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Research Article

Sentinel Lymph Node Biopsy versus Elective Neck Dissection: Long-Term Oncologic Outcomes in Clinically Node-Negative Tongue Cancer

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Abstract

Objectives: To compare the long-term oncologic outcomes of sentinel lymph node biopsy (SLNB) versus elective neck dissection (END) in clinically node-negative (cN0) tongue cancer.

Patients and Methods: This is a retrospective cohort study of patients with cN0 tongue cancer from a single institution, including 91 patients in the SLNB group and 120 patients in the END group.

Results: Overall recurrence rate was no significant difference in the recurrence rate between the two groups. The regional control rate was also comparable between the two groups (p =0.49). The 5-year RFS was slightly better in the SLNB group (p = 0.427). The 5-year OS was 89.9% in the SLNB group vs. 91.9% in the END group (p = 0.737). In propensity-matched subgroup analysis, the type of neck management did not affect RFS or OS.

Conclusions: SLNB showed non-inferior oncologic outcomescompared to END in patients with cN0 tongue squamous cell carcinoma.

Keywords: Neck dissection; Node metastasis; Propensity score matching; Oral cancer; Sentinel lymph node biopsy

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Introduction

Since the presence of lymph node metastases is one of the most critical factorsin the survivalandrecurrence rate of oral cancer, accurate detection, and proper management of the nodal disease are essential [1,2]. It is well known that the occult metastasis rate in clinically node-negative (cN0) patients with oral cancer ranges from 21 to 35% and is challenging to detect, even with thorough physical examination and imaging studies [3,4]. There has been a long controversy about proper neck management of cN0 oral cancer patients.Arecent randomized, controlled trial tested the treatment options for cN0 neck; elective neck dissection (END) vs. therapeutic neck dissection [5]. The patients who had undergone END were reported with improved 3-year overall survival over therapeutic neck dissection (80% vs. 67.5%), with an occult metastasis rate of 26.5%. Based on this landmark study, END is accepted as a standard treatment for cN0 oral cancer patients. However, debates remain about the necessity of surgical procedures for over half of patients who do not have any metastatic disease [4].

Recently, sentinel lymph node biopsy (SLNB) is gaining popularity because many studies support that SLNB is a useful staging procedure to detect occult nodal metastasis accurately, theoretically helping three-quarters of patients with cN0 oral squamous cell carcinoma to avoid unnecessary surgery [6-15]. According to other prospective, multicenter trials, the negative predictive value of the SLNB procedure is reported to be around 95%, depending on the subsite of the tumor [6,10]. False-negative or false-omission rates were 9.8%~14%, which should be maintained beneath 5% [16]. Despite recognizing the acceptable diagnostic accuracy of detecting the occult nodal metastasis using the SLNB procedure, there are still hurdles for its widespread application in clinical practice by many head and neck surgeons [17]. One of the hurdles is the scarcity of directly comparingoncological outcomes of SLNB with END to justify routine SLNB application [18,19].

This study aims to evaluate the oncologic safety of SLNB in the management of cN0 oral tongue cancer in direct comparison with END. From a retrospective cohort study of a single institution, we compared the regional control rate, the recurrence-free survival (RFS), and the two groups' overall survival (OS). A propensity score analysis was performed for more balanced comparisons, matching the resection margin to reduce the retrospective design's potential bias.

Patients and Methods

Patients

Retrospective cohort enrollments and review of medical records were exempt from the patients' informed consent by the institutional review board of our institution. We enrolled patients who had tongue cancer with cN0 early tongue squamous cell carcinoma treated surgically in Samsung Medical Center between January 1995 and December 2018 in the study. Patients with advanced T stage (T3 or T4) or those who had undergone other tongue cancer treatments before surgery were excluded. To distinguish the recurrence and failure of positive node detection, cases with short follow up within six months were also eliminated. Physical evaluation, computed tomography, magnetic resonance imaging, and positron emission tomography were evaluated as a preoperative workup for clinical nodal staging. If necessary, ultrasonography-guided fine-needle aspiration cytology was also performed.

