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Association of neck dissection with survival for early stage N0 tongue cancer

A SEER population-based study

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Abstract

The management of the node negative neck in patients with tongue cancer remains a complex and controversial issue, especially in those with early stage tumors. Patients with negative cervical lymph nodes generally have a good prognosis. However, in patients without neck dissection, neck recurrences may occur after excision of the primary tumor due to occult cervical metastases. It often results in poor salvage therapy options and short survival. We used Surveillance, Epidemiology, and End Results data from 2004 to 2013 to investigate the association of neck dissection with survival among early stage tongue cancer patients with negative lymph node metastasis. A total of 4274 eligible patients were subdivided into 2 groups according to their neck management strategies: neck dissection and observation. Univariate and multivariate Cox proportional hazards regression models were used to determine the independent factors of survival. The Kaplan–Meier method was employed for survival analysis. In the overall cohort, patients who underwent neck dissection had better survival than those who were managed with observation in both tongue cancer specific survival and overall survival. After adjusting for confounding variables, neck dissection strategy remains an independent prognostic factor for better survival. When stratifying the patients according to age, gender, race, marital status, histologic grade, stage and radiotherapy, patients in the neck dissection group had significantly better survival than those in the observation group. Neck dissection may improve survival for early stage tongue cancer patients with negative lymph node metastasis. These results may assist clinicians in selecting the most appropriate neck management strategy for individual patients.

Abbreviations: AJCC = American Joint Committee on Cancer, END = elective neck dissection, HR = hazards ratio, ND = neck dissection, OBS = observation, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results, SLNB = Sentinel lymph node biopsy, TCSS = tongue cancer-specific survival.

Keywords: Cox model, neck dissection, prognosis, SEER, tongue cancer

1. Introduction

Tongue cancer is the most common type of oral cancer worldwide and can affect any part of the tongue. It contributes to about 40% to 60% of all oral cancer deaths, and is considered a significant component of the global burden of cancer.[1] Surgical excision has been the preferred treatment modality for tongue cancer (American Joint Committee on Cancer [AJCC] stage I and II) at many institutions. However, the management of lymph node negative (N0) neck in patients with early stage tongue cancer varies between institutions and remains controversial.[2–5]

Metastatic involvement of cervical lymph nodes is currently one of the most important prognostic factors for outcome.[6] Although most patients with early stage tongue cancer present with negative lymph nodes, a proportion of these patients harbor occult regional lymph node metastases. Many studies have demonstrated that occult lymph node metastases were significantly associated with increased tumor recurrence and poor survival.[7–10] For this reason, some researchers suggest that neck dissection (ND) can reduce the risk of cancer recurrence and should be performed routinely in all patients. However, ND will inevitably increase postoperative morbidity, including shoulder morbidity, pain and sensibility disorders, and thus has a major impact on the quality of life.[11] Previous studies reported that the incidence of occult cervical metastasis among tongue cancer patients range widely, from about 20% to 40%.[12–16] It implies over-treatment and treatment associated morbidity in the majority of patients, and that neck dissection may be unnecessary or even harmful.[17] Moreover, many studies have demonstrated that patients who underwent prophylactic neck dissection had similar long-term survival compared to those managed with close observation alone.[18–20] Therefore, many clinicians advocate observation (OBS, the "wait and see" approach) for patients with N0 neck in tongue cancer. At the moment, a standardized neck management strategy for early stage tongue cancer patients without nodal metastases remains to be established. Although a number of studies have examined the association between ND and survival in tongue cancer, there is no consensus regarding its survival benefit.[15,16] Furthermore, most of the published studies

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are of limited sample size, population diversity, or follow-up time.

In this study, we aim to provide further insights into the neck management strategy for T1-2N0 tongue cancer patients, and help improve treatment selection. We extracted data from the Surveillance, Epidemiology, and End Results (SEER) (http://www.seer.cancer.gov) registry and identified a total of 4274 patients with early stage N0 tongue cancer who were included in the registry from 2004 to 2013. We compared cancer specific and overall survival between patients with different neck treatment strategies. We also identified subgroups of patients who may derive survival benefit from ND. These results will assist clinicians in selecting the most appropriate neck management strategy for individual patients.

