Elective Neck Dissection can Improve the Overall Survival and Cancer-Specific Survival of T3cN0M0 Glottic Squamous Cell Cancer

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Abstract

How to treat clinically node-negative (cN0) neck in larynx squamous cell cancer (LSCC) has been subject to considerable discussion. The role of elective neck dissection (END) in patients with T3 glottic squamous cell cancer (GSCC) with cN0 is remain unclear. The objective of this study is to elucidate the role of END in improve the outcome of T3cN0M0 GSCC. Patients with T3cN0M0 GSCC in the Surveillance, Epidemiology, and End Results database (SEER) from 2004 to 2015 were extracted and stratified into END and Non-END cohorts, we found that only 22–58% T3cN0M0 GSCC were performed with END. After Propensity score matching (PSM), END cohort had better overall survival (OS) (median survival time: 93 vs 40 months, respectively; $p < 0.0001$) and cancer-specific survival (CSS) (HR 0.40, 95%CI 0.26 to 0.64, $p = 0.0012$) than non-END cohort. In addition, Subgroup analysis also indicated END cohort had better OS or CSS than non-END cohort. This study demonstrated that in patients with T3cN0M0 GSCC, END significantly associated with better survival outcomes compared with non-END.

Background

Laryngeal cancer represents 4.5% of all human malignancies and is one of the most common cancers in the upper aerodigestive tract [1]. Larynx squamous cell cancer (LSCC) is the most common type of laryngeal cancer. It is well known that LSCC is characterized by cervical lymph node metastasis that is the most important adverse prognostic factor in patients with LSCC [2–3]. Nonetheless, how to treat clinically negative cervical lymph nodes (cN0) in LSCC has been subject to considerable discussion. Options for treatment include elective neck dissection (END) at the time of the excision of the primary tumor and “wait and see” strategy (delaying neck dissection until neck metastasis is clinically detectable). The questions remain that whether END would overtreat these patients who without occult metastasis, resulting in increased complications and expenses, or whether delaying END until nodal metastasis occurs would result in declined survival in patients with occult neck disease [4].

According to National Comprehensive Cancer Network (NCCN) guidelines, treatment strategy for cN0 LSCC differed depending on the location and stage of the tumor. However, there still existed certain confusing area. For instance, whether to offer END in T3cN0M0 glottic of the larynx squamous cell cancer is unclear. NCCN suggested in certain T3N0M0 glottic squamous cell cancer (GSCC), pretracheal and inslateral paratracheal lymph node dissection should be performed, while in some cases neck dissection is needed as indicated [5]. Nevertheless, the detailed indications for neck dissection were lacked, and it confused clinicians to decide which strategy to select. Some studies showed the benefits of END in T3cN0M0 GSCC [6], but others suggested that a “wait and see” protocol with close follow-up should be considered in T3cN0M0 GSCC [7, 8]. Therefore, no consensus has been attained on this issue so far.

Even though the GSCC occurred more frequently than supraglottic carcinoma [9], cN0 neck in GSCC didn't receive enough concern for its lower lymphatic metastasis risk, in comparison to supraglottic carcinoma

[10]. Therefore, it is deserve more investigation to make clear whether END benefits the survival of cN0 patients with T3 GSCC. And further help clinicians make the optimal treatment.

The purpose of this study was to retrospectively analyzed 1589 T3cN0M0 GSCC patients in the SEER database from 2004 to 2015, then to investigate the potential effect of END on overall survival(OS) and cancer-specific survival(CSS) and provide clinicians more accurate and evidence-based guidance to treat the T3, cN0 GSCC patients.

Methods

Study Cohorts

We collecte our study data extracted from the Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov/>). The SEER database collects and publishes cancer incidence and survival data from 18 registries recording data from the USA population which is a population-based database cancer registry sponsored by the National Cancer Institute in the USA. Available data include patient demographics, primary tumor data, regional nodal data, vital status, and survival. The SEER database is freely and publicly accessible, and we obtained approval to use the data for our research before initiating this study.

