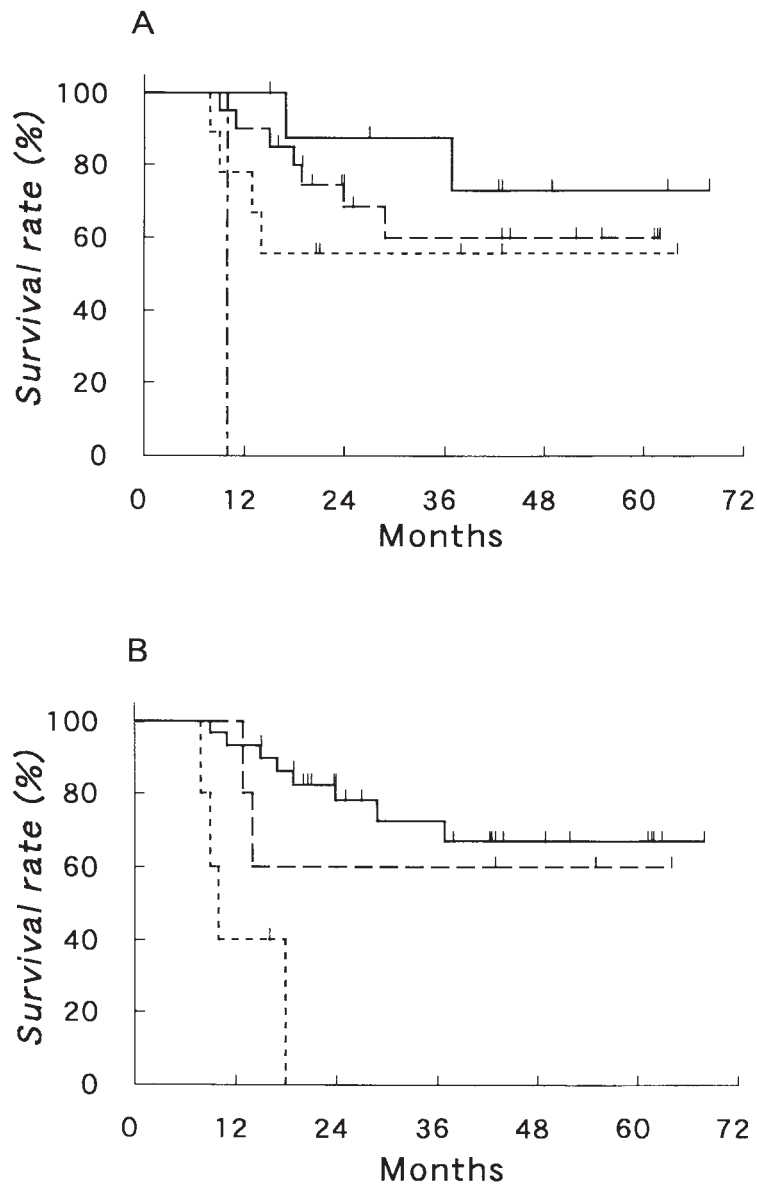


Fig. 2. A: Cumulative survival curves by pT classification. Survival rates of the patients with tumors was diagnosed as pT1 and pT2 were significantly higher than those of the patients with tumors was diagnosed as pT4 ($p < 0.01$).

— pT1 ($n=9$) 73%; --- pT2 ($n=19$) 59%; - · - · - pT3 ($n=9$) 55%;
 · · · · · pT4 ($n=2$) 0%.

B: Cumulative survival curves by number of metastatic cervical lymph nodes. Survival rate of the patients evaluated pN0, including clinically N0, was better than that of the patients who had 2 or more metastatic lymph nodes ($p < 0.01$).

— no metastatic lymph node ($n=29$) 67%;
 --- one metastatic lymph node ($n=5$) 60%;
 · · · · · 2 or more metastatic lymph nodes ($n=5$) 0%.

patients were lung metastasis in 4, bone metastasis in 2, and skin metastasis in 2. Second primary cancer occurred in 3 patients who developed metachronous gastric cancer, esophageal cancer and lung cancer, respectively.

