Original Article

Early Stage Squamous Cell Cancer of the Oral Tongue—Clinicopathologic Features Affecting Outcome

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BACKGROUND: The objective of this study was to report the authors' experience in the management of patients with early stage squamous cell cancer (SCC) of the oral tongue and determine clinicopathologic factors predictive of outcome. **METHODS:** Two hundred sixteen patients with early stage (cT1T2N0) SCC of the oral tongue were identified from a pre-existing database of patients with oral cancer who were treated at Memorial Sloan-Kettering Cancer Center from 1985 to 2005. Patient, tumor, and treatment characteristics were recorded. Overall survival (OS), disease-specific survival (DSS), and recurrence free survival (RFS) were calculated using the Kaplan-Meier method. Predictors of outcome were identified using multivariate analysis. **RESULTS:** With a median follow-up of 80 months (range, 1-186 months), the 5-year DSS, OS, and RFS rates were 86%, 79%,and 70%, respectively. Local, neck, and distant recurrences occurred in 24 patients (11%), 40 patients (18%), and 5 patients (2%), respectively. Multivariate analysis identified occult neck metastases as the main independent predictor of OS, DSS, and RFS; patients who had occult metastases had a 5-fold increased risk of dying of disease compared with patients who did not have occult metastases (5-year DSS, 85.5% vs 48.5%; $P = .001$). A positive surgical margin was the main independent predictor for local RFS (91% vs 66% for a negative surgical margin; $P = .0004$), and depth of invasion was the main predictor for neck RFS (91% vs 73% for depth of invasion <2 mm and >2 mm, respectively; $P = .02$). **CONCLUSIONS:** In the authors' experience, patients with early stage oral tongue cancer have excellent outcomes. In the current study, the presence of occult metastases was the main predictor of survival outcome. ***Cancer*** **2012;118:101-111.** © *2011 American Cancer Society.*

KEYWORDS: depth of invasion, oral tongue cancer, outcome, prognostic factors.

Worldwide, there are an estimated 405,000 new cases of oral cancer diagnosed each year, and >50% are cancers of the oral tongue. The incidence of oral tongue squamous cell carcinoma in the United States has increased over the past 3 decades and currently is estimated at 3.0 per 100,000 population. In 2007, the 5-year disease-specific survival rate for patients with oral tongue cancer in the SEER registry was 60.2%, reflecting only a marginal improvement in the past 20 years.[1] In patients with early stage disease (T1T2N0), outcomes generally are good, and the reported 5-year survival rates range between 75% and 89%.[2-5] In the literature, there are few reports from studies that carried out a comprehensive analysis of the clinical and pathologic factors predictive of outcome in patients with early stage oral tongue cancer, because large numbers of patients are required to produce meaningful data supported by robust statistical analysis. Therefore the objective of the current study was to report our experience in the management of a large series of patients with early stage oral tongue cancer who were treated in a single institution and to identify the clinical and pathologic factors predictive of outcome using multivariate analysis.

MATERIALS AND METHODS

After we received approval from the institutional review board of Memorial Sloan-Kettering Cancer Center (MSKCC), 216 patients with early stage (clinical [c] T1N0-cT2N0) squamous cell cancer of the oral tongue were identified from a pre-existing database of patients with squamous cell carcinoma of the oral cavity who received treatment at MSKCC between the 1985 and 2005. Only patients who underwent surgery and received postoperative radiation therapy (PORT)

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Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	No. of Patients	%
Age, y		
<60	115	53
≥60	101	47
Sex		
Men	115	53
Women	101	47
Tobacco		
None	56	26
Yes	109	50
Not recorded	51	24
Alcohol		
None	62	29
Yes	77	36
Not recorded	77	36
Clinical tumor classification		
cT1	110	51
cT2	106	49
Pathologic tumor classification		
pT1	109	50
pT2	107	50
Pathologic lymph node status, n=110		
pN0	79	72
pN1	18	16
pN2b	13	12
Extracapsular spread, n=31		
None	16	52
Yes	13	42
Not recorded	2	6
Depth of invasion, mm		
<2	38	18
≥2	126	58
<4	59	27
≥4	105	49
Not recorded	52	24
Margin status		
Negative	177	82
Positive/close	28	13
Not recorded	11	5
Histologic grade		
Well differentiated	65	30
Moderately differentiated	101	47
Poorly differentiated	8	4
Not recorded	42	19
Management		
S	179	83
S+PORT	37	17
Management class		
PG alone	105	49
PG+PORT	1	0
PG+ND	74	34
PG+ND+PORT	36	17
ND		
No	106	49
Yes	110	51
Type of ND, n=110		
SOHND	102	92
MRND	4	4
RND	2	2
Bilateral	2	2

Abbreviations: MRNS, modified radical neck dissection; ND, neck dissection; PG, partial glossectomy; PORT, postoperative radiotherapy; RND, radical neck dissection; S, surgery; SOHND, supraomohyoid neck dissection.

at MSKCC were analyzed. Patients who either underwent surgery or received radiation at other hospitals were excluded. Details on patient characteristics, tumor characteristics, index treatment, and surgical outcomes were available for analysis.