In our institution, the treatment of choice for the patients with cN0 tongue cancer has been surgical resection of the primary tumor with END since the establishment of the head and neck cancer center in January 1995. As described in the previous study, SLNB was introduced in our institution after 2002, starting with the validation phase to test the feasibility and the safety of the procedure [20]. After 2007, an SLNB alone trial was applied in eligible patients, designed to do the subsequent neck dissection only in cases with positive sentinel lymph node(s) in the pathologic examination. Since 2007, cN0 tongue cancer patients who consented to the SLNB procedure have undergone SLNB alone trial, while the rest received conventional END for the cN0 neck management.

Adjuvant treatments, including radiation with/without chemotherapy, were performed onpatients with a high-risk feature in the final pathologic report, such as a positive node or advanced T stage.

Neck management

We used END to remove the ipsilateral lymph nodes located in neck-level I-III or IV, depending on preoperative imaging studies' findings. The SLNB procedure was performed,as described previously [21]. The radioactive tracer, technetium 99m prepared with tin colloid (Amerscan™ Hepatate II™; Nycomed Amersham Health, London, U.K.), was injected in the submucosal layer around the circumference of the primary tumor (5-6 mCi in 0.6 mL). Dynamic lymphoscintigraphy was done in the anterior and lateral views before surgery. During operation, all radioactive lymph nodes were identified with a Navigator GPS hand-held gamma probe (Tyco Health Care, Mansfield, MA, U.S.A.) and were given thorough transcervical dissection for the removal of the primary tumor. If the sentinel lymph node was not detected by lymphoscintigraphy preoperatively nor by gamma probe during surgery, END was to be performed. In our study, none of the cases showed the failure of sentinel node identification. The mean number of sentinel nodes dissected during surgery was 2.84 (range 1-7).

Sentinel lymph nodes were divided into multiple equal levels of approximately 2-mm thickness through their longest axes and separately frozen with an Optimal Cutting Temperature compound. One section for each block was evaluated using frozen section analysis with hematoxylin and eosin (H&E) staining. After the frozen section diagnosis, the frozen tissue blocks were melted, fixed in 10% neutral buffered formalin, and embedded in paraffin. These paraffin blocks were serially sectioned at 250 µm (step-serial sectioning), and six sections from each level within the block were H&E stained and examined for possible metastasis. We did further immunohistochemical analysis for cytokeratin (AE1/AE3) to reveal any undetected micrometastasis if the node was free from tumors. If sentinel lymph node(s) showed a metastatic tumor in frozen biopsy or permanent pathology, subsequent therapeutic neck dissection was done. Decisions on the postoperative, adjuvant treatment were made by the multidisciplinary tumor board, assessing all the clinicopathological factors.

Recurrence was defined as a new diagnostic lesion inthe neck detected at least six months after the end of treatment. The lesion developed within six months was regarded as a failure of neck dissection.

Statistical analysis

The two groups' clinical characteristics were evaluated, including age, sex, clinical and pathologic stage based on the AJCC 7th edition, resection margin, depth of invasion, and presence of perineural invasion / lymphovascular invasion.

Patient characteristics were compared for equality by the Mann-Whitney U-test for continuous variables and χ^2 test or Fisher's exact test for categorical data.Propensity score matching analysis allowed the adjustment of baseline patients' characteristics between the END and the SLNB groups (one-to-one matching based on propensity scores). We used a binary logistic regression model to develop a propensity score for each patient. The depth of invasion, a critical factor for recurrence and survival, wasincluded in the propensity score model. Matching was done using calipers of a width of 0.5 of the standard deviation of the propensity score's logit. The standardized difference between unmatched and matched groups was 0.17. A doubly robust method was performed to correct the remained bias.

RFS and OS were analyzed by Kaplan-Meier statistics. We used the log-rank test to compare survival rates between the two groups and multivariate analysis to find the correlation between survival and each clinicopathological variable. Statistical packages of R and SAS version 9.4 (SAS Institute, Cary, NC) were used for statistical analyses, and a $p<0.05$ was considered statistically significant.

Results

A total of 211 patients were enrolled in the study, with 91 patients in the SLNB group and 120 in the END group. Subject characteristics are described in table 1. Age and sex distribution were similar between the two groups. The SLNB group had more patients diagnosed as cT1 stage than the END group (SLNB vs. END, 80.2% vs. 54.2%, $p<0.001$).