We analysed tumor recurrence in early stage oral tongue cancer ($n=25$). Six

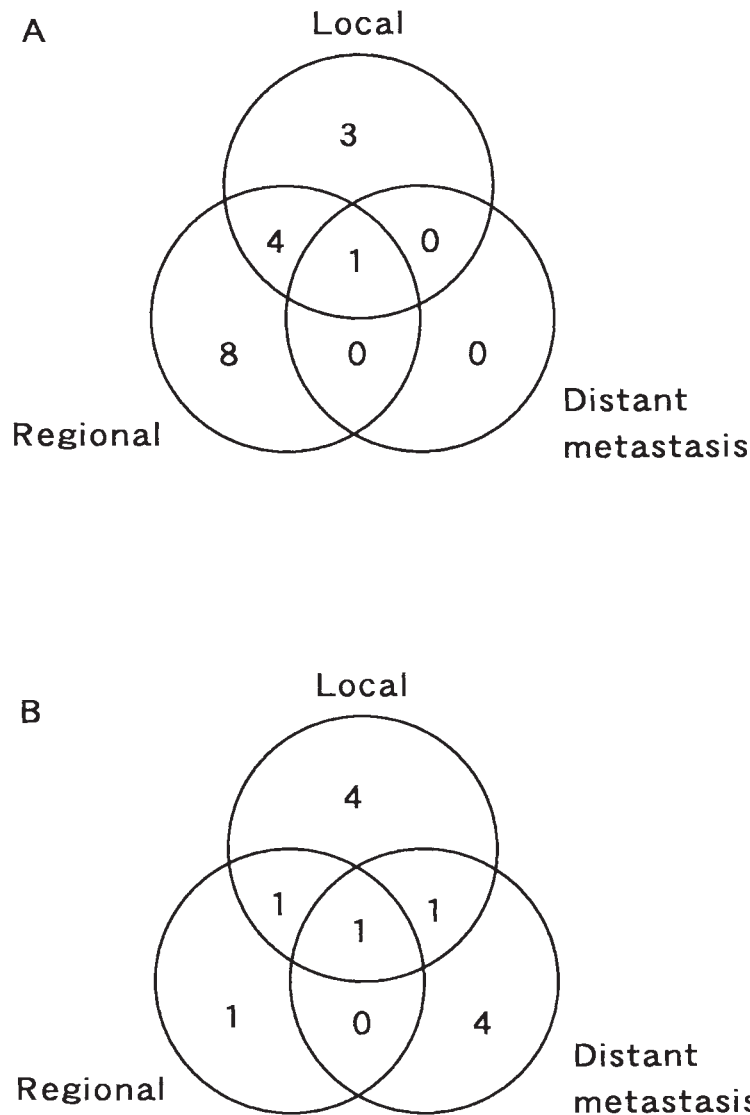


Fig. 3. A: The pattern and the frequency of recurrence. The local control rate was 79%. Regional recurrence was most frequent. Local recurrence=8/39 (21%). Regional recurrence=13/39 (33%). B: The pattern of cause of death. The frequency of death due to local recurrence and that due to distant metastasis were almost the same. Local death=7/39 (18%). Regional death=3/39 (8%). Death due to distant metastasis=6/39 (15%).

patients underwent selective neck dissection (ND), and 9 patients underwent chemotherapy (CT), namely, conventional CDDP (cisplatin) and 5FU-combined therapy. Results are summarized in Table 3. Patients who had undergone ND experienced no recurrence. The frequency of tumor recurrence in the patients who did not receive ND was 53% in early stage and 73% in stage II, significantly higher rates than that of the patients with ND. The frequency of the recurrence in patients who received CT was 66% in the patients whose tumors were classified as early stage and 75% in the patients whose tumors were classified as stage II. A significant difference was observed between these two groups. In patients who did not receive ND, the frequency of the recurrence in the patients who received