Patient, tumor, and treatment characteristics are listed in Table 1. The median patient age was 59 years (range, 14-88 years), 53% of patients were men, 50% were smokers, and 36% were drinkers of alcohol. On clinical examination, 50% of tumors were classified as T2. One hundred seventy-nine patients (83%) underwent surgery as their only treatment, including 105 patients who underwent partial glossectomy and 74 patients who underwent partial glossectomy plus neck dissection. Thirty-seven patients (17%) underwent surgery and also received PORT, including 36 patients who underwent both partial glossectomy and neck dissection and 1 patient who underwent partial glossectomy without neck dissection. One hundred ten patients underwent elective neck dissection (END), the majority of whom underwent supraomohyoid neck dissection (103 patients; 93%). At our institution, levels I through IV are dissected routinely for supraomohyoid neck dissection because of the small risk of skip metastases to level IV for oral tongue cancers. For primary tumors, pathology revealed that 50% were pathologic T2 (pT2) tumors, and 18% had close or positive margins (a close margin was defined as a margin $\leq$1 mm), 58% had a tumor depth $\geq$2 mm, and 49% had a tumor depth $\geq$4 mm. Of the 110 patients who had a clinically negative neck, histopathologic examination revealed occult metastases in 31 patients (28%). Of these, 13 patients (42%) had evidence of extracapsular spread in the lymph nodes (8 patients had gross evidence, and 5 patients had microscopic evidence).

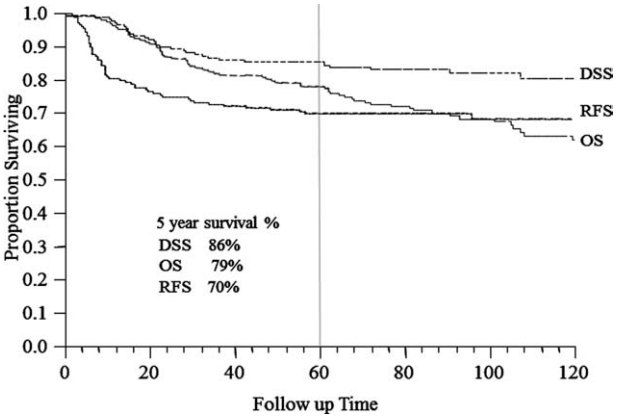

Figure 1. Disease-specific survival (DSS), overall survival (OS), and recurrence-free survival (RFS) are illustrated for patients with early stage tongue cancer.

Overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), local RFS (LRFS), neck RFS (NRFS), and distant RFS (DRFS) were determined by using the Kaplan-Meier method. To identify factors that were predictive of survival, the following variables were subjected to univariate analysis using the log-rank test: age, sex, tobacco and alcohol status, cT classification, pT classification, pathologic lymph node (pN) status, differentiation of tumor, margin status, depth of invasion, type of treatment, and PORT. Clinical and pathologic factors that were significant on univariate analysis were assessed next by multivariate analysis using a Cox regression model and the log-rank test. Statistical analyses were carried out using the statistical software packages SPSS for Windows (version 11.01; (SPSS Inc., Chicago, Ill) and JMP (version 4.0; SAS Institute Inc, Cary, NC).

RESULTS

At a median follow-up of 80 months (range, 1-186 months), the 5-year DSS, OS, and RFS rates for all patients were 86%, 79%, and 70%, respectively (Fig. 1). Overall, 59 patients developed recurrent disease, including 24 local recurrences (11%), 40 regional recurrences (18%), and 5 distant recurrences (2%). The factors that were predictive of OS, DSS, and RFS in univariate analysis are listed in Table 2. The factors that were predictive of LRFS, NRFS, DRFS in univariate analysis are listed in Table 3.

Because of the small number of events for each outcome measure and the large number of variables that were significant on univariate analysis, we could not perform multivariate analysis on all clinical and pathologic variables in the same model. Therefore, we created a multivariate model for clinical predictors of outcome and a model for pathologic predictors of outcome (Tables 4 and 5).