In postoperative pathological data, the END group showed worse features than did the SLNB group, with greater depth of invasion (6.96 mm vs. 5.29 mm, $p=0.009$) andthe more frequent presence of lymphovascular invasion (15.8% vs. 4.4, $p = 0.013$). The resection margin of SLNB was greater than END's (5.66 mm vs. 4.63mm, $p=0.001$). The mean follow-up was 47.2 months, with 38.2 months in the END group and 58.9 months in the SLNB group.

The total number of pN+ patients after cN0 neck management was 25 (11.8%). It was significantly higher in END group (15.9%) than in SLNB group (6.6%) ($p=0.040$) (Figure 1). In pN+ in END group, 89.5% of patients had adjuvant treatment (postoperative radiotherapy with or without chemotherapy),while 66.7% of the SLNB group underwent adjuvant treatment.

32 of 211 patients (15.1%) were reported with recurrence. The rate of regional recurrence was 10.0% (21/211). 11 patients of SLNB group (12.0%) and 10 patients of ENB group (8.3%) showed regional recurrence ($p=0.49$). Duration to recur is similar between the two groups (SLNB vs. END, 592.26 vs. 606.19 days, range 23-4214 days). The failure of neck dissection (rates of regional metastasis within six months) in both groups was similar; 4.4% (4/91) in the SLNB group and 3.3% (4/120) in the END group ($p=0.73$).

No. (%)	Total patients (*N*=211)	END (*n*=120)	SLNB (*n*=91)	*P*
Demographic data				
Sex, *n* (%)				
Male	129 (56.9)	70 (58.3)	59 (64.8)	0.414
Female	82 (38.9)	50 (41.7)	32 (35.2)	
Age (years)	53.12±13.63	54.52±13.34	51.27±13.86	0.086
Preoperative data				
cT1/T2	138/73	65/55	73/18	<0.001
Postoperative data				
pT1/T2/T3/T4	127/74/6/4	57/57/5/1	70/17/1/3	<0.001
Resection margin (mm)	5.07±2.34	4.63±2.00	5.66±2.63	0.001
Depth of invasion (mm)	6.24±4.63	6.96±4.80	5.29±4,25	0.009
Lymphovascular invasion, *n* (%)	23(10.9)	19 (15.8)	4 (4.4)	0.013
Perineural invasion, *n* (%)	29(13.7)	21 (17.5)	8 (8.8)	0.106
Pathologically positive lymph node, *n* (%)	25(11.8)	19 (15.9)	6 (6.6)	0.040
Follow up period (month), mean [range]	47.2 [5.8-193.9]	38.2 [5.8-193.9]	58.9 [7.9-160.0]	<0.001

Table 1: Subject characteristics.