2. Methods

2.1. Data sources and inclusion criteria

All relevant data were obtained using SEER*Stat software (http://seer.cancer.gov/data/options.html), version 8.3.4. The study design and procedures were approved by the Ethics Committee of Shanghai Jiaotong University Affiliated Ninth People's Hospital. As the study is based on nonidentifiable registry data, the need to obtain written informed consent was waived. We queried the database for patients diagnosed between 2004 and 2013 with tongue cancer. The flowchart of patient selection was shown in Supplementary Figure S1, http://links.lww.com/MD/C711. Only patients for whom primary tongue cancer was the first or only cancer diagnosis were included. The tumor needed to be pathologically confirmed, not diagnosed at death or autopsy. For inclusion, patients also needed to be diagnosed with T1N0M0 or T2N0M0. The SEER major tumor site codes of interest were: border of tongue (C02.1), anterior 2/3 of tongue (C02.3), tongue (C02.9), base of tongue (C01.9), ventral surface of tongue (C02.2), overlapping lesion of tongue (C02.8), dorsal surface of tongue (C02.0), and lingual tonsil (C02.4). Patients with missing or unknown data were not included in the analysis. Further exclusion criteria include incomplete follow-up information, no explicit type of primary or regional lymph node surgery and unknown radiotherapy status. Finally, a total of 4274 patients were eligible for our study. Table 1 describes the steps for the inclusion of patients in the cohort.

Demographic and clinical variables obtained from the SEER database included age, sex, race, marital status, histologic grade, tumor stage, radiotherapy, and neck treatment strategy. Patients were divided into 2 groups according to the neck treatment strategy, which was classified as neck dissection and observation. Race was categorized as white, black, and other. Marital status was categorized as married and not married. Unmarried patients included those who were never married, divorced, separated, domestic partner, and widowed. The histologic grade was categorized as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated in the SEER database. For tumor stage, patients were divided into stage I and stage II according to the AJCC TNM staging system.

The primary outcomes of this study were tongue cancer-specific survival and overall survival. Tongue cancer-specific survival was defined as survival until death from tongue cancer, with tongue cancer as the underlying cause of death, and death as a result of other causes was censored. Overall survival was defined as the interval between the date of surgery and the date of death from any cause or of the last follow-up.

2.2. Statistical analysis

Statistical analysis was performed using the R (www.r-project.org) package "survival" (version 2.40.1). The following clinical and histopathological variables were analyzed in the study: age, sex, race, marital status, AJCC stage, histologic grade, and radiation therapy. The Chi-square test was used to assess the differences in clinical characteristics between neck dissection and observation groups. Survival curves were generated using the Kaplan–Meier method, and survival rates between subgroups were evaluated using the log-rank test. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of TCSS and OS. Univariate Cox regression analysis was used to assess the association between each variable and survival, and all variables were included in the multivariate Cox proportional hazards regression analysis. All reported P values were 2-sided and considered statistically significant when <0.05.

3. Results

3.1. Patient demographic characteristics and clinical features

We identified 4274 patients that met our inclusion criteria. In general, these patients were diagnosed with primary early stage (AJCC stage I or II) tongue cancer between 2004 and 2013. All patients had negative lymph node status. The histologic type of most tumors (98%) was squamous cell neoplasms (ICD-O-3 code 8050-8089), while the rest includes mucoepidermoid neoplasms

Table 1

Criteria for cohort selection from the primary SEER database.

Criterion	No. of patients	Excluded	
		No. of patients	Percentage
Entire tongue cancer cohort	52,391	0	0.0%
Tongue cancer is the first or only cancer	42,013	10,378	19.8%
Diagnosis between 2004 and 2013	22,109	19,904	47.4%
AJCC TNM staging system T1 or T2	12,891	9218	41.7%
AJCC TNM staging system N0	6141	6750	52.4%
AJCC TNM staging system M0	6078	63	1.0%
Treated with radical excision of the primary tumor	5251	827	13.6%
With definite information of regional lymph node surgery	5242	9	0.2%
Nonmissing values for all variables	4274	968	18.5%

AJCC = American Joint Committee on Cancer, SEER = Surveillance, Epidemiology, and End Results.