For OS, univariate analysis indicated that age >60 years, tobacco and alcohol use, T2 tumor classification, positive pN status, depth of the primary tumor (≥2 mm and ≥4 mm), and PORT were predictive of a poor outcome. Multivariate analysis of clinical predictors indicated that only age >60 years remained an independent predictor of OS (Table 4); patients aged >60 years had a 3-fold increased risk of dying compared with patients aged <60 years. Multivariate analysis of pathologic predictors revealed that only pathologic neck status remained an independent predictor of OS (Table 5); patients who had N2b neck status had a 2.7-fold increased risk of dying compared with patients who had N0 neck status.

For DSS, univariate analysis indicated that T2 tumor, positive pN status, depth of the primary tumor (≥2 mm and ≥4 mm), positive surgical margins, PORT, and neck dissection were predictive of a poor outcome. In a multivariate analysis of clinical predictors, only cT classification remained an independent predictor of DSS (Table 4, Fig. 2); patients with T2 tumors had a 2.2-fold increased risk of dying from disease compared with patients who had T1 tumors. Multivariate analysis of pathologic predictors indicated that only pathologic neck status remained an independent predictor of DSS (Table 5); patients who had pN2b neck status had a 4.8-fold increased risk of dying compared with patients who had N0 neck status (Fig. 3).

For RFS, univariate analysis indicated that positive pN status, depth of the primary tumor ≥2 mm, positive surgical margins, and PORT were predictive of a poor outcome. Multivariate analysis of pathologic predictors indicated that only pathologic neck status remained an independent predictor of RFS (Table 5); patients who had pN2b neck status had a 2.6-fold increased risk of developing recurrent disease compared with patients who had N0 neck status.

For LRSF, univariate analysis indicated that tobacco use, positive surgical margins, and PORT were predictive of outcome. Multivariate analysis of pathologic predictors indicated that pathologic neck status and margin status were independent predictors of LRFS (Table 5); patients who had pN2b neck status had a 5.4-fold increased risk of developing recurrent disease compared with patients who had N0 neck status, and patients who had positive or close margins had a 3.2-fold increased risk of local recurrence

Table 2. Prognostic Factors for Overall, Disease-Specific, and Recurrence-Free Survival: Univariate Analysis

Variable	No. of Patients	5-Year OS, %	*P*	5-Year DSS, %	*P*	5-Year RFS, %	*P*
Age, y							
<60	115	85		87.5		69.3	
≥60	101	71.6	<.0001[a]	83.2	.25	69.4	.82
Sex							
Men	115	80.8		85.5		69.1	
Women	101	76.3	.98	85.8	.86	69.9	.96
Tobacco							
None	56	85		86		66.2	
Yes	109	71.6	<.0001[a]	84.2	.73	72.7	.32
Alcohol							
None	62	88		89.5		72.5	
Yes	77	75.3	.01[a]	84.9	.49	69.3	.74
Clinical tumor classification							
cT1	110	84.2		91.8		72.2	
cT2	106	73.1	.02[a]	79	.03[a]	66.6	.62
Pathologic tumor classification							
pT1	109	84		91.7		71.9	
pT2	107	73.3	.03[a]	79.3	.04[a]	66.9	.69
Pathologic lymph node status							
pN0	79	80.3		85.5		69.4	
pN1	18	58.8		61.4		61.9	
pN2b	13	45.8	.007[a]	48.5	.001[a]	31.2	.04[a]
Extracapsular spread							
None	16	56.2		56.2		50	
Yes	13	50	.8	54.7	.55	46.9	.8
Depth of invasion, mm							
<2	38	89.2		97.1		79.1	
≥2	126	73.7	.004[a]	79.9	.02[a]	62	.06[a]
<4	59	85.7		94.1		74.6	
≥4	105	72.7	.003[a]	78.4	.01[a]	61	.09
Margin status							
Negative	177	80		86.7		71.9	
Positive/close	28	65.6	.06	72.5	.003[a]	49.1	.04[a]
Histologic grade							
Well differentiated	65	81.7		90.5		70.6	
Moderately differentiated	101	73.4		79.5		66.7	
Poorly differentiated	8	71.4	.29	71.4	.14	57.1	.86
Management							
S	179	82.7		89.6		72.6	
S+PORT	37	58.9	.0002[a]	66.2	<.0001[a]	54.2	.05[a]
Management class							
PG alone	105	83.2		92.4		74.7	
PG+PORT	1	100		100		100	
PG+ND	74	81.9		85.8		69.7	
PG+ND+PORT	36	57.6	.003[a]	65.1	<.0001[a]	52.8	.16
ND							
No	106	83.3		92.5		75	
Yes	110	73.8	.07	78.9	.002[a]	64.3	.16

Abbreviations: DSS; disease-free survival; ND, neck dissection; OS, overall survival; PG, partial glossectomy; PORT, postoperative radiotherapy; RFS, recurrence-free survival; S, surgery.
[a] Significant *P* value.

