Patients With cT1N0M0 Oral Squamous Cell Carcinoma Benefit From Elective Neck Dissection: A SEER-Based Study

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ABSTRACT

Background: The incidence of oral squamous cell carcinoma (OSCC) is increasing, with an estimated 369,000 new patients each year worldwide. Surgery is the primary treatment modality for early-stage OSCC, but there is scant evidence to prove the value of elective neck dissection (END) for relatively small early-stage OSCC. This study aimed to identify factors predicting survival for patients with clinical stage T1N0M0 (cT1N0M0) OSCC and whether up-front END improved survival. **Patients and Methods:** Patients with cT1N0M0 OSCC who underwent tumor resection with or without END were identified and extracted from the SEER database. Kaplan-Meier survival analysis was used to assess overall survival and disease-specific survival. Prognostic factors were determined using Cox regression analysis. **Results:** A total of 5,752 patients with cT1N0M0 OSCC were extracted, of whom 2,194 (38.1%) underwent tumor resection surgery with concurrent END and 3,558 (61.9%) underwent only tumor resection. In a multivariate Cox analysis, a relatively advanced age (>62 years) and relatively high pathologic grade were the significant negative predictors, but married status (hazard ratio, 0.709; $P=.006$) and undergoing END (hazard ratio, 0.708; $P<.001$) were identified as significant independent positive factors. **Conclusions:** Patients with cT1N0M0 OSCC gain significant overall and disease-specific survival benefit from END.

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See page 474 for related commentary.

Background

Oral squamous cell carcinoma (OSCC) is among the most common cancers worldwide, with approximately 369,000 new cases reported in 2012, and increasing each year.¹ As presented in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers,² surgery is the primary treatment modality for all stages of OSCC, whereas the addition of adjuvant therapeutic regimens, including radiation therapy and chemotherapy, and the use of targeted therapy are indicated for the most advanced disease (stages III–IV).^{3–5} With regard to the neck management of patients with clinically node-negative early-stage OSCC, there are no consistent conclusions or standardized policies because of the presence of occult neck metastases that are clinically and radiologically undetectable.^{6–8} This practice has especially applied to T1 OSCC tumors <10 mm in diameter with no evidence of metastasis in the neck, which have historically been treated with local primary tumor resection only. However, occasionally some of these patients may not be salvageable when untreated occult neck metastases become clinically apparent.⁹ A United Kingdom nationwide study that enrolled 250 randomized and 346 observational cohort patients from 27 hospitals found occult neck disease in 19.1% and 34.7% of patients with clinical stage T1 and T2 disease, respectively.¹⁰

The NCCN Guidelines suggest that patients with initial preoperative staging of at least levels I–III may undergo elective neck dissection (END), which is determined at the discretion of the surgeon.² But it is still debatable whether patients with early-stage node-negative OSCC should receive END. Many clinicians in head and neck surgery still follow the protocol of performing selective techniques on patients with clinically negative necks (N0), but only when the tumor size exceeds ≥ 4 cm (T2). END requires a longer, more complex operation than tumor resection alone and increases the complication risk. In considering the necessity of END versus the benefit, some surgeons choose not to offer up-front END due to concern about overtreatment, reserving neck dissection as a salvage treatment for

subsequent neck metastasis. Similarly, some studies have concluded that patients with node-negative OSCC should not receive up-front END to avoid additional complications and costs.^{11,12} Currently, increasingly more researchers advocate that END should be performed routinely during resection of the primary tumor, in consideration of postoperative recurrence and poor prognosis due to the high rate of occult cervical metastasis in early OSCC.¹³

Because of the lack of consensus in characteristics, study populations, and patient management, the results supporting either recommendation may not be readily generalizable.^{14–16} However, although a meta-analysis from 2011¹⁷ and prospective randomized studies from 2015¹⁸ and 2019¹⁰ showed a benefit for END in both T1N0 and T2N0 OSCC, 2 retrospective studies^{13,19} and the UK prospective randomized study and meta-analysis¹⁰ have shown a benefit for T1N0 OSCC alone. The difference between the management of T1N0 and T2N0 is still a contentious point.