TABLE 3. *Analysis of the treatment pattern and recurrence rate of the patients with early stage tongue cancer*

	Recurrence rate			
	Early stage (stage I+II)		Stage II	
	<i>n</i>	%	<i>n</i>	%
Neck dissection (ND)				
ND	0/6	0	0/5	0
No ND	10/19	53	8/11	73
<i>p</i> -value	<0.05		<0.01	
Chemotherapy (CT)				
CT	6/9	66	6/8	75
No CT	4/16	25	2/8	25
<i>p</i> -value	<0.05		<0.05	
Chemotherapy without ND				
CT	6/8	75	6/7	86
No CT	4/11	36	2/4	50
<i>p</i> -value	>0.05		>0.05	
Neck dissection without CT				
ND	0/5	0	0/4	0
No ND	4/11	36	2/4	50
<i>p</i> -value	>0.05		>0.05	

CT was higher than that of the patients who did not receive CT. However, no significant difference was observed between these two groups. Patients who underwent ND without CT also experienced no recurrence. In patients without CT, the frequency of the recurrence in the patients who did not receive ND was higher than that of the patients who did. However, no statistically significant difference was observed between these two groups.

We also analysed the relationship between the location and the frequency of lymph node metastasis. In the total course of follow-up, we found histologically metastatic lymph nodes in 2 out of 9 patients (22%) with pT1 tumors, in 12 out of 19 patients (63%) with pT2 tumors, in 5 out of 9 patients (56%) with pT3 tumors and in 2 out of 2 patients (100%) with pT4 tumors. On initial treatment, by histological examination, we found 4 ipsilateral metastatic lymph nodes (10%) in the submandibular region, 8 (21%) such nodes in the upper jugular region, 2 (5%) such nodes in the mid-jugular region, one (3%) such node in the lower jugular region, and one (3%) such node in the submental region. In 19 patients who did not undergo ND on initial treatment and who experienced late lymph node metastasis, we found 6 (32%) metastatic lymph nodes in the submandibular region, 5 (26%) such nodes in the upper jugular region, and 2 (11%) such nodes

TABLE 4. *Analysis of young adult patients with oral tongue cancer*

	≤ 40	> 40
Number of patients	9	30
Mean age	31	60
Male/female	3/6	22/8
Early stage	6 (67%)	19 (63%)
Advanced stage	3 (33%)	11 (37%)
Treatment failure	2 (22%)	14 (47%)
Died of disease	1 (11%)	11 (37%)
5-year survival rate	80.3% ^a	61.5% ^a

a, n.s.

in the mid-jugular region. Metastatic lymph nodes were mainly located at levels I, II and III. Contralateral lymph node metastasis was found in one patient histologically.

We also analysed and compared the patients who were 40 years or younger than 40 years of age with those who were older than 40 years of age. Results are summarized in Table 4. The age of young adult patients ranged from 23 to 39 years with a mean age of 31 years. A mean age of older patients was 60 years. The ratio of early stage and advanced stage of these two groups was similar. The frequency of the failure of primary treatment and the frequency of death from disease of younger patients were lower than those of older patients. The 5-year survival rate of young adult patients (80.3%) was higher than that of older patients (61.5%). However, there was no significant difference as shown by statistical analysis.

DISCUSSION

As the cumulative survival rate at 5 years was 75% for the patients with stage III tumors and 25% for the patients with stage IV tumors, the results of our efforts against advanced cancer seemed to be satisfactory. However, results of our treatment of early cancer were unsatisfactory. Points at issue concerning the therapy for the patients with tongue cancer include death due to other diseases, administration or non-administration of ND, and administration or non-administration CT.

In cases of early stage oral tongue cancer, the recurrence rate of the patients who received ND was lower than that of those who did not. When patients who received CT are excluded, the recurrence rate of the patients who received ND was lower than that of the patients who did not, although there was no significant difference between these two groups. We thus conclude that elective neck dissection was beneficial, at least for patients with stage II cancers, because the frequency of metastasis to the regional lymph nodes was 63% in our results.