Table 3. Prognostic Factors for Local, Neck, and Distant Recurrence-Free Survival: Univariate Analysis

Variable	No. of Patients	5-Year LRFS, %	*P*	5-Year NRFS, %	*P*	5-Year DRFS, %	*P*
Age, y							
<60	115	86.7		80.2		96	
≥60	101	89.4	.49	76.8	.76	98.4	.29
Sex							
Men	115	91.8		74.5		96.6	
Women	101	83.8	.16	83	.22	97.5	.72
Tobacco							
None	56	77.5		82		100	
Yes	109	93.6	.004[a]	77.8	.66	96.4	.21
Alcohol							
None	62	85.6		82.8		100	
Yes	77	92.1	0.25	76.2	.43	98.4	.35
Clinical tumor classification							
cT1	110	89.4		78.4		100	
cT2	106	86.5	0.83	79	.79	93.7	.02[a]
Pathologic tumor classification							
pT1	109	89.3		78.2		100	
pT2	107	86.7	0.88	79.2	.73	93.8	.02[a]
Pathologic lymph node status							
pN0	79	87.1		76.3		96.8	
pN1	18	77.9		93.8		86.5	
pN2b	13	67.3	0.2	69.3	.29	80	.11
Extracapsular spread							
None	16	80.4		87.5		74.7	
Yes	13	64.3	0.91	75	.52	100	.23
Depth of tumor invasion, mm							
<2	38	88		91		100	
≥2	126	85.7	0.81	72.8	.02[a]	96.5	.28
<4	59	91.7		82.4		100	
≥4	105	82.8	0.15	74	.19	95.9	.16
Surgical margin status							
Negative	177	90.6		78.2		98.5	
Positive/close	28	66.4	.0004[a]	80.7	.89	86.7	.002[a]
Histologic grade							
Well differentiated	65	85		81.7		100	
Moderately differentiated	101	86.1		76.4		94.4	
Poorly differentiated	8	100	.54	66.7	.76	85.7	.08
Management							
S	179	90.8		77.8		98.6	
S+PORT	37	74	.01[a]	84.8	.47	88.1	.003[a]
Management class							
PG alone	105	92.2		79.1		100	
PG+PORT	1	100		100		100	
PG+ND	74	88.8		75.8		96.5	
PG+ND+PORT	36	73.1	.07	84.3	.82	87.6	.01[a]
ND							
No	106	92.3		79.4		100	
Yes	110	83.9	.19	78.2	.83	94	.02[a]

DRFS, disease recurrence-free survival; LRFS, local recurrence-free survival; ND, neck dissection; NRFS, neck recurrence-free survival; PG, partial glossectomy; PORT, postoperative radiotherapy; S, surgery.

[a] Significant *P* value.

compared with patients who had negative margins (Fig. 4).

For NRFS, univariate analysis indicated that depth of invasion ≥2 mm was predictive of outcome. Multivariate analysis of pathologic predictors indicated that only depth of invasion of the primary tumor remained an independent predictor of NRFS (Table 5); patients who had a depth of invasion >2 mm had a 3.7-fold increased risk of developing a regional recurrence compared with patients who had a depth of invasion <2 mm (Fig. 5). For DRFS, several factors were predictive on univariate analysis (T2 tumor, positive pN status, positive surgical margins, PORT, and neck dissection), but the number of distant recurrences were so small that multivariate analysis could not be carried out.

Table 4. Clinical Factors Predictive of Outcome on Multivariate Analysis

	OS		DSS	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y				
<60	Referent		Referent	
≥60	3.1 (1.5-6.4)	.002		NS
Tobacco				
None	Referent			
Yes		NS		—
Alcohol				
None	Referent			
Yes		NS		—
Clinical tumor classification				
cT1	Referent		Referent	
cT2		NS	2.2 (1-4.5)	.04

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.