We first filtered cases according to values associated with the "Primary site labeled" variable in order to choose all the patients with cases with tumors originating from the larynx and diagnosed from 2004 to 2015. Subsequently, cases with larynx squamous cell carcinoma were identified on the basis of histology.

Using the SEER*Stat software, version 8.3.5 (<https://seer.cancer.gov/seerstat/>), we extracted the following variables from the database: age at diagnosis, sex, year of diagnosis, race, marital status, grade, stage (6th AJCC, 2004–2015), surgical method, histological type, radiation sequence with surgery, survival months, survival status and cancer-specific survival (CSS). Finally, the T3cN0M0 GSCC with completed surgical information were included in the study.

Statistical analyses

We divided these cases into 2 groups according to the END status. Descriptive parameters between the END and non- END groups were compared using Chi-square test or Fisher's exact test. Propensity score matching (PSM) was used to minimize selection bias among the baseline variables in two groups, including patients' age, sex, race, tumor grade, year of diagnosis, radiotherapy. It was performed via R package "MatchIt". The "nearest" method and 1:1 matching ratio was selected in the PSM. PSM is a commonly used tool which can greatly minimize selection bias of unequally sized treatment groups and preserve an adequate sample size [11–12]. The Kaplan–Meier method was used to construct survival curves, and the log-rank test was used to assess the difference in overall survival (OS) and cancer-specific survival (CSS) between the two treatment groups, before and after PSM. After PSM, we analyzed the clinicopathologic characteristics and treatment outcomes to identify which patient subgroups might

benefit from END. Univariate and multivariate Cox proportional hazard regression analysis was performed to calculate the hazard ratio (HR) and determine independent prognostic factors. Statistical analysis in our study were carried out using SPSS software (version 24.0) and R (version 4.0.3). A two-tailed p-value < 0.05 was considered as statistically significant for all analysis executed.

Results

Baseline characteristics and propensity score matching

Clinical data of 1589 T3N0M0 GSCC patients from 35065 larynx squamous cell carcinoma between 2004 to 2015 were obtained from the SEER database. There are 445 T3cN0M0 GSCC with complete surgical data among these cases, and we classified them into two cohorts (272 non-END, and 173 END) according to END status (Fig. 1S). The baseline clinical features were shown in Table 1, the results revealed that there were significant differences between the non-END group and the END group for age and radiotherapy ($p < 0.05$). In the raw cohort, most patients were males (387, 87%), white race (348, 78.2%), Grade I-II (359, 80.7%), and 282 of 445 patients received radiotherapy. After PSM, there were no significant differences in the baseline variables between the two groups ($p > 0.05$), which indicated that the variables became well-balanced between the two groups after matching.

Table 1

Clinical characteristics of the patients with T3cN0M0 GSCC, before and after propensity score matching (PSM)

	No. of patients (%) characteristics in raw data			No. of patients (%) characteristics after PSM		
Variables	Non-END (n = 273)	With END (n = 172)	p-value	Non-END (n = 172)	With END (n = 172)	p-value
Age						
< 65	106 (38.8)	99 (57.6)	< 0.001*	89 (51.7)	99 (57.6)	0.330
≥ 65	167 (61.2)	73 (42.4)		83 (48.3)	73 (42.4)	
Race						
White	216 (79.1)	132 (76.7)	0.665	142 (82.6)	132 (76.7)	0.286
Black	47 (17.2)	35 (20.3)		24 (14.0)	35 (20.3)	
Others	10 (3.7)	5 (2.9)		6 (3.5)	5 (2.9)	
Sex						
Male	235 (86.1)	152 (88.4)	0.579	144 (83.7)	152 (88.4)	0.276
Female	38 (13.9)	20 (11.6)		28 (16.3)	20 (11.6)	
Grade						
1	53 (19.4)	23 (13.4)	0.265	25 (14.5)	23 (13.4)	0.957
2	172 (63.0)	111 (64.5)		109 (63.4)	111 (64.5)	
3	46 (16.8)	35 (20.3)		36 (20.9)	35 (20.3)	
4	2 (0.7)	3 (1.7)		2 (1.2)	3 (1.7)	
Year of diagnosis						
2004–2009	142 (52.0)	82 (47.7)	0.427	88 (51.2)	82 (47.7)	0.590
2010–2015	131 (48.0)	90 (52.3)		84 (48.8)	90 (52.3)	
Radiotherapy						

* Chi-square test, bold values mean $p < 0.05$, which represent statistically significant.