To our knowledge, only one article to date has reported a prospective randomized study and meta-analysis that quantifies the benefit of END in T1N0 and T2N0 OSCC.¹⁰ Our study concentrated on patients with only clinical stage T1N0M0 (cT1N0M0) OSCC. We aimed to gather sufficient evidence to make strong, well-supported recommendations to either support or refute the findings of the single published study, which suggested that patients with cT1N0M0 OSCC gained significant overall survival (OS) and disease-specific survival (DSS) benefit.¹⁰ In addition, we sought to determine the clinical features and prognostic factors associated with cT1N0M0 OSCC that affected OS and DSS in this patient cohort. To address these issues, a retrospective investigation was conducted using a study population from the internationally renowned SEER database.

Patients and Methods

The study population was extracted from the SEER database using its exclusive software (SEER*Stat 8.3.6). Patients were identified via ICD-O-3 as described elsewhere.²⁰ Briefly, patients with OSCC were selected through the ICD-O-3 morphologic and topographic codes 8050–8076, 8078, 8083, 8084, 8094, C01.9, C02.0, C02.1, C02.2, C02.3, C02.8, C02.9, C03.0, C03.1, C03.9, C04.0, C04.9, C05.0, C06.0, C06.1, and C06.2. We then selected only patients with primary AJCC stage I OSCC. Because our study used established data and did not involve interactions with human patients, Institutional Review Board approval was not required.

Statistical Analysis

Clinical and demographic features were compared across subgroups using the chi-square or Fisher exact test.

Survival curves were generated using the Kaplan-Meier method, and the log-rank test was used to evaluate survival differences between subgroups. Adjusted hazard ratios (HRs) along with 95% confidence intervals were calculated using univariate and multivariate Cox proportional hazards regression models. Statistical analysis was performed using the statistical packages R version 3.4.3 (R Foundation for Statistical Computing), Empower R (X & Y Solutions Inc.), and SPSS Statistics, version 23 (IBM Corp). *P* values <.05 were considered statistically significant, and all statistical tests were 2-tailed.

Results

Summary Statistics

In total, 5,752 patients with cT1N0M0 OSCC who fulfilled all inclusion criteria were identified: 3,209 (55.8%) were male, and 2,543 (44.2%) were female. The follow-up time period for the cohort ranged from 1 to 155 months, with a mean follow-up of 62.43 months (SD, 39.90). Mean patient age at diagnosis was 62.02 years (SD, 13.74; range, 21–105 years). Furthermore, nearly 55% of all patients in this cohort were from the age groups of 50–59 and 60–69 years. Most patients were White (*n*=5,004; 87.9%), followed by other races (*n*=511; 9.0%) and Black (*n*=176; 3.1%). Most patients were married (*n*=3,260; 62.0%), but 831 (15.8%) were single and 1,167 (22.2%) were listed as other. The numbers of patients with histologic grade 1, 2, or 3/4 disease were 1,949 (37.6%), 2,757 (53.1%), and 483 (9.3%), respectively.

In this cohort, 2,194 patients (38.1%) underwent END concurrent with tumor resection, whereas 3,558 (61.9%) received only tumor resection with a wait-and-observe approach for the neck.

In addition, there were 4,778 patients with OSCC-specific mortality data available for DSS analysis, including 2,154 women (45.1%) and 2,624 men (54.9%). Mean age was 60.46 years (SD, 13.38; range, 21–105 years), and mean follow-up time was 64.22 months (range, 1–155 months). Basic clinical and demographic characteristics are summarized in Table 1, and notable differences were detected between subgroups.