DISCUSSION

In the current study of patients with early stage SCC of the oral tongue, we observed 5-year DSS and OS rates of 86% and 79%, respectively. These outcomes compare very favorably with those reported in the literature, which

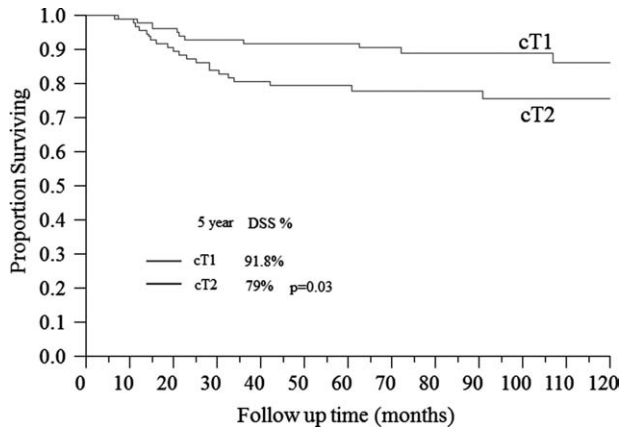

Figure 2. Disease-specific survival (DSS) is illustrated for patients with early stage tongue cancer stratified according to clinical tumor (cT) classification.

Table 5. Pathologic Factors Predictive of Outcome on Multivariate Analysis

	OS		DSS		RFS		LRFS		NRFS	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Pathologic tumor classification										
pT1	Referent		Referent		Referent		Referent			
pT2		NS		NS		NS		NS		—
Pathologic lymph node status										
pN0	Referent		Referent		Referent		Referent			
pN1	1.4 (0.6-3.6)	NS	1.9 (0.6-5.6)	NS	0.9 (0.3-2.3)	NS	1.7 (0.4-6.8)	NS		
pN2b	2.7 (1-6.9)	.04	4.8 (1.6-14.1)	.004	2.6 (0.9-6.9)	.05	5.4 (1.3-21.4)	.02	—	
Depth of invasion, mm										
<2	Referent		Referent		Referent		Referent		Referent	
≥2		NS		NS		NS		NS	3.7 (1.1-12.2)	.03
Margin status										
Negative	Referent		Referent		Referent		Referent			
Positive/close		NS		NS		NS	3.2 (1.1-9.3)	.04		—

Abbreviations: CI, confidence interval; DSS, disease-specific survival; LRFS, local recurrence-free survival; OS, overall survival; NRFS, neck recurrence-free survival; NS, nonsignificant; OR, odds ratio; RFS, recurrence-free survival.

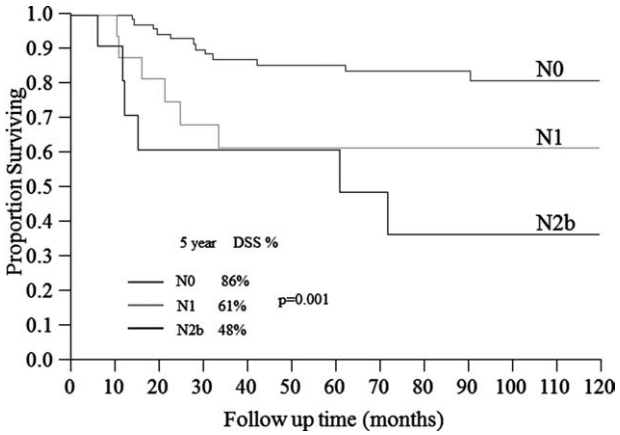

Figure 3. Disease-specific survival (DSS) is illustrated for patients with early stage tongue cancer stratified according to pathologic lymph node (pN) status.

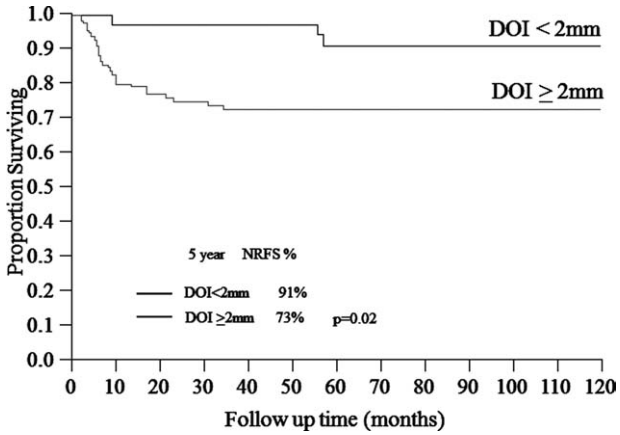

Figure 5. Neck recurrence-free survival (NRFS) is illustrated for patients with early stage tongue cancer stratified according to the depth of invasion (DOI) of the primary tumor.