(ICD-O-3 code 8430-8439), cystic, mucinous and serous neoplasms (ICD-O-3 code 8440-8499), and others. The median follow-up time for the cohort was 39 months (interquartile range [IQR], 17–70 months). The median age at diagnosis was 60 years (IQR, 51–70 years). We separated the cohort into 2 groups, using the age of 50 as a discrete variable (under 50 years and over 50 years). Since for oral cancer including tongue cancer, tobacco use is the most important risk factor. However, according to recent publications, HPV may be replacing tobacco as the primary cause of oral cancer for individuals under the age of 50.[21] Furthermore, oral cancer rates increase with age, and the increase becomes more rapid after age 50. Among the 4274 patients, 2370 (55%) were men and 1904 (45%) patients were women. The most common race in the study population was white (86%, n = 3695), followed by other races (10%, n = 424) and black (4%, n = 155). For marital status, most of the patients, 62% (n = 2639) were married. For histologic grade, 1345 (32%), 2322 (54%), and 593 (14%) tumors were well, moderately, and poorly differentiated, respectively, and only 14 (0.3%) tumors were undifferentiated. Around one-fifth (22%, n = 935) patients had received radiation therapy as part of their cancer therapy. All patients were categorized into 2 groups according to their neck treatment strategies: neck dissection group (2064 of 4274 patients; 48.3%) and observation group (2210 of 4274 patients; 51.7%). Table 2 summarizes the demographic and treatment characteristics of the 2 cohorts. Patients of both groups did not differ significantly with respect to race and marital status. White patients accounted for the largest proportion of both groups (85.7% and 87.2% for ND and OBS, respectively). For all other clinical and pathological characteristics, notable differences were detected between the 2 groups. Compared with patients in the observation group, patients who underwent neck dissection were more likely to be male (57.2% vs 53.8%, $P < .031$). When compared with the OBS group, ND group showed a higher percentage of younger patients ($\leq$ 50 years, 29.6% vs 20.0%; $P < .001$). Moreover, the ND group tended to present a more malignant clinical phenotype, such as higher grade (poorly differentiated, 15.5% vs 12.3%; $P < .001$) and later AJCC stage (stage II, 37.3% vs 20.5%; $P < .001$). Significantly more patients in the ND group received radiotherapy compared to the OBS group (24.6% vs 19.3%; $P < .001$).

3.2. Univariate and multivariate analyses of prognostic variables

To identify the prognostic factors associated with long-term survival for early stage tongue cancer patients, the Cox proportional hazards regression model was used for univariate and multivariate analyses. The influence of the following factors on tongue cancer-specific survival (TCSS) and overall survival (OS) was investigated: age, sex, race, marital status, histologic grade, AJCC stage, radiation therapy, and neck treatment policy. The results of univariate Cox regression analysis are presented in Table 3. All the considered variables were significantly associated with TCSS and OS, except for sex. There was no significant difference on survival between undifferentiated and well-

Table 2

Clinicopathological features of early stage tongue cancer patients in the study population.

	ND (n = 2064)		OBS (n = 2210)		Total (n = 4274)		
Characteristics	**No**	**%**	**No**	**%**	**No**	**%**	***P*‡**
Median follow-up (months) (IQR)	39 (18–71)		38 (16–68)		39 (17–70)		
Median age (years) (IQR)	57 (49–67)		62 (53–73)		60 (51–70)		
Age, years							**<.001**
≤50	610	29.6	441	20.0	1051	24.6	
>50	1454	70.4	1769	80.0	3223	75.4	
Sex							**.031**
Male	1180	57.2	1190	53.8	2370	55.5	
Female	884	42.8	1020	46.2	1904	44.5	
Race							.36
White	1769	85.7	1926	87.2	3695	86.5	
Black	81	3.9	74	3.3	155	3.6	
Other*	214	10.4	210	9.5	424	9.9	
Marital status							.709
Married	1268	61.4	1371	62.0	2639	61.7	
Not married†	796	38.6	839	38.0	1635	38.3	
Histologic grade							**<.001**
WD	514	24.9	831	37.6	1345	31.5	
MD	1224	59.3	1098	49.7	2322	54.3	
PD	320	15.5	273	12.3	593	13.9	
UD	6	0.3	8	0.4	14	0.3	
AJCC stage							**<.001**
I	1294	62.7	1757	79.5	3051	71.4	
II	770	37.3	453	20.5	1223	28.6	
Radiation therapy							**<.001**
Yes	508	24.6	427	19.3	935	21.9	
No	1556	75.4	1783	80.7	3339	78.1	

AJCC = American Joint Committee on Cancer, IQR = interquartile range, MD = moderately differentiated, ND = neck dissection, OBS = observation, PD = poorly differentiated, UD = undifferentiated, WD = well differentiated.