Survival Analysis

Survival analysis was performed using Kaplan-Meier estimate for OS. There were significant differences in OS depending on age group (*P*<.0001), age at diagnosis (*P*<.0001), sex (*P*=.0026), marital status at diagnosis (*P*<.0001), race (*P*<.0001), primary tumor site (*P*<.0001), pathologic grade (*P*<.0001), and neck dissection status (*P*=.0004) (Figure 1). DSS analysis was performed the same as OS analysis, and significant differences were found for age group (*P*<.0001), age at diagnosis (*P*<.0001), pathologic grade (*P*<.0001), tumor site (*P*=.0002), marital

Table 1. Epidemiologic and Clinicodemographic Characteristics of Patients With cT1N0M0 OSCC

Variable	Disease-Specific Survival								Overall Survival							
	Wait and Observe				END				Wait and Observe				END			
	Alive	Dead	Total	P Value	Alive	Dead	Total	P Value	Alive	Dead	Total	P Value	Alive	Dead	Total	P Value
Sex				.997				.036				.041				.001
Female	1,152	199	1,351		724	79	803		1,194	430	1,624		733	186	919	
Male	1,331	230	1,561		925	138	1,063		1,362	572	1,934		937	338	1,275	
Age range, y				<.001				<.001				<.001				<.001
20–29	30	1	31		33	1	34		30	3	33		33	2	35	
30–39	105	5	110		114	7	121		105	8	113		114	10	124	
40–49	311	36	347		262	21	283		315	55	370		264	41	305	
50–59	690	87	777		510	58	568		707	172	879		517	128	645	
60–69	739	98	837		413	68	481		765	230	995		421	147	568	
70–79	404	100	504		232	36	268		422	239	661		235	117	352	
≥80	204	102	306		85	26	111		212	295	507		86	79	165	
Race				.247				.164				<.001				.001
White	2,127	376	2,503		1,421	194	1,615		2,193	903	3,096		1,441	467	1,908	
Black	69	17	86		41	8	49		72	39	111		41	24	65	
Other	243	35	278		172	15	187		247	58	305		173	33	206	
Marital status				<.001				<.001				<.001				<.001
Single	358	56	414		252	34	286		372	125	497		257	77	334	
Married	1,460	217	1,677		998	103	1,101		1,495	500	1,995		1,012	253	1,265	
Other	414	129	543		267	61	328		430	308	738		269	160	429	
Pathologic grade				<.001				<.001				<.001				<.001
1	1,018	102	1,120		500	39	539		1,042	293	1,335		504	110	614	
2	991	235	1,226		897	137	1,034		1,026	493	1,519		908	330	1,238	
3/4	138	59	197		166	32	198		142	111	253		172	58	230	
Primary tumor site				.022				<.001				<.001				<.001
Upper gum	104	17	121		23	0	23		105	44	149		23	2	25	
Lower gum	101	19	120		70	13	83		106	47	153		71	32	103	
Hard palate	49	12	61		6	0	6		52	22	74		6	0	6	
Cheek mucosa & vestibule of mouth	130	38	168		78	9	87		134	69	203		78	18	96	
Retromolar area	55	15	70		40	10	50		59	33	92		43	29	72	
Tongue	1,735	271	2,006		1,186	128	1,314		1,779	611	2,390		1,199	296	1,495	
Floor of mouth	309	57	366		246	57	303		321	176	497		250	147	397	

Abbreviations: END, elective neck dissection; OSCC, oral squamous cell carcinoma.

status at diagnosis ($P<.0001$), and neck dissection status ($P=.0037$) (Figure 2).

Multivariate Analysis

To determine the efficacy of END based on various clinicopathologic characteristics, all factors identified as significant in the survival analysis were entered into a multivariate analysis based on the Cox regression model. Details of the multivariate Cox regression analysis are

presented in Figure 3. In addition to age, pathologic differentiation of OSCC was an important independent prognostic indicator. A relatively high pathologic grade (grade 2 or 3/4) was adversely associated with DSS (grade 2: HR, 2.019; 95% CI, 1.650–2.470; $P=.000$; grade 3/4: HR, 3.078; 95% CI, 2.340–4.048; $P<.0001$) and OS (grade 2: HR, 1.450; 95% CI, 1.280–1.644; $P=.000$; grade 3/4: HR, 1.826; 95% CI, 1.154–2.203; $P=.000$) compared with grade 1. More important, END was favorably associated with

Figure 1. Overall survival curves of patients with cT1N0M0 oral squamous cell carcinoma compared according to (A) age range, (B) mean age at diagnosis (62 years), (C) sex, (D) marital status at diagnosis, (E) race, (F) tumor orientation, (G) pathologic differentiation, and (H) END. Abbreviations: cT1N0M0, clinical stage T1N0M0; END, elective neck dissection.