END elective neck dissection, SNLB sentinel lymph node biopsy

*AJCC 7th edition

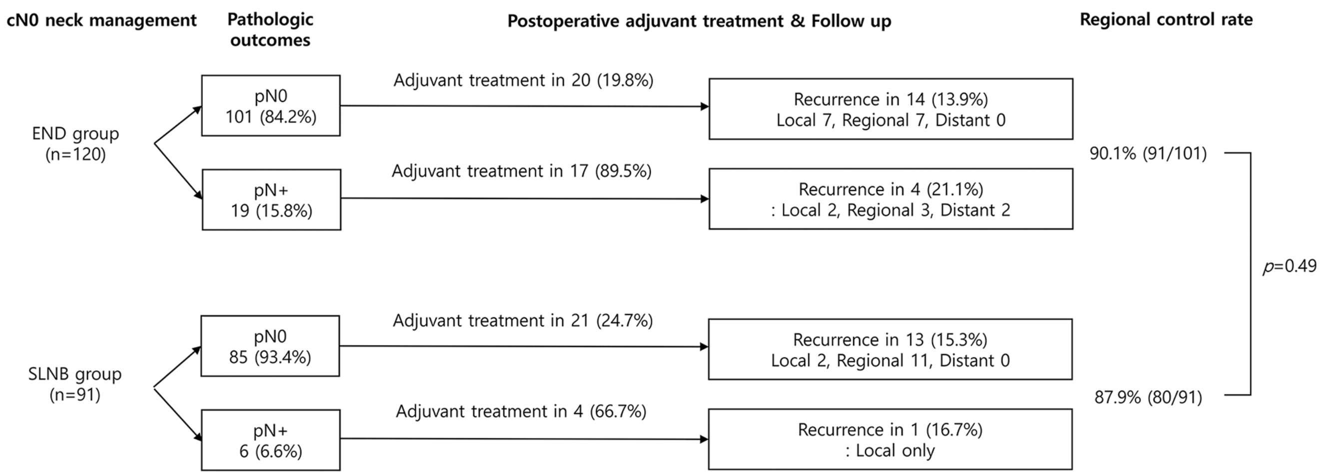

Figure 1: Adjuvant treatment and pattern of recurrence.

Most patients with recurrence (28/32, 87.5%) had had salvage surgery for recurrence. Only four patients got radiation or chemotherapy for recurrence due to refusal of surgery and distant metastasis. 18 patients alive without disease, three patients alive with disease, and 11 patients died for the disease at the last follow-up. Regional control rate showed no statistical difference (SLNB vs END, 87.9% vs 90.1%, p=0.49).

RFS was slightly better in the SLNB group; however, there was no statistical significance (84.6% in the SLNB group vs. 79.5% in the END group, p =0.427) (Figure 2A). The Kaplan-Meier survival estimate of the two groups was compared as the 5-year OS of patients was 89.9% in the SLNB group vs. 91.9% in the END group (p = 0.737) (Figure 2B).

Cox regression analysis was done to identify the prognostic factors for the RFS and OS. For the RFS, sex and the depth of invasion tended toward significance, but not the type of neck management (Table 2). The deeper invasion was the significant prognostic factor for worse OS (hazard ratios 1.114) (Table 3).

We used propensity score matching to adjust the uneven distribution of critical factors, depth of invasion for the primary oncologic outcomes. As a result, subgroups of 79 patients from each group were generated (Table S1). When the two subgroups were analyzed with the Cox regression method, the neck management type did not influence the prognosis nor recurrence (Table 4). After doubly robust method analysis, the type of neck management effect on the RFS and OS was not evident (Figure 3).