Abbreviations: cN0, clinically negative cervical lymph nodes; GSCC, glottic squamous cell cancer; END, elective neck dissection.

	No. of patients (%) characteristics in raw data			No. of patients (%) characteristics after PSM		
NO	72 (26.4)	90 (52.3)	< 0.001*	72 (41.9)	90 (52.3)	0.066
YES	201 (73.6)	82 (47.7)		100 (58.1)	82 (47.7)	
* Chi-square test, bold values mean p < 0.05, which represent statistically significant.						
Abbreviations: cN0, clinically negative cervical lymph nodes; GSCC, glottic squamous cell cancer; END, elective neck dissection.						

After analyzing the treatment decision from clinicians in T3cN0M0 GSCC, we found that the percentage of END in T3N0M0 GSCC ranged from 22 to 58, while no obvious change was observed from 2004 to 2015, which indicated that in clinical practice, clinicians might prefer “wait and see” strategy in lymph node negative patients (Fig. 1).

Impact of END on overall survival and cancer-specific survival

As the result showed, before PSM, patients with END presented longer OS compared with those who did not undergo END (median survival time: 93 vs 49 months, $p < 0.001$; Fig. 2(A)). Moreover, improved 3-year (73% vs 56%, $p < 0.0001$), 5-year (64% vs 43%, $p = 0.004$) and 8-year OS estimates (44% vs 36%, $p < 0.0001$) were also observed in END group. Consistent results were observed after PSM. In comparison to non-END group, longer OS was observed in END group (median survival time: 93 vs 40 months, respectively; $p < 0.0001$; Fig. 2(B)), as well as improved 3 year (73.9% vs 52%, $p < 0.0001$), 5-year (64.2% vs 42%, $p = 0.005$) and 8-year OS estimates (44.5% vs 34.9%, $p < 0.0001$).

In addition, END group had improved CSS than non-END group before (89% vs 71% for 3-year CSS, 84% vs 64% for 5-year CSS; Fig. 2C) and after (93.8% vs 86.6% for 3-year CSS, 89.2% vs 77.8% for 5-year CSS; Fig. 2D) PSM. The comparison of CSS at different time points between the two groups showed that p values were all ≤ 0.01 . These results indicate that the T3cN0M0 GSCC patients who underwent END obtained a survival benefit.

Prognostic factors

We further investigated the correlation between survival and clinical variables. As for OS, END and age were significant predictors in univariate or multivariate survival analysis. As shown in Table 2, patients ≥ 65 years (HR = 2.23, 95% CI: 1.653–3.009; $p < 0.001$) had a poorer prognosis, while END (HR = 0.554, 95% CI: 0.411–0.746; $p < 0.001$) were associated with lower mortality. As for CSS, we found END remained to be a significant predictor in T3cN0M0 GSCC patients (HR = 0.381, 95% CI: 0.238–0.61; $p < 0.001$), while age didn't affect the CSS in neither univariate nor multivariate survival analysis (Table 3). Radiotherapy was identified to be a significant risk factor for CSS in univariate or multivariate analysis, but didn't influence the OS. Our study showed that the risk of death was lower in patients with END than in patients

without END, suggesting that END was an independent prognostic factor favorable for OS (HR = 0.553, 95%CI: 0.41–0.748; $p < 0.001$) and CSS (HR = 0.392, 95%CI: 0.244–0.63; $p < 0.001$) in T3CN0M0 GSCC.