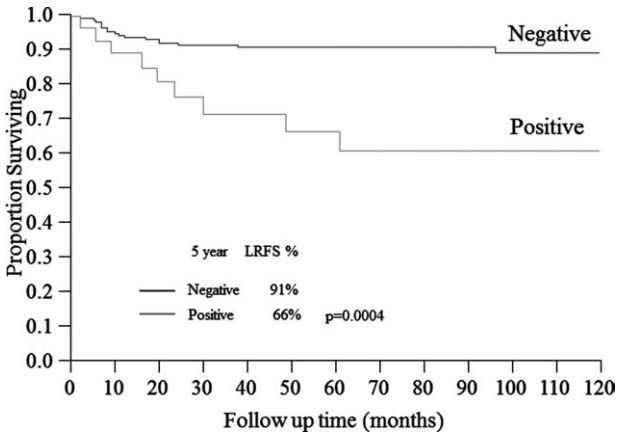

Figure 4. Local recurrence-free survival (LRFS) is illustrated for patients with early stage tongue cancer stratified according to margin status (negative or positive).

range from 75% to 89%.[2-5] The main reason for failure in early stage oral tongue cancer is locoregional recurrence, and distant metastases are rare. In our study, the local recurrence rate of 11% and the regional recurrence rate of 18% were similar to those reported in the literature.[6-8] Because of our large patient series, it was possible to perform statistical analysis to identify predictors of outcome. Multivariate analysis indicated that local recurrence was determined mainly by margin status. Our positive margin rate of 13% compares favorably with reports in the literature of positive margins in the range between 7% and 22%.[8,9] With regard to neck recurrence, we observed that depth of invasion of the primary tumor was the main predictor, and patients who had tumors >2 mm in depth had an almost 4-fold risk of neck recurrence.

The most important finding in our study was the impact that occult regional metastases had on survival. In our multivariate analysis, the main independent predictor for DSS and OS was the status of the neck; patients who had occult metastases had a 5-fold increased risk of dying from disease compared with patients who had no occult metastases. In our study, the incidence of occult metastases was 28%, which is similar to that reported by Pimenta Amarel et al[10] (23%) and Kligerman et al[5] (21%). It is well recognized that the status of the clinically positive neck is a major determinant of survival outcome in other head and neck cancers. Our study indicates that this holds true even in the occult metastases scenario for oral tongue cancer. Because the status of the neck has a major impact on outcome, treatment of the neck is an important aspect in the management of these patients. There are many studies in the literature reporting on the therapeutic benefit of END.[5,11-13] END is advocated in general for the majority of tongue cancers except for very early stage (cT1), superficial tumors. In addition, END has the extra advantage of enabling the accurate staging of patients, which then allows for better patient counseling with regard to prognosis as well as allowing the clinician to identify patients who are at high risk of a poor outcome and selecting patients who need PORT. Recently, reports by Yuen et al[3] and D'Cruz et al[14] have advocated a policy of observation of the N0 neck in patients with early stage tongue cancer. Yuen et al[3] carried out a prospective randomized trial of END versus observation and reported similar DSS in both groups. In that study, 11 of 35 patients in the observation group developed neck recurrence compared with 2 patients in the neck dissection

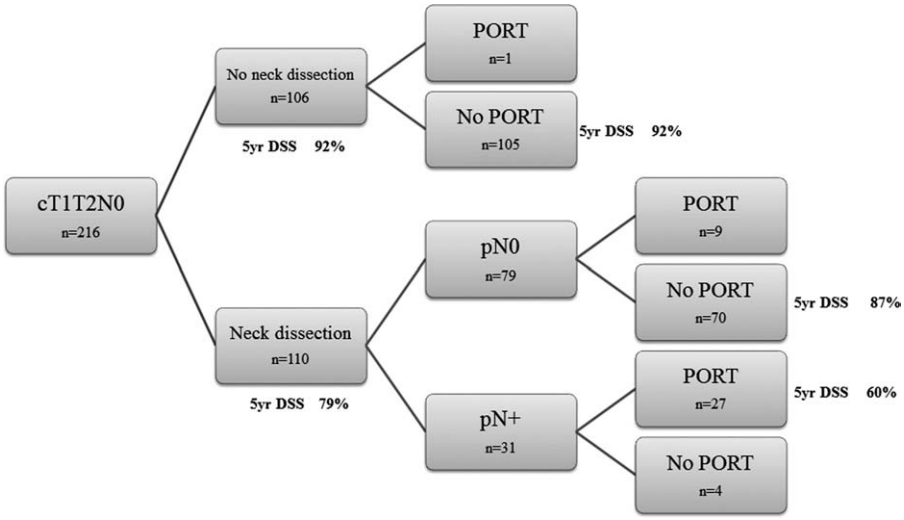

Figure 6. This flow diagram illustrates the management of patients with early stage tongue cancer stratified according to neck dissection, pathologic lymph node (pN) status, and postoperative radiotherapy (PORT). cT indicates clinical tumor classification; DSS, disease-specific survival