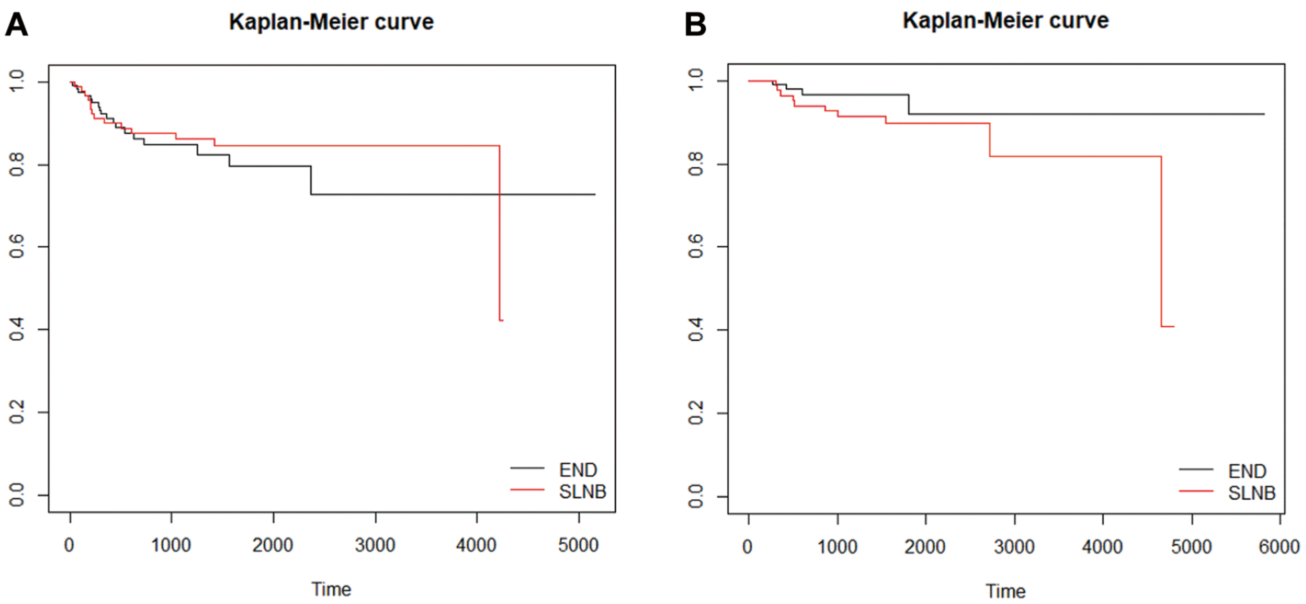

Figure 2: Recurrence rate and overall survival (A) The 5-year recurrence rate. END 79.5% vs SLNB 84.6% (p =0.427) (B) The 5-year overall survival. END 91.9% vs SLNB 89.9% (p=0.737).

Variables			Univariate analysis			Multivariate analysis		
	Reference		HR	95% C.I.	*P*	HR	95% C.I.	*P*
Sex	Male	Female	0.291	0.108-0.788	0.015	0.332	0.136-0.814	0.016
Age	Continuous		0.991	0.962-1.021	0.544			
T stage*	T1 T2 T3 T4		1 3.045 3.116 0.000	 1.158-8.004 0.285-34.133 0.000-	 0.024 0.352 0.999			
N stage*	N0	N+	1.126	0.329-3.855	0.850			
Resection margin	Continuous		0.972	0.807-1.170	0.764			
Depth of invasion	Continuous		1.078	0.974-1.192	0.146	1.070	1.002-1.143	0.043
LVI	Absent	Present	0.000	0.000-	0.998			
PNI	Absent	Present	0.673	0.156-2.907	0.596			
Type of neck management	END	SLNB	1.368	0.551-3.394	0.499	0.914	0.448-1.865	0.804

Table 2: Cox regression analysis of risk factors affecting recurrence-free survival.

LVI lymphovascular invasion, PNI perineural invasion, END elective neck dissection, SNLB sentinel lymph node biopsy

*AJCC 7th edition

Discussion

This study compared the long-term oncologic outcomes between END and SLNB in cN0 tongue cancer patients with a mean follow-up of 47.2 months, using a retrospective cohort from a single institution. We found that the two groups' regional control rates were comparably excellent (91.7% vs. 88.9%, p =0.49) and without statistical difference. Also, the 5-year OS and RFS did not differ between the two groups (SLNB group vs. END group: OS, 89.9% vs. 91.9%, log-rank p = 0.737; RFS, 84.6% vs. 79.5%, log-rank p =0.427). The analysis of patients from 2007 revealed comparable results with the whole data set (Table S2 and Figure S1). Furthermore, postoperative clinical progress was described and compared in detail between the two groups. This finding could give head and neck surgeons informative data to introduce the SNLB procedure in their clinical practice.

The study's oncologic results are similar to a previous study, which retrospectively compared 30 SLNB patients and 52 END patients with oral tongue squamous cell carcinoma [19]. According to the previous study, the regional recurrence rate was 13.3% (4/30) in the SLNB group and 9.6% (5/52) in the END group, and RFS, as well as OS, were comparable between the two groups without statistical differences (10-year RFS, 72.3% vs. 73.3%; 10-year OS, 43.3% vs.

Variables			Univariate analysis			Multivariate analysis		
	Reference		HR	95% C.I.	*P*	HR	95% C.I.	*P*
Sex	Male	Female	0.262	0.048-1.420	0.120	0.279	0.061-1.267	0.098
Age	Continuous		1.018	0.970-1.068	0.474	1.046	1.002-1.092	0.038
T stage*	T1 T2 T3 T4		1 4.493 0.000 68.498	 0.968-20.858 0.000- 2.787-1683.532	 0.055 0.999 0.010			
N stage*	N0	N+	2.403	0.462-12.494	0.297			
Resection margin	Continuous		1.090	0.850-1.397	0.498			
Depth of invasion	Continuous		1.101	0.952-1.274	0.194	1.114	1.013-1.225	0.026
LVI	Absent	Present	0.000	0.000-	0.998			
PNI	Absent	Present	0.489	0.044-5.390	0.559			
Type of neck management	END	SLNB	5.374	1.160-24.893	0.032	2.754	0.844-8.983	0.093

Table 3: Cox regression analysis of risk factors affecting overall survival.