Table 2

Univariate and multivariate Cox hazard regression analysis of the risk factors for overall survival in T3cN0M0 GSCC

Univariate analysis		Multivariate analysis		
Variables	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
END				
NO	reference		reference	
YES	0.554 (0.411–0.746)	< 0.001*	0.553 (0.410–0.748)	< 0.001*
Age				
< 65	reference		reference	
≥ 65	2.230 (1.653–3.009)	< 0.001*	2.30 (1.658–3.189)	< 0.001*
Race				
White	reference		reference	
Non-White	0.795 (0.539–1.172)	0.246	0.944 (0.633–1.406)	0.775
Sex				
Male	reference		reference	
Female	1.112 (0.738–1.675)	0.613	0.959 (0.629–1.462)	0.844
Grade				
G1-2	reference		reference	
G3-4	1.145 (0.812–1.613)	0.440	1.069 (0.752–1.521)	0.710
Year of diagnosis				
2004–2009			reference	
2010–2015	0.867 (0.628–1.197)	0.387	0.888 (0.635–1.241)	0.486
Radiotherapy				
NO	reference		reference	
YES	0.836 (0.623–1.122)	0.232	1.096 (0.790–1.523)	0.581
* means p < 0.05, which represent statistically significant.				
Abbreviations: GSCC, glottic squamous cell cancer; END, elective neck dissection; HR, hazard ratio; CI, confidence interval.				

Table 3
Univariate and multivariate Cox hazard regression analysis of the risk factors for cancer-specific survival in T3cN0M0 GSCC

Univariate analysis		Multivariate analysis		
Variables	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
END				
NO	reference		reference	
YES	0.381 (0.238–0.61)	< 0.001*	0.392 (0.244–0.63)	< 0.001*
Age				
< 65	reference		reference	
≥ 65	1.195 (0.765–1.868)	0.433	1.496 (0.917–2.442)	0.107
Race				
White	reference		reference	
Non-White	0.839 (0.47–1.498)	0.554	0.93 (0.515–1.68)	0.81
Sex				
Male	reference		reference	
Female	1.012 (0.535–1.915)	0.97	0.842 (0.441–1.607)	0.602
Grade				
G1-2	reference		reference	
G3-4	1.296 (0.786–2.135)	0.309	1.206 (0.726–2.005)	0.47
Year of diagnosis				
2004–2009			reference	
2010–2015	0.992 (0.628–1.568)	0.973	0.911 (0.568–1.462)	0.7
Radiotherapy				
NO	reference		reference	
YES	1.658 (1.045–2.63)	0.0319*	1.809 (1.084–3.018)	0.023*

* means $p < 0.05$, which represent statistically significant.

Abbreviations: GSCC, glottic squamous cell cancer; END, elective neck dissection; HR, hazard ratio; CI, confidence interval.

Subgroup analysis stratified by patients' characteristics

To better illustrate the influence of END on survival in T3cN0M0 GSCC, patients were divided into different subgroups based on clinical variables and further compared the effects of END on OS and CSS of each subgroup. The results were shown in the forest graph (Figure. 3) and the Kaplan–Meier survival curves (Figure. 4, 5). As seen in Fig. 3, Fig. 4 and Fig. 5, with the exception of the subgroup of patients < 65 years, nonwhite race, grade 3–4, other subgroup all benefitted significantly from END (all $p < 0.05$), END group had better OS than no-END group. Subgroup analysis on CSS showed consistent results with analysis on OS. Exception of the subgroup of female, nonwhite race and grade 3–4, other subgroup all benefitted significantly from END (all $p < 0.05$), END group had better CSS than no-END group.

Discussion

For head and neck squamous cell carcinoma, even in patients with cN0 the incidence of occult metastasis ranges from 10 to 50% [13–14]. Robert et al [15] reported that after cervical lymph node dissection in 44 patients with T3cN0 GSCC, 6 patients (14%) were pathologically confirmed to have positive lymph nodes (5 were N1 and 1 was N2b). Zhang et al [16] reported a similar rate of occult neck metastasis of 14.3% in patients with T3cN0 GSCC. Kligerman et al [17] performed selective bilateral neck dissection in patients with T3-4cN0 and found that the incidence of occult cervical lymph node metastasis of T3cN0 was as high as 29%. At present, it has been clear that lymph node metastasis plays a significantly and negatively role in the prognosis of patients with GSCC [18–19]. However, even though GSCC accounted for the majority of laryngeal cancer, the role of END might be ignored due to its lymph node metastasis risk relative to other laryngeal tumors is lower [20]. Moreover, whether END should be performed in T3cN0M0 GSCC remains unclear. The guidelines for some types of glottic squamous cell carcinoma were confusing. For example, NCCN guidelines provided accurate guidance for T1, T2 and T4 glottic squamous cell carcinoma, however, the description in T3N0M0 glottic squamous cell carcinoma remained uncertain, and controversies still existed in previous studies [5].