* Other includes American Indian/Alaskan native and Asian/Pacific Islander.

† Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed.

‡ *P* values for the Chi-square test were calculated between the END and OBS groups; bold type indicates significance.

Table 3

Univariate Cox proportional hazard model of tongue cancer-specific survival and overall survival.

Variables	TCSS		OS	
	HRs (95% CI)	P‡	HRs (95% CI)	P‡
Age, years				
≤50	Reference		Reference	
>50	1.498 (1.217–1.844)	**<.001**	2.308 (1.930–2.759)	**<.001**
Sex				
Male	Reference		Reference	
Female	1.046 (0.886–1.235)	.596	0.905 (0.798–1.026)	.119
Race				
White	Reference		Reference	
Black	1.246 (0.834–1.863)	.2830	1.391 (1.046–1.849)	**.023**
Other*	0.721 (0.528–0.984)	**.0394**	0.665 (0.522–0.847)	**<.001**
Marital status				
Married	Reference		Reference	
Not married†	1.394 (1.181–1.646)	**<.001**	1.554 (1.373–1.760)	**<.001**
Histologic grade				
WD	Reference		Reference	
MD	1.7985 (1.440–2.246)	**<.001**	1.404 (1.203–1.638)	**<.001**
PD	3.8513 (2.989–4.962)	**<.001**	2.639 (2.190–3.179)	**<.001**
UD	0.9649 (0.135–6.916)	.972	2.122 (0.875–5.147)	.096
AJCC stage				
I	Reference		Reference	
II	1.802 (1.522–2.133)	**<.001**	1.672 (1.471–1.90)	**<.001**
Radiation therapy				
Yes	2.417 (2.040–2.864)	**<.001**	1.784 (1.561–2.039)	**<.001**
No	Reference		Reference	
Neck dissection				
Yes	0.767 (0.649–0.907)	**<.001**	0.783 (0.690–0.887)	**<.001**
No	Reference		Reference	

AJCC = American Joint Committee on Cancer, CI = confidence interval, HRs = hazard ratios, MD = moderately differentiated, OS = overall survival, PD = poorly differentiated, TCSS = tongue cancer-specific survival, UD = undifferentiated, WD = well differentiated.

* Other includes American Indian/Alaskan native and Asian/Pacific Islander.

† Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed; bold type indicates significance.

differentiated tongue cancer patients. This may be attributed to the low percentage of patients (0.3% of the whole cohort) diagnosed with undifferentiated cancer. Patients receiving neck dissection showed a significant benefit in TCSS and OS compared with those who were managed with observation only (HR, 0.767; 95% CI, 0.649–0.907; $P < .001$ for TCSS; and HR, 0.783; 95% CI, 0.690–0.887; $P < .001$ for OS).

All the key prognostic factors were included in multivariate Cox proportional hazards regression model. The detailed results of the multivariate analysis are presented in Table 4. After adjusting for confounding variables, the multivariate analysis revealed that race was no longer an independent prognostic factor for tongue cancer patients in TCSS. Patient gender is also not an independent risk factor for survival. However, compared with white patients, minority ethnic group patients had a decreased risk of overall mortality (HR, 0.781; 95% CI, 0.612–0.995; $P = .0461$). The clinical pathological characteristics of age, marital status, histologic grade, AJCC stage, radiotherapy, and neck treatment policy were independent factors for early stage tongue cancer. According to the results, advanced age, not married status, higher histologic grade, advanced AJCC stage, receiving radiotherapy, and neck observation were associated with poor TCSS and OS. Overall, compared with observation, therapeutic neck dissection resulted in a significant survival advantage in patients with early stage tongue cancer (HR, 0.652; 95% CI, 0.548–0.774; $P < .001$ for TCSS; and HR, 0.705; 95% CI, 0.619–0.803; $P < .001$ for OS).

To further investigate the effects of ND on survival, Kaplan–Meier survival curves were plotted for groups of patients subdivided according to their neck treatment policies. The survival curves demonstrated that patients who underwent ND had significantly better TCSS ($P = .0018$) and OS ($P < .001$) than patients in the observation group (Fig. 1).