LVI lymphovascular invasion, PNI perineural invasion, END elective neck dissection, SNLB sentinel lymph node biopsy

*AJCC 7th edition

Variables			Recurrence-free survival			Overall survival		
	Reference		HR	95% C.I.	*P*	HR	95% C.I.	*P*
Resection margin			0.909	0.758-1.090	0.305	0.943	0.736-1.208	0.943
Depth of invasion			1.063	0.977-1.158	0.157	1.113	0.990-1.252	0.074
Type of neck management	END	SLNB	0.814	0.356-1.860	0.626	2.144	0.563-8.172	0.264

Table 4: Multivariate analysis of risk factors affecting recurrence and survival after propensity matching.

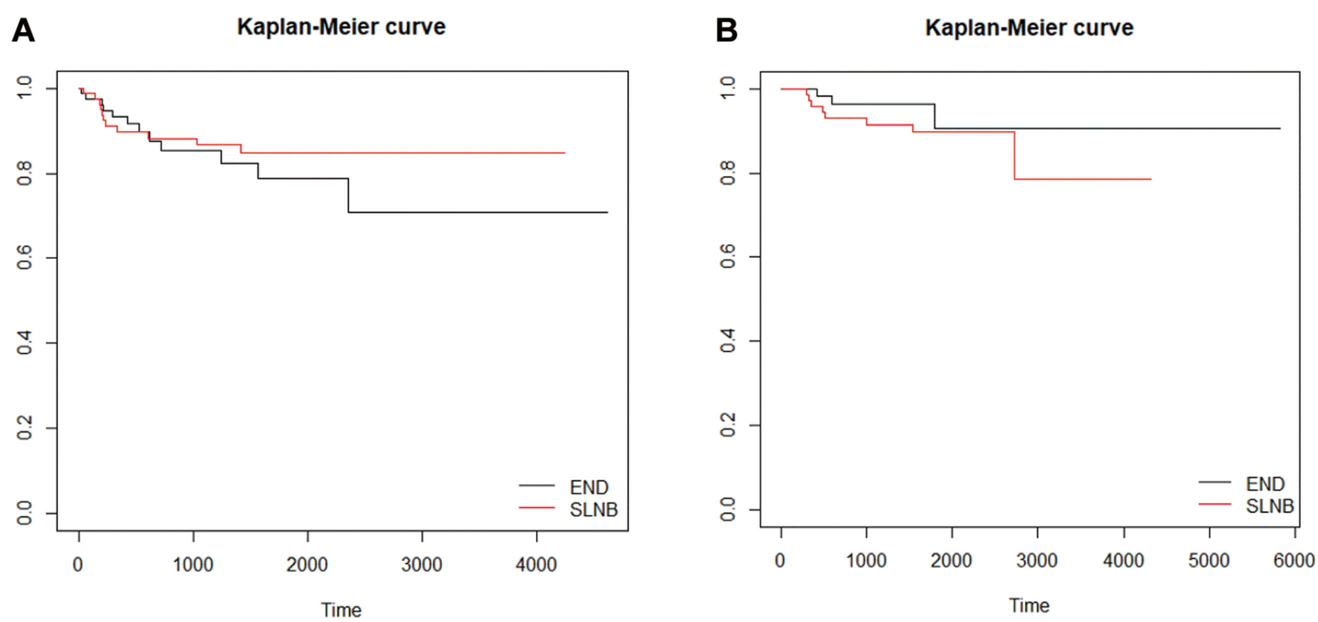

Figure 3: Propensity matching analysis (A) The 5-year recurrence rate. END 78.7% vs SLNB 84.8% (p=0.423) (B) The 5-year overall survival. END 90.6% vs SLNB 89.7% (p=0.899).

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44.2%). These findings suggest that the SLNB could be a substitute modality for END without any influence on the survival.