group. This result corresponds to an occult metastases rate of 30%, which is similar to that reported in our current study. Despite the high incidence of recurrence in the observation group, all of the patients in the study by Yuen et al were salvaged because of a policy of strict surveillance. Thus, in that study, DSS in the observation group after salvage was similar to that in the END group. The authors concluded that a policy of observation was safe provided a policy of strict neck surveillance was implemented. However, this policy depends on regular follow-up and the use of regular imaging studies, such as ultrasound, to identify patients with neck recurrence. In general, such a management policy can be carried out only in large academic centers. In the report by D'Cruz et al[14] on 359 patients, similar DSS was observed in patients who underwent neck dissection and those who were observed (DSS rate, 74% vs 68%, respectively). However, that was not a prospective randomized trial, and there were no data indicating whether patients were matched adequately with regard to depth of invasion, margin status, histologic grade, and tumor size. Therefore, those results are susceptible to selection bias. Recent evidence against neck observation from Tsang et al[15] indicated that patients with early tongue cancer who underwent observation had poor survival. In our study, we did not include treatment (type of primary surgery, neck dissection, and the receipt of PORT) in our multivariate analyses because of the inherent selection bias from the physician, patient, and institutional preferences involved in treatment decision making. A flow diagram illustrating DSS in our patients stratified according to neck dissection, pN status, and PORT is provided in Figure 6. On univariate analysis, patients who underwent partial glossectomy alone had better survival than patients who underwent both partial glossectomy and neck dissection (DSS rate: 92% vs 79%; $P = .002$). However, an analysis of the pathology of the primary tumors in each cohort indicated that patients in the partial glossectomy group were highly selected and were more likely to have small T1 tumors that were not deeply infiltrating (Table 6). Thus, neck observation can be justified in some patients who have small, superficial tumors. Clearly, the identification of factors that predict for the presence of occult metastases is important. Previous studies have reported that the depth of invasion of the primary tumor is predictive of occult metastases.[5,16-27] A recent meta-analysis by Huang et al[28] concluded that a primary tumor thickness $\geq$4 mm was the most predictive tumor thickness for occult metastases. Other studies also have reported that poor histologic grade[23] was predictive of occult metastases. When we analyzed these factors in our cohort, we produced similar results (Table 7); 100% of patients with occult metastases had primary tumors with $\geq$2 mm depth of invasion, and 92% had tumors with $\geq$4 mm depth of invasion. In addition, 93% patients with occult metastases had either moderately or poorly differentiated tumors. Therefore, occult metastases were never identified in patients who had superficial, well differentiated tumors. The difficulty is how to assess depth of invasion at the time of surgery. Frozen section analysis may be helpful, but this may be restricted to centers where it is

Table 6. Pathologic Comparison of the Partial Glossectomy Cohort Versus the Partial Glossectomy and Neck Dissection Cohort

Variable	PG Alone	PG+ND	*P*[a]
Pathologic tumor classification			
pT1	77	26	
pT2	28	48	<.0001[b]
Depth of invasion, mm			
<2	30	8	
≥2	39	54	<.0001[b]
<4	42	16	
≥4	27	46	<.0001[b]
Margin status			
Negative	91	64	
Positive/close	7	6	.73
Grade			
Well differentiated	38	23	
Moderately differentiated	33	39	
Poorly differentiated	2	2	.16

Abbreviations: ND, neck dissection; PG, partial glossectomy.
[a] *P* values were calculated using the chi-square test.
[b] Significant *P* value.

Table 7. Pathologic Factors Predictive of Occult Metastases in Patients With Early Stage Squamous Cell Cancer of the Oral Tongue

	Pathologic Lymph Node Status		
Variable	Negative	Positive	*P*[a]
Pathologic tumor classification			
pT1	26	6	
pT2	53	25	.15
Depth of invasion, mm			
<2	8	0	
≥2	59	27	.02[b]
Depth of invasion, mm			
<4	15	2	
≥4	52	25	.07
Margin status			
Negative	62	24	
Positive/close	13	7	.53
Tumor grade			
Well differentiated	25	2	
Moderately differentiated	42	25	
Poorly differentiated	3	3	.004[b]

[a] *P* values were calculated using the chi square test.
[b] Significant *P* value.