3.3. Subgroup analysis for survival outcomes

To evaluate the potential effect modification, we performed stratified analyses according to the following characteristics: age, sex, race, marital status, histologic grade, AJCC stage, and radiation therapy. The Kaplan–Meier method was used for survival analysis, and subgroups were compared with the log-rank test. The survival curves indicated that ND conferred a survival benefit in patients aged >50 years ($P = .009$ and $P = .003$ for TCSS and OS, respectively), but not in those aged ≤50 years (Supplementary Figure S2, http://links.lww.com/MD/C711). Similarly, neck treatment policy can stratify the outcome of unmarried patients ($P < .001$ for TCSS and OS, respectively), but not married patients (Supplementary Figure S3, http://links.lww.com/MD/C711). In the subgroup analysis by ethnic populations, the survival advantage achieved with ND was observed in white patients ($P = .003$ and $P < .001$ for TCSS and OS, respectively), but not in black and minority ethnic patients (Supplementary Figure S4, http://links.lww.com/MD/C711). One of the possible reasons may be the relatively small number of patients in black and minority ethnic

Table 4

Multivariate Cox proportional hazard regression model of Tongue cancer-specific survival and overall survival.

Variables	TCSS		OS	
	HRs (95% CI)	P‡	HRs (95% CI)	P‡
Age, years				
≤50	Reference		Reference	
>50	1.409 (1.142–1.737)	**.0014**	2.197 (1.835–2.631)	**<.001**
Sex				
Male	Reference		Reference	
Female	1.081 (0.912–1.281)	.369	0.880 (0.774–1.001)	.0533
Race				
White	Reference		Reference	
Black	1.002 (0.668–1.501)	.992	1.178 (0.884–1.571)	.2615
Other*	0.805 (0.588–1.101)	.175	0.781 (0.612–0.995)	**.0461**
Marital status				
Married	Reference		Reference	
Not married†	1.328 (1.120–1.574)	**<.001**	1.532 (1.348–1.741)	**<.001**
Histologic grade				
WD	Reference		Reference	
MD	1.736 (1.385–2.175)	**<.001**	1.382 (1.182–1.617)	**<.001**
PD	3.188 (2.448–4.150)	**<.001**	2.325 (1.914–2.823)	**<.001**
UD	1.027 (0.142–7.381)	.979	2.740 (1.125–6.674)	**.0265**
AJCC stage				
I	Reference		Reference	
II	1.492 (1.240–1.793)	**<.001**	1.488 (1.295–1.710)	**<.001**
Radiation therapy				
Yes	1.784 (1.480–2.149)	**<.001**	1.364 (1.179–1.578)	**< 0.001**
No	Reference		Reference	
Neck dissection				
Yes	0.652 (0.548–0.774)	**<.001**	0.705 (0.619–0.803)	**<.001**
No	Reference		Reference	

AJCC = American Joint Committee on Cancer, CI = confidence interval, HRs = hazard ratios, MD = moderately differentiated, OS = overall survival, PD = poorly differentiated, TCSS = tongue cancer-specific survival, UD = undifferentiated, WD = Well differentiated.

* Other includes American Indian/Alaskan native and Asian/Pacific Islander.

† Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed; bold type indicates significance.

groups. Black and minority ethnic group patients accounted for only 3.6% (n = 155) and 9.9% (n = 424), respectively, of the overall sample. The small number of patients may not provide enough statistical power to detect significant differences between treatment groups. In addition, the Kaplan–Meier curves of both groups indicated that the patients underwent neck dissection have a trend toward a relatively better prognosis in comparison to those who received observation only, but did not reach significant levels. Furthermore, there was no statistically significant difference in TCSS and OS for patients