Commonly cited advantages of the SLNB are that patients with no sign of metastases on sentinel lymph nodes could avoid neck dissection. Individual treatment could reduce both morbidity and cost [7]. Moreover, based on the postoperative course's detailed analysis, the number of patients who had adjuvant treatments (SLNB 27.5% vs. END 30.8%, p = 0.65) was similar in the two groups without any adverse effect on prognosis (Figure 1). Both groups' recurrence rates showed similar outcomes, even though pN0 patients in the SLNB group did not receive additional therapeutic neck dissection nor adjuvant treatment. About a third of pN+ patients in the SLNB group did not receive postoperative adjuvant treatments, and they did not experience any recurrence during follow up.

To maintain an acceptable oncologic outcome in SLNB alone trial, the false-negative rate must be as low as 5% (pN0 sentinel lymph-node progressing within two years)[16]. There wereeight regional recurrent cases (3.3% and 4.4%) within six months in each group, considereda failure of neck management or false-negative. Salvage operations were done in all eight patients, and as result, five patients survived without any evidence of disease, one patient still alive with the disease, and two patients died from the disease. This finding is comparable with a previous study that reported long-term follow-up outcomes and a nodal failure pattern of SLNB in oral squamous cell carcinoma [22]. Among 11 patients with regional recurrence in SLNB group, it was found that three cases of contralateral nodal recurrences and one ipsilateral nodal recurrence at almost ten years after the SLNB. As highlighted in our previous report about the SLNB alone trial, a stringent follow-up protocol with salvage treatment is critical to maintaining acceptable oncologic outcomes [20]. Close follow-up is mandatory for positive SLNB patients, who are at higher risk of nodal recurrence and worse prognosis than do negative SLNB patients.

In a recent study, a large number of patients with stage I-II oral squamous cell carcinoma (240 patients of the SLNB group and 8088 patients of the END group) were retrieved and analyzed from the National Cancer Data Base (NCDB) of the United States [18].The study's outcomes were similar to the present study in that 3-year OS was equivalent between the two groups (82.0% after SLNB vs. 77.5% after END, p =0.40). Interestingly, SLNB showed a significantly decreased length of postoperative hospital stay over END and an absolute difference in a 30-day mortality rate (0% in SLNB vs. 0.7% END). Despite all these advantages, it is found that the SLNB procedure are rarely used for stage I-II oral cancer, warranting a multicenter randomized control trial comparing the SLNB vs. the END to produce level-I evidence for SLNB in early oral cancer [18].

This study contains the common drawbacks of all studies using a retrospective cohort, including the selection bias. Firstly, in the subject characteristics, key pathologic features, such as surgical resection margin and the depth of invasion, were not equally distributed between the SLNB group and the END group. To overcome the inequality of adverse pathologic factors, we used propensity score matching analysis based on the resection margin to generate 79 subgroup patients from each group. Secondly, we did not investigate the other controversial issues related to each procedure, for example, cost-effectiveness, surgery-related complications, or quality-of-life comparisons.

Conclusions

According to this retrospective cohort analysis, the SLNB did not have worse oncologic outcomes than the END in patients with cN0 tongue squamous cell carcinoma. Considering that many patients could avoid unnecessary, invasive treatment after nodal staging by the SLNB, this procedure is highly recommended in clinical practice. A watchful follow-up protocol, as well as a potential plan for salvage management, should be warranted to obtain excellent outcomes in a long-term period.

Contributions of Authors

Young-Ik Son, Han-Sin Jeong, Man Ki Chung, and Chung-Hwan Baek collected the data and designed the study.

Woori Park, Hokyung Jin, Yujin Heo,Man Ki Chung, and Chung-Hwan Baek interpreted the experimental data, prepared all figures, and wrote the main manuscript text.

All authors reviewed and confirmed the manuscript.

Conflict of Interest

None.

No. (%)	END (n = 79)	SLNB (n = 79)	P
Demographic data			
Sex, n (%)			
Male	53 (67.1)	50 (63.3)	0.738
Female	26 (32.9)	29 (36.7)	
Age (years, SD)	53.46 (12.26)	52.18 (14.07)	0.543
Preoperative data			
cT1/T2	56/23	61/18	0.468
Postoperative data			
Resection margin (mm, SD)	4.84 (2.10)	5.49 (2.61)	0.275
Depth of invasion (mm, SD)	5.95 (4.11)	5.25 (4.07)	0.171
Lymphovascular invasion, n (%)	7 (8.9)	4 (5.1)	0.150
Perineural invasion, n (%)	7 (8.9)	8 (10.1)	0.043
Pathologically positive lymph node, n (%)	4 (5.1)	5 (6.3)	0.055

Table S1: Subject characteristics (matching).