Figure 2. Disease-specific survival curves of patients with cT1N0M0 oral squamous cell carcinoma compared according to (A) age range, (B) mean age at diagnosis (61 years), (C) pathologic differentiation, (D) tumor orientation, (E) marital status at diagnosis, and (F) END. Abbreviations: cT1N0M0, clinical stage T1N0M0; END, elective neck dissection.

Figure 3. Forest plots summarizing HR for (A) disease-specific survival and (B) overall survival. Abbreviation: HR, hazard ratio.

prolonged DSS (HR, 0.708; 95% CI, 0.592–0.846; $P=.000$) and OS (HR, 0.828; 95% CI, 0.738–0.930; $P=.001$) compared with observation.

Discussion

Previously, age and sex were reportedly not associated with OSCC survival rate. In contrast, in our survival analyses depending on demographic factors such as age, sex, and race and concentrating on only cT1N0M0 OSCC, all of these factors were independent prognostic indicators for OS. Furthermore, our results showed a lower DSS rate among elderly individuals (aged >61 years) compared with younger individuals, which was consistent with the findings of some previous studies.^{21,22} With regard to marital status, our results showed that married status at diagnosis had a significant independent protective effect on cT1N0M0 OSCC survival. Another study that aimed to evaluate the impact of marital status on OSCC survival supported the same conclusion.²³

However, more research is needed on the association of marital status with increased survival.

To date, many studies have confirmed that histologic grade correlates with survival rate in patients with OSCC.^{19,24} Our study produced a similar conclusion. Typical survival differences were found among different pathologic grades for both DSS and OS. Based on our retrospective analysis of a large cohort of 5,752 patients, we confirmed that tumor site is another important factor affecting patient outcome. Significantly poorer DSS and OS were observed for tumors originating from the cheek mucosa and vestibule of the mouth compared with the upper gum. We tentatively interpret this as a probable consequence of the increased incidence of cervical lymph node metastasis and the relatively complicated resection procedure for tumors in the cheek mucosa and vestibule of the mouth. Similarly, OSCC site played an important role in disease prognosis, as presented in another study.²⁵

One of the most common causes of treatment failure in early-stage OSCC is the high incidence of occult metastases and recurrence in the neck. It has also been suggested that recurrence in the neck is associated with a significant decrease in DSS.²⁶ A prospective randomized controlled trial of 496 patients showed that those who received END at the time of the primary surgery were less likely to experience nodal recurrence (29.6%) than those who did not (45.1%).¹⁸ In a retrospective administrative database analysis, END was proven to improve DSS versus neck observation in patients with T1/T2N0M0 OSCC of the tongue with moderately differentiated, poorly differentiated, or undifferentiated histologic grade tumors >1 cm. However, those with well-differentiated tumors benefited from END only when the tumor was >2 cm.¹³ Meanwhile, a recent study also recommended END for moderately and poorly differentiated T1N0 tumors irrespective of depth of invasion but did not support the idea that END may be necessary for well-differentiated tumors.¹⁹ In another prospective randomized study and meta-analysis of 6 randomized trials of END in early-stage OSCC,¹⁰ the pooled HR for OS indicated a 31% reduction in the risk of death with END (HR, 0.69; $P=.002$) and a 33% reduction in the risk of recurrence/death (HR, 0.67; $P=.04$ for DSS). It also showed a benefit for T1 tumors and even for tumors <10 mm in diameter.

However, the 2009 prospective randomized study by Yuen et al⁸ showed no benefit for END in patients with OSCC of the tongue, with a 5-year DSS rate of 87% for the observation arm and 89% for the END arm (the 2% difference was not significant). In a study on variation in OSCC management strategies between representatives of head and neck cancer treatment centers, high variation in management of the neck was seen in early OSCC.⁶ There appears to be a need for direct evidence on optimal management decisions to establish more evidence-based management and uniform practice. Many surgeons still underestimate the rate at which occult neck metastases occur in patients with smaller oral tumors, especially T1 tumors.