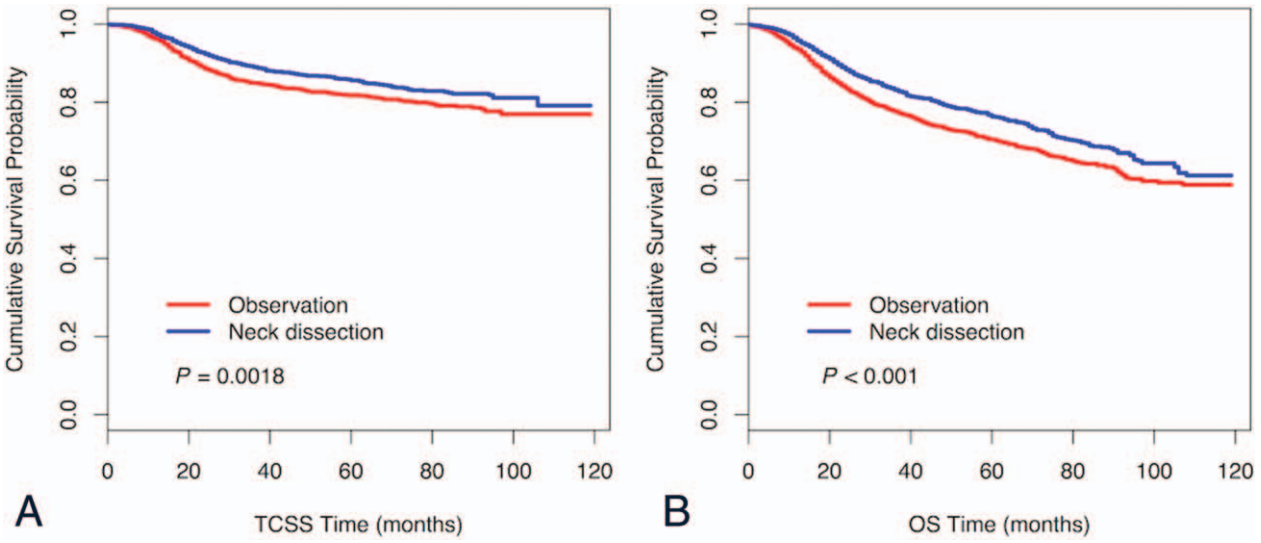

Figure 1. Kaplan–Meier curves for survival by neck management groups. (A) Tongue cancer-specific survival (TCSS) and (B) overall survival (OS). OS = overall survival, TCSS = tongue cancer-specific survival.

Table 5

Multivariate Cox proportional hazard regression model of tongue cancer-specific survival and overall survival comparing elective neck dissection (END) with OBS, stratified according to clinical variables.

	ND vs OBS*			
	TCSS		OS	
Variables†	HRs (95% CI)	P‡	HRs (95% CI)	P‡
Age, years				
<=50	0.646 (0.441–0.946)	**.025**	0.709 (0.504–0.999)	**.049**
>50	0.657 (0.541–0.797)	**<.001**	0.699 (0.608–0.804)	**<.001**
Sex				
Male	0.705 (0.559–0.889)	**.003**	0.734 (0.620–0.870)	**<.001**
Female	0.589 (0.454–0.765)	**<.001**	0.649 (0.530–0.795)	**<.001**
Race				
White	0.655 (0.545–0.786)	**<.001**	0.719 (0.626–0.824)	**<.001**
Black	0.462 (0.181–1.175)	.105	0.544 (0.281–1.054)	.071
Other‡	0.625 (0.332–1.180)	.147	0.559 (0.338–0.921)	**.022**
Marital status				
Married	0.826 (0.657–1.038)	.101	0.780 (0.654–0.931)	**.005**
Not married§	0.475 (0.364–0.620)	**<.001**	0.616 (0.510–0.745)	**<.001**
Histologic grade				
WD	0.998 (0.668–1.492)	.995	0.932 (0.708–1.226)	.614
MD	0.599 (0.476–0.753)	**<.001**	0.663 (0.558–0.787)	**<.001**
PD	0.548 (0.388–0.774)	**<.001**	0.609 (0.460–0.807)	**<.001**
AJCC stage				
I	0.653 (0.520–0.820)	**<.001**	0.718 (0.608–0.847)	**<.001**
II	0.640 (0.490–0.836)	**.001**	0.671 (0.546–0.824)	**<.001**
Radiation therapy				
Yes	0.655 (0.498–0.861)	**.0024**	0.676 (0.538–0.848)	**<.001**
No	0.620 (0.496–0.775)	**<.001**	0.698 (0.597–0.818)	**<.001**

AJCC = American Joint Committee on Cancer, CI = confidence interval, HRs = hazard ratios, MD = moderately differentiated, ND = neck dissection, OBS = observation, OS = overall survival, PD = poorly differentiated, TCSS = tongue cancer-specific survival, WD = well differentiated.

* Using OBS as a reference.

† Adjusted using a multivariate Cox proportional hazard regression model, including age, race, marital status, grade, AJCC stage and radiation therapy.

‡ Other includes American Indian/Alaskan native and Asian/Pacific Islander.

§ Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed; bold type indicates significance.

with well-differentiated tongue cancer who underwent ND compared with those who did not (Supplementary Figure S5, http://links.lww.com/MD/C711). However, among patients with moderately or poorly differentiated tumors, improved TCSS ($P<.001$ and $P=.004$ for moderately and poorly differentiated tumors, respectively) and OS ($P<.001$ and $P=.003$ for moderately and poorly differentiated tumors, respectively) were observed in patients who received ND. For patients stratified by tumor stage and radiation therapy, ND was associated with longer survival in all subgroups (Supplementary Figure S6 and S7, http://links.lww.com/MD/C711).

The multivariate Cox proportional hazards model was also applied to calculate hazard ratios and 95% confidence intervals for all subgroups (Table 5). After multivariate adjustment, in most subgroups, there was an associated protective effect for patients who received ND compared with those who did not. The results for TCSS and OS were similar. Notably, ND led to significantly improved survival in both young (HR, 0.646; 95% CI, 0.441–0.946; $P=.025$ for TCSS; and HR, 0.709; 95% CI, 0.504–0.999; $P=.049$ for OS) and elderly patients (HR, 0.657; 95% CI, 0.541–0.797; $P<.001$ for TCSS; and HR, 0.699; 95% CI, 0.608–0.804; $P<.001$ for OS). The benefits of ND were also observed in both male (HR, 0.705; 95% CI, 0.559–0.889; $P=.003$ for TCSS; and HR, 0.734; 95% CI, 0.620–0.870; $P<.001$ for OS) and female (HR, 0.589; 95% CI, 0.454–0.765; $P<.001$ for TCSS; and HR, 0.649; 95% CI, 0.530–0.795; $P<.001$ for OS) patients.

4. Discussion

The optimal management of node negative neck in tongue cancer has been debated extensively, especially for early stage tumors.[3,4,22] However, there is no consistent conclusion, and the management policies vary across different institutions. Therefore, a standardized neck management strategy needs to be established. Some researchers advocate that ND should be performed routinely, given the high rate of occult cervical metastasis in tongue cancer. This kind of metastasis is the main risk factor of postoperative recurrence and may lead to a poor prognosis.[7,23] Despite improvements in diagnostic tools, such as ultrasonography, computed tomography and magnetic resonance imaging, accurate diagnosis of occult lymph node micrometastasis is still difficult. Montes and Schmidt[24] found that neck dissection is better than observation at improving recurrence-free survival. The alternative neck management policy is "wait-and-see." In this case, patients will receive radical excision and close follow-up monitoring to avoid ND. The proponents of "wait-and-see" policy claimed that patients with node negative tongue cancer should not be over-treated in order to avoid additional morbidity and costs.[18,19] There is not enough evidence to assert that ND is superior to the policy of observation without neck surgery, with regard to survival and control of neck disease. In a retrospective study, Patel et al[25] found that neck dissection improved cancer specific survival in T1/T2N0M0 patients with moderately differentiated, poorly

differentiated or undifferentiated grade tumors that were >1 cm in size. Also patients with well-differentiated tumors benefited from neck dissection only when tumor size was >2 cm. However, in a prospective randomized study, the authors reported that neck dissection and observation showed similar treatment outcomes, as long as patients can be followed-up closely.[20]

In this study, we used SEER data sets to compare the outcomes of different treatment policies for N0 neck in early stage tongue cancer. Patients who underwent neck dissection demonstrated a significant survival benefit in TCSS and OS than those who were managed with observation only. We further conducted stratified analyses by factors that could potentially confound or modify the relationship between neck treatment policy and survival. ND showed better survival than OBS in all subgroups, except for race and well differentiated tumors. These results indicated that ND is necessary for patients with AJCC stage I or II tongue cancer, even if there is no evidence of cervical metastasis. Although there have been similar studies on this topic, the main limitations of these studies were related to their small sample size, short follow-up period, and the relatively small number of prognostic parameters included. Several factors strengthen our study conclusions. First, our results are based on the analysis of a large cohort of 4274 patients. All relevant data were retrieved from the SEER database, which contains population-based data on cancer incidence and survival, and represents about 28% of the US population. The results may be generalized to a wider population of patients. Second, we incorporated a comprehensive range of factors into the Cox proportional model for multivariate analysis. To our knowledge, the impact of marital status on tongue cancer survival has not been studied yet. Third, our study cohort is large enough to conduct stratified analysis according to a wide range of prognostic factors. These results will provide clinicians with valuable information to assist them in selecting the most appropriate treatment policy for patients with early stage tongue cancer.