No. (%)	Total patients (*N*=186)	END (*n*=102)	SLNB (*n*=84)	*P*
Demographic data				
Sex, *n* (%)				
Male	110 (59.1)	57 (55.9)	53 (63.1)	0.369
Female	76 (40.9)	45 (44.1)	31 (36.9)	
Age (years)	53.00±13.98	54.27±14.06	51.45±13.82	0.171
Preoperative data				
cT1/T2	126/60	57/45	69/15	<0.001
Postoperative data				
pT1/T2/T3/T4	115/62/6/3	49/47/5/1	66/15/1/2	<0.001
Resection margin (mm)	5.12±2.40	4.57±1.97	5.79±2.69	0.001
Depth of invasion (mm)	5.97±4.57	6.59±4.62	5.17±4.42	0.037
Lymphovascular invasion, *n* (%)	23(12.4)	19 (18.6)	4 (4.8)	0.006
Perineural invasion, *n* (%)	29(15.6)	21 (20.6)	8 (9.5)	0.044
Pathologically positive lymph node, *n* (%)	20(10.8)	14 (13.7)	6 (7.1)	0.163
Follow up period (month), mean [range]	40.39[6.2-141.6]	39.0[6.2-119.7]	52.9[7.9-141.6]	<0.001

Table S2: Subject characteristics (data from 2007).

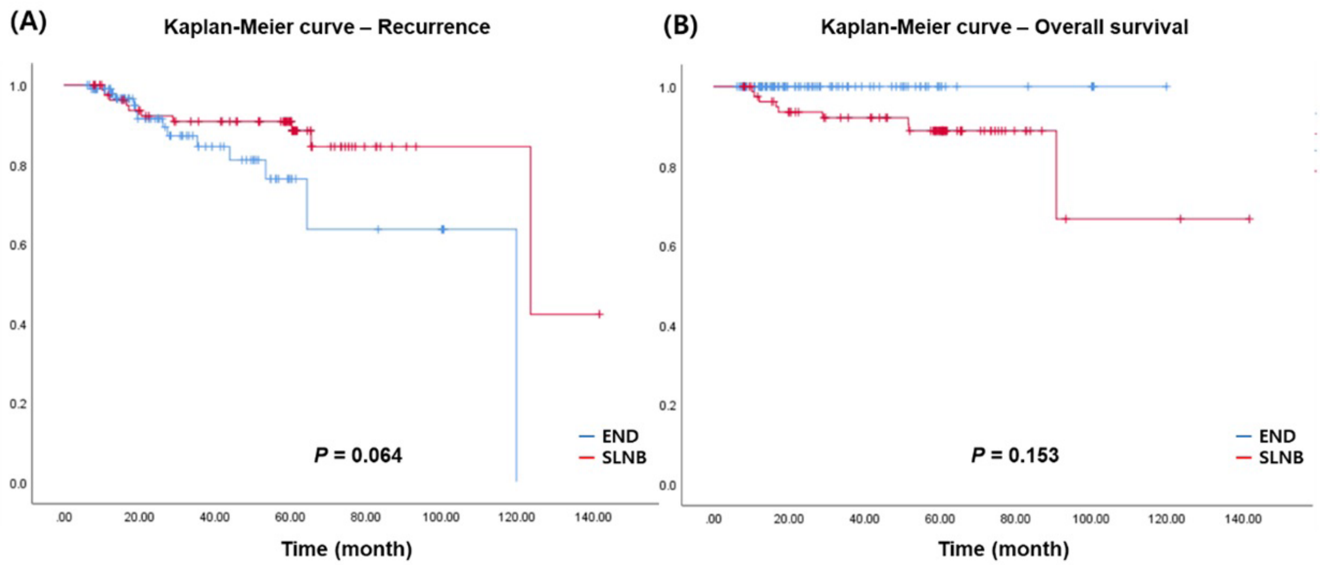

Figure S1: (A) Recurrence rate (p=0.064) and (B) overall survival (p=0.153) (data from 2007).

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