In a retrospective study enrolled 1476 CN0 laryngeal carcinoma patients, the lymph node metastasis rate of glottic T3-4 tumor was 8.3%, and the OS rate in the neck dissection group was similar to that in the control group. Their data showed that it was reasonable for T3-4 tumors to adopt a “wait and see” approach to avoid overtreatment [7]. Another study estimated the incidence of occult neck disease, and suggested that END would be restricted to T2 supraglottic squamous cell cancer with epilaryngeal involvement, T3-4 supraglottic squamous cell cancer and T4 glottic cancer, for other lesions, a “wait and see” strategy depending on imaging techniques and cytological assessment could be considered [21]. However, some institutions favor performed neck dissection in patients with T3cN0 GSCC [16]. An analysis of 327 T3-4cN0 laryngeal cancer patients revealed that END could effectively prevent the local recurrence of the tumor, and the recurrence rate was closely correlated with the overall survival [6]. A study in 2014 investigated the lymph node metastasis and prognosis in 212 laryngeal cancer patients, and figured out that unilateral lymph node dissection were supposed to be considered for T3 and T4 unilateral lesions [22].

Our study revealed the benefit of END at the time of primary surgery in patients with T3N0M0 GSCC, both in the raw and PSM cohorts. After PSM to baseline covariates, longer median survival was observed in the END group, as well as improved 3-year, 5-year and 8-year overall survival. Improved 3-year and 5-year cancer-specific survival of the END group was also presented, which indicated that END can significantly improve the OS and CSS of T3N0M0 GSCC.

To further explore the prognostic impact of END, exerting univariate and multivariate Cox hazard regression analysis, we revealed that END was an independent positive prognostic factor for T3cN0M0 GSCC.

Furthermore, the subgroup analysis indicated that the patients aged ≥ 65 years who underwent END had better OS than those who did not undergo END. Similar to the present results, previous studies have demonstrated that neck lymph node metastasis was associated with declined survival rate in elderly patients [19], thus, neck dissection was suggested to be performed in the elderly. It is worth mentioning that, our study of CSS (CSS reflected survival more representative to certain cancers than OS) has confirmed that both youth and elderly had a better outcome with END. This may be due to the fact that cervical lymph node metastasis caused by “wait and see” strategy contributes less to death than other factors for the youth, so OS was similar between END group and non-END group in the patients aged < 65 years. But CSS analysis might rule out other causes of death, suggesting that patients could benefit from END regardless of age. The results of univariate and multivariate survival analysis on OS and CSS also showed the impacts of age on the OS, but it was not an independent predictor on CSS.

In terms of pathological grade, it was observed that patients with G3-4 pathological grade could not benefit from END in OS and CSS. This is inconsistent with the traditional conception that patients with poorly differentiated GSCC tended to be with higher risk of cervical lymph node metastasis and lower mortality and needed to be performed with END [23]. Actually, we observed that the END group seemed to have a better CSS, although the differences were not significant in patients with poorly differentiated GSCC ($p = 0.08$). Possible explanation was that the degree of tumor differentiation exerted a greater impact on survival rate, in compared with node metastasis. Despite the fact that neck dissection effectively reduced the risk of cervical lymph node metastasis, it failed to improve the low survival rate caused, which indicated that adjuvant therapies such as radiotherapy or chemotherapy were needed in patients with poorly differentiated GSCC.