Since neck dissection is associated with postoperative morbidity of the neck, it is important to identify patients who would benefit from ND. Recently, advanced surgical methods for lymph node assessment have been extensively studied. Sentinel lymph node biopsy (SLNB) is a minimally invasive technique that has recently been used to detect occult lymph node metastases.[26] The sentinel node refers to the first lymph node reached by metastasizing cancer cells from a primary tumor. Due to its high sensitivity in detecting metastatic lymph nodes in patients with early stage cancer, SLNB can be used to identify and select suitable candidates for neck dissection.[27] If metastasis is not detected in sentinel lymph node, neck dissection is avoidable. Moreover, elective neck dissection (END) is commonly used to stage the neck and treat occult metastases.[28,29] The advantages of END include reduced morbidity and negligible effect on quality of life. Recent studies have reported that END can improve overall survival and reduce the risk of recurrence when compared with observation policy in early node negative squamous cell oral cancer.[30–34] In the future, these methods will play an important role in selecting the most suitable neck management option for individual patients.

To eliminate the potential influence of the confounding factors, we performed stratified analyses. In our results, ND did not show a survival advantage for well-differentiated tumors. This is possibly due to the low malignant potential and low recurrence rate of well-differentiated tumors. These patients have significantly better survival than those with moderately or poorly differentiated tumors. Thus, in the well-differentiated tumor group, many patients may be over-treated with ND. These results were consistent with a previous population-based study using SEER data.[25] In the study, the authors focused on tumor size and histologic grade. In our study, we further found that neck dissection yielded survival benefits for unmarried patients, but not for married patients. This may be explained by the psychosocial perspective. For married patients, their spouses could help them receive close observation and appropriate care. As mentioned above, there is a prospective randomized study reported that neck dissection and observation showed similar treatment outcomes, as long as patients can be followed-up closely. Moreover, married patients are also more likely than unmarried patients to have better family financial status, to seek treatment at more prestigious medical facilities, and to comply with medication recommendations. Furthermore, existing literature has shown that marital status is an independent prognostic factor for survival in many cancers, including breast cancer,[35] gastric cancer,[36] colorectal cancer,[37] prostate cancer,[38] pancreatic cancer,[39] etc. Therefore, more social and psychological supports should be provided for unmarried patients. Moreover, neck dissection can significantly prolong survival in tongue cancer patients, regardless of whether they received radiotherapy. We also noted that ND conferred a survival advantage for patients with stage I tumor. Patients with early stage tongue cancer usually have a fairly good prognosis and a low incidence of occult cervical metastasis. In our subgroup analysis, stage I patients who underwent ND also had a higher survival rate than those who received observation only. Part of the reason might be that for patients who underwent neck observation alone, the close surveillance protocols were not steadily implemented after surgical excision of the tumors, and some patients developed advanced neck recurrences and had poor salvage results.[20] In this case, meticulous follow-up examination should be emphasized.

Our study has several limitations common to observational studies. First, the pharmacy claims data were not available for this study. Thus, there was some uncertainty regarding data completeness and accuracy. We were unable to control for the effect of chemotherapy in some patients, which may exert an influence on the results. Second, the information of neck lymph node metastasis after operation was not included in this analysis. These data can be used to estimate the proportion of patients with occult neck lymph node metastases, and to develop a more robust model for assessing the association between ND and survival in lymph node negative patients. Third, the implementation status of surveillance in patients who underwent neck observation was not available. For example, the frequency of the neck examination during the postoperative period. The implementation condition can influence the outcome of patients. Despite these limitations, our study provides insights into the debatable issue of the management of the node negative neck in tongue cancer.

5. Conclusion

According to our results, neck dissection may improve survival for early stage tongue cancer patients with negative lymph node metastasis. Multivariate analysis stratified by cancer stage showed that ND can be beneficial even for patients with very early stage tumors. Recent advances in the methods of neck dissection will continue to reduce morbidity after surgery and to improve the quality of life. The results of this study should motivate future research to determine the best neck management option for early stage tongue cancer patients.

Author contributions

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Methodology: Yufei Xie, Gang Shen.
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