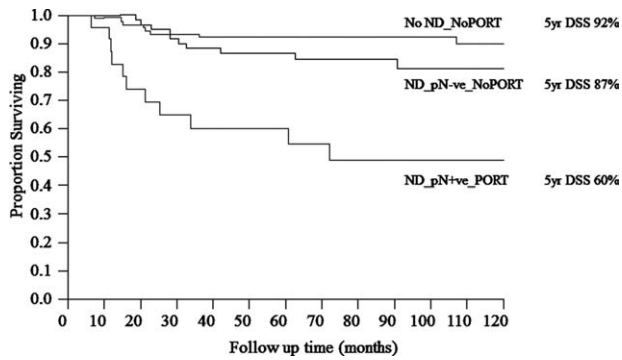

Figure 7. Disease-specific survival (DSS) is illustrated for patients with early stage tongue cancer stratified according to neck dissection (ND), pathologic lymph node (pN) status (negative [−ve] or positive [+ve]), and postoperative radiotherapy (PORT).

readily available with experienced head and neck pathologists. An alternative method currently being investigated by several groups is the use of preoperative ultrasonography and intraoperative ultrasonography.[29,30] This method reportedly demonstrated a high correlation between ultrasound measurement and pathologic measurement of tumor thickness with an accuracy of >90%. Therefore, this method may be used to select patients with thin tumors who can be offered partial glossectomy alone without END.

An alternative option to having all patients undergo END may be sentinel lymph node biopsy (SLNB). Given our high incidence of occult metastases, SLNB may be particularly useful in these patients. The majority of oral tongue cancers are visualized easily and, in general, are accessible to direct injection. This technique for squamous cell carcinoma of the oral cavity was reported first in 2001 by Shoaib et al,[31] who used SLNB before END in patients who had clinically negative neck status. Ross et al[32] investigated 57 SLNBs in 48 patients with clinically N0 neck status and reported that 15 patients (35%) were upstaged by SLNB, and 28 patients (65%) were staged as sentinel lymph node-negative. At a mean follow-up of 18 months, only 1 patient developed regional neck disease after being staged negative on SLNB. The overall sensitivity of the technique was 94%. Since then, 2 multicenter prospective trials in Europe[33] and the United States,[34] with 5-year and 3-year follow-up data, respectively, have reported that the technique is a reliable and reproducible method for staging the neck. In the most recent study reported by Civantos et al[34] on 140 patients with T1T2 oral cancer, SLNB correctly predicted a pathologically negative neck in 96% of patients. However, this technique does require experience and currently is recommended only for centers

with the necessary expertise and the appropriate volume of patients, because, as demonstrated by Ross et al,[35] centers that perform this technique with <10 patients per year have much lower sensitivity. Technical problems of "shine through," in which the radioactivity level in the primary site potentially obscures the sentinel lymph node, is 1 potential problem. The role of SLNB in larger tumors also can be limited because of false-negative biopsies resulting from obstruction of lymphatic flow caused by tumor and redirecting of flow to neighboring lymph nodes.

The significant negative effect of occult metastases on outcome in patients who undergo neck dissection is illustrated in Figures 6 and 7, which indicated that, even when patients with occult metastases receive PORT, their DSS still is poorer compared with patients who have pathologically negative necks (DSS rate, 60% vs 87%). Although PORT improves neck recurrence rates in patients with head and neck cancer,[36-39] it does not improve DSS to rates comparable to the rates for patients who have a pathologically negative neck. It is noteworthy that, among the patients who had pathologically positive cervical lymph nodes, 42% (13 of 31 patients) had extracapsular spread. These patients did not receive postoperative chemoradiation. However, it is now accepted that extracapsular spread, along with positive margin status, is the main criterion for chemoradiation after surgery.[40,41] Our current study was for the years 1985 through 2005, when PORT was our normal practice in these patients. However, since then, patients with positive neck disease and extracapsular spread have received chemoradiation. It is possible that this may improve DSS for these patients. Our results clearly suggest that strategies using chemotherapeutic agents or new molecular therapies are required to improve the survival of patients with occult metastases. Such therapies can arise only from a better understanding of the genetic events involved in invasion and metastases in tongue cancer.

In conclusion, our experience in the management of patients with early stage tongue cancer indicates that these patients have a good prognosis. However, just as the presence of clinically positive neck disease is the main predictor of outcome in patients with head and neck cancer, the presence of occult neck metastases is the main predictor of outcome in patients with early stage tongue cancer.

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