Elective neck dissection is controversial (O'Brien et al. 1986; Hughes et al. 1993; Yuen et al. 1997; Haddadin et al. 1999). It has frequently been reported that the survival rate of "watchful waiting" was worse than that of elective neck dissection (Ho et al. 1992; Lydiatt et al. 1993; Yuen et al. 1997; Persky and Lagmay 1999). In fact, the 5-year survival rate of our patients with early stage cancer and stage II cancer after salvage treatment was 30% and 37%, respectively, significantly different from that of the patients with no recurrent tumors. In 4 patients who died from distant metastasis without local and regional metastasis, 3 patients had early stage cancers. When late regional metastasis occurred in the patients who did not undergo elective neck dissection, they were treated successfully by ND. In those patients, regional control was thought to be important, therefore elective neck dissection was a useful initial therapy.

It is well documented that regional lymph node metastasis of oral tongue cancer is usually located at levels I, II and III. In our results also, regional metastasis was mainly located at these levels in the patients who underwent initial neck dissection and in those who underwent such treatment after late regional metastasis. One patient who had a metastatic lower jugular lymph node (level IV), also experienced multiple lymph node metastases in other regions. It has been reported that there is no significant difference between elective radical neck dissection and selective neck dissection of levels I, II and III with regard to the improvement of treatment results (Yuen et al. 1997). We thus conclude that elective neck dissection of levels I, II and III is the first choice of treatment strategy for the patients with stage II cancer.

The recurrence rate of the patients who received CT was significantly higher than that of those who did not. When patients who received ND are excluded, this difference of recurrence rate was not significant between these two groups. However, the recurrence rate of the patients who underwent CT was higher than that of those who did not. We thus deduced that CT was a factor of decreasing survival rate. It can at least be said that CT was not effective in reducing late lymph node metastasis. In the patients with early stage tongue cancer, CT might have increasing potential against late lymph node metastasis in clinically N0 patients.

Many authors have reported worse results of oral tongue cancer in patients who were 40 years or younger than 40 years of age than in older patients (Son and Kapp 1985; Sarkaria and Harari 1994). In our institution, there were 9 patients who were 40 years or younger than 40 years of age (23%). The ratio of early stage and advanced stage cancer was almost the same between the younger and older groups. The 5-year survival rate of the patients younger than 40 years of age was 80.3%, higher than that of the older patients (61.5%). Perhaps racial differences and/or environmental factors contribute to the good prognosis of young adult patients with oral tongue cancer. We conclude that treatment strategy for young adult patients with oral tongue cancer should be the same as that for older

patients.

In oral squamous cell carcinoma, many histopathologic parameters have been reported as predictive factors for neck metastasis. The studies of tumor thickness and the depth of invasion have often been documented (Mohit-Tabatabai et al. 1986; Spiro et al. 1986; Urist et al. 1987; Brown et al. 1989; Rasgon et al. 1989; Jones et al. 1992; Fukano et al. 1997; Asakage et al. 1998; Byers et al. 1998). However, the indication of elective neck dissection for N0 patients is controversial. The treatment results for patients who have undergone elective neck dissection according to the thickness or depth of tumor have not been reported. This is related to the clinical difficulty of accurate measurement of tumor thickness and depth in initial treatment. We think that the TNM classification, especially tumor diameter, could support the present treatment strategy to some extent. There have been few reports referring to the relationship between tumor diameter and tumor thickness or depth. It is desirable that many authors report details of the relationship between tumor diameter and tumor thickness or depth, growth type of tumor and tumor thickness or depth precisely.

In conclusion, as the frequency of regional lymph node metastasis of stage II tumors was unexpectedly relatively high in our study, elective neck dissection in stage II patients with oral tongue cancer is thought to be necessary to improve the prognosis.

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