We performed this analysis to determine the effect of END for patients with only cT1N0M0 OSCC. Our findings showed that END significantly improved both OS and DSS in these patients, which is consistent with the findings of 2 large-scale prospective randomized studies and a meta-analysis of all prospective randomized studies.^{10,18} Our retrospective analysis using the SEER database to analyze 5,752 patients with only cT1N0M0 OSCC complements those studies, and together with the meta-analysis provides evidence supporting a review of head and neck cancer guidelines.

However, several patient characteristics in the 2 previous studies differed from ours: (1) mean ages were 48 years (Mumbai)¹⁸ and 63 years (UK)¹⁰ versus

62.02 years in our study, so age was similar between our analysis and the UK trial; (2) patients were 75% (Mumbai) and 64% (UK) male versus 55.8% in our study; (3) 85.6% of patients in the previous trials were White versus 87.9% in our study; (4) most patients had well-/moderately differentiated disease (grade 1/2), accounting for 82.3% (Mumbai) and 70.8% (UK) of patients in the previous studies versus 90.7% in our study; and (5) the tongue was the most common site for primary tumors in all 3 studies, with incidence rates of 85% (Mumbai) and 61% (UK) versus 67.5% in our study.

Despite these differences, all 3 studies showed improvements in OS and DSS. Compared with results generated by combining the UK and Mumbai studies,^{10,18} which had a pooled HR for OS of 0.66 (95% CI, 0.49–0.89; $P=.006$) and an HR for DSS of 0.53 (95% CI, 0.37–0.77; $P<.001$), our results were more conservative in regard to the benefit of END for OS (HR, 0.828) and DSS (HR, 0.708). In addition, the OS HRs were 0.75 and 0.42 for T1 and T2 tumors, respectively, in the Mumbai study¹⁸ (suggesting that END may be a more favorable approach in larger vs smaller tumors), but the difference was not statistically significant. However, evidence from the UK randomized trial¹⁰ indicated that END also benefits T1 tumors. Similarly, our study also provides evidence for the benefit derived from END in patients with T1 OSCC.

END is occasionally performed at the same time as tumor resection for cT1N0M0 OSCC.¹⁷ In terms of postoperative morbidity of the neck and costs related to the procedure, END is associated with an increased risk of adverse effects, including those involving swallowing function and sensory nerves, but has minimal impacts on most quality-of-life components.¹⁰ One study presented a cost-effectiveness analysis of END in the initial surgical management of early-stage oral cavity cancer.²⁷ The researchers constructed a Markov model to simulate primary, adjuvant, and salvage therapy; disease recurrence; and survival in patients with T1/T2 clinically node-negative oral cavity squamous cell carcinoma. Their base-case model found that over a lifetime, the addition of END to primary surgery reduced overall treatment costs by \$6,000 and improved effectiveness by 0.42 quality-adjusted life-years compared with primary surgery alone. The decrease in overall cost despite the added neck dissection was a result of less use of salvage therapy. Therefore, increasingly more clinicians believe that the addition of END reduces costs and improves health outcomes, making it a cost-effective treatment strategy for patients.

Some limitations of our study should be noted. First, other oncologic outcome data were absent, such as tumor depth of invasion, which has drawn much recent attention as a better predictor of disease prognosis, as represented in the 8th edition of the *AJCC Cancer Staging Manual*.³ The true oncologic benefit

of END could not be determined accurately. Further research on tumor depth of invasion should be explored. Second, a research data bias may potentially exist for the selection of END due to surgeon bias and patient choice. Because younger patients were more likely to undergo END than older patients, and multiple studies have shown improved OS in younger patients, age may play a role in the frequency of END. Therefore, additional translational studies to identify favorable subgroups of patients should be performed. Third, the long-term complications of neck dissection are not addressed in our study but should be further presented to provide more comprehensive evidence. Finally, information on neck lymph node metastasis after surgery is not included in this analysis but may be used to estimate a more convincing result.

Conclusions

Older age (>62 years), male sex, high pathologic grade, and unmarried status were associated with an increased

risk of death in patients with cT1N0M0 OSCC. END performed at the same time as treatment of the primary site for patients with cT1N0M0 OSCC confers a significant OS and DSS benefit.

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