In subgroup analysis of both genders, females' CSS analysis indicated that they may not benefit from END. Previous studies did not considered the sex differences on the prognosis of laryngeal cancer, although the incidence of larynx cancer in males was originally higher than that in females [24]. Large-scale prospective study was still needed to provide evidence in this area.

Although our results confirmed the benefits of END, the analysis of the SEER database from 2004 to 2015 still found that for T3N0M0 glottic cancer, only 22% – 58% patients were performed with END, and there was no increasing trend. This may be due to the lack of a large-scale retrospective clinical study and the ambiguity of the guidelines, so that clinicians did not attain agreement on the benefit of END. This study

would fill this gap, and the analysis was more convincing by PSM to match the confounding factors. It suggests that clinicians should choose END more frequently in practice, so as to increase the survival rate of T3N0M0 GSCC patients. Although clinicians preferred the “wait and see” strategy rather than END on T3N0M0 GSCC in the past decades, it is time to change and END needs to be performed on these patients for the survival benefit. Nonetheless, prospective randomized controlled trials are still needed to further clarify the role of END in T3N0M0 patients.

Our research has several advantages. First, using a large amount of population-based data from SEER, rather than from a single organization, could avoid heterogeneity among different centers. Secondly, propensity score matching was used to minimize the selection deviation. Third, analysis of OS and CSS promoted the understanding of the END impact on survival. Nevertheless, this study has several limitations. For one thing, it was a retrospective study. For another, this study only analyzed the variables provided in the database, other variables such as surgical methods, radiotherapy methods and so on were not included.

Conclusions

Our study demonstrated that END resulted in favorable survival outcomes for T3cN0M0 GSCC patients and was an independent predictor of a good prognosis in patients with T3cN0M0 GSCC, which provided insights into the treatment strategy for cervical lymph nodes in T3 GSCC with cN0.

Abbreviations

cN0

Clinically node-negative; LSCC:Larynx squamous cell cancer; END:Elective neck dissection; GSCC:Glottic squamous cell cancer; SEER:Surveillance, E, Epidemiology, and End Results database; PSM:Propensity score matching; OS:Overall survival; CSS:Cancer-specific survival; NCCN:National Comprehensive Cancer Network

Declarations

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Contributions: ZMC, LC, and WBL conceived or designed the study. ZMC, JWZ, LC acquired, analyzed, or interpreted the data. ZMC and JWZ drafted the manuscript. WBL critically revised the manuscript for important intellectual content. ZMC and LC performed the statistical analysis. WBL provided supervision. All authors have given the final approval of the manuscript for submission and publication.

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Availability of data and materials

The datasets analyzed in this study are collected from SEER repository (<https://seer.cancer.gov/>).

Ethics approval and consent to participate

Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified. The study was exempted from Institutional Review Board approval, due to the use of a large cancer database with unidentifiable patient information.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Trends of the END rate in T3N0M0 GSCC in SEER dataset during 2004 to 2015.

Figure 2

Kaplan–Meier survival curves for overall survival and cancer-specific survival between the END group and non-END group with T3cN0M0 glottic cancer: (A), OS in the raw cohort (B), OS in the PSM cohort (C), CSS in the raw cohort (D), CSS in the PSM cohort. END, elective neck dissection; cN0, clinically negative cervical lymph nodes; PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival

Figure 3

Forest plot for the OS (A) and CSS (B) subgroup analysis of the prognostic value of END in the matched cohort. END, elective neck dissection; OS, overall survival; CSS, cancer-specific survival.

Figure 4

Kaplan–Meier survival curves for overall survival of the subgroup of patients older than 65 years (A), white (B), male (C), female (D), grade 1–2 (E), treated from 2004 to 2009 (F), treated from 2009 to 2015 (G), with radiotherapy (H), without radiotherapy (I) ($p < 0.05$)

Figure 5

Kaplan–Meier survival curves for cancer-specific survival of the subgroup of patients older than 65 years (A), younger than 65 years (B), white (C), male (D), grade 1–2 (E), treated from 2004 to 2009 (F), treated from 2009 to 2015 (G), with radiotherapy (H), without radiotherapy (I) ($p < 0.05$)

Supplementary Files

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