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Elective neck dissection versus observation in the management of early tongue carcinoma with clinically node-negative neck: A retrospective study of 229 cases

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ABSTRACT

Background: The aim of the study is to evaluate the results of elective neck dissection (END) versus conservative management (observation) in the treatment of stages I and II squamous cell carcinoma of tongue.

Patients and methods: This is a retrospective study including 229 patients with surgical treatment between June 1993 and May 2010.

Results: There were 15 (9.6%) patients in the END group and 14 (19.2%) patients in the observation group who developed nodal recurrence alone without associated local recurrence or distant metastasis. Node-related mortality rate was 5.1% (8/156) for END and 12.3% (9/73) for observation. Further analysis for subgroups of stage T1 showed that the patients from END group had a better 5-year disease-specific survival (DSS) than those from the observation group in spite of no statistical difference (87.2% vs. 76.0%, Log-rank $p = 0.282$). END compared with observation for patients with stage T2 had a better 5-year DSS (74.2% vs. 41.2%, Log-rank $p = 0.008$).

Conclusions: Elective neck dissection significantly reduces mortality due to lymph nodal metastasis and also increases the 5-year DSS, most marked in patients with stage T2 OSCC. This retrospective study suggests that END should be a preferred treatment strategy for tongue carcinoma in stage T2.

1. Introduction

Oral tongue squamous cell carcinoma (OSCC) has the propensity for occult nodal metastasis in the early stage (Pimenta Amaral et al., 2004). Although screening of clinically N0 neck by ultrasound, CT, MRI, or positron emission tomography (PET) can help to detect some of these nonpalpable nodal metastases, the recurrence rate in the observed N0 neck is 23.7%–42% (Brugère et al., 1996; Khafif et al., 1991; Okamoto et al., 2002).

There is no greater controversy in the management of tongue carcinoma than the optimal treatment for clinically T1-2N0 neck. The present conclusions drawn from RCT's and/or meta-analysis do not serve as level 2 evidence due to insufficient sample size and other limitations, both elective neck dissection and "observation" have their proponents in different centres (D'Cruz and Dandekar, 2011; Fakih et al., 1989; Kligerman et al., 1994; Thiele et al., 2012; Vandenbrouck et al., 1980; Yuen et al., 1997, 2009).

In our department, the majority of treatment chosen for tongue SCC is simultaneous END, with the "observation" policy more often adopted in patients with the clinically T1N0 tumour. The aim of the present study is to review the results of the surgical treatment of stage I and stage II oral carcinoma treated with END versus observation in our department. Basis on the results of different neck management, a more strategic treatment policy may be adopted in the future.

2. Material and methods

This study was approved by the stomatological hospital of Peking University Institutional Review Board. During June 1993 and May 2010 Patients treated at the department of oral and maxillofacial surgery, at that hospital diagnosed with tongue squamous cell carcinoma, were included for the study. Patient inclusion criteria included:

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(1) patients with clinically node-negative neck: preoperative staging of the neck lymphatic metastases was based on physical palpation and computerized tomography (CT). CT criteria for negative neck was nodal size < 1.0 cm (Yu et al., 2006);
(2) a primary tumour without distant metastasis evidence (clinical stage I/II; UICC/AJCC. 7ed., 2009);
(3) no previous treatment;
(4) complete medical information and follow-up data.

229 consecutive patients were included in the study. Identifier data were terminally coded in order to maintain patient anonymity.

All the patients were initially treated surgically. The surgical procedure was selected by surgeons according to tumour site and local practice. Standardized surgery, including radical tumour resection, neck dissection and the reconstruction of tissue defects (as necessary), was performed. The local excision of primary site was performed with a planned safe margin of 15 mm. For routine histopathological work-up of neck dissection specimens, we put each level of node in different pots. Sides and different levels were delineated with the help of landmark stitches placed just after the removal of the specimens. Standard HE staining was used.

Postoperative patients were advised to return visit regularly at intervals of 2 months in the first year, 3 months in the second year, 6 months in the third, fourth and fifth year, and thereafter once every 6 months to 1 year. If any patients did not comply with our policy of return visit, a telephone interview was completed every 6 months for survivors.

The baseline demographic data between the two groups were compared by non-parametric tests as appropriate for categorical variable and *t* test for continuous variable. The main outcome assessment parameter was node-related mortality. It was defined as the percentage of patients who died of nodal metastasis not associated with local recurrence or distant metastasis. The secondary outcome assessment parameter was the 5-year disease-specific survival (DSS), which only included patients who had undergone treatment for the first time in the previous 5 years. The 5-year DSS was calculated from the time of first operation to the time of death or the last follow-up. The Kaplan–Meier curve of DSS was generated for each group and compared using the log-rank test. *P* values < 0.05 were considered as significant. All statistical analyses were performed using SPSS for windows version 17.0 (SPSS, Chicago, USA).

3. Results

3.1. Patient characteristics

229 eligible patients were enrolled in this study, 156 patients in END group and 73 patients in observation group. There were 104 males and 125 females and the mean age was 58.1 years (range 22–86 years). The preoperative clinical stages were 109 T1N0M0 (61 in END group and 48 in observation group) and 120 T2N0M0 (95 in END group and 25 in observation group). Stage T2 was mainly distributed in END group and stage T1 was a higher proportion in observation group ($p < 0.001$). The demographic data of the 229 patients is shown in Table 1. The two were well matched groups in gender, age, pathologic grade, growth pattern and tobacco/alcohol habit except for T stage. In these patients' data, the cutoff date of following-up was March 1, 2013 for survivors. The median follow-up for the whole cohort was 58 months [interquartile range (IQR), 42–86] for END group and 51 months [interquartile range (IQR), 35–69.5] for observation group.

Table 1
Baseline demographics for the 229 patients in the study.

Variable	END group ($n = 156$)		Observation group ($n = 73$)		*P*
	No.	%	No.	%	
Age, yrs: mean ± SD	57.0 ± 12.7		60.2 ± 13.8		0.088
Gender					
Male	73	46.8	31	42.5	0.602
Female	83	53.2	42	57.5	
Clinical stage					
T1N0M0	61	39.1	48	65.8	<0.001
T2N0M0	95	60.9	25	34.2	
Pathologic grade					
I	87	55.8	44	60.3	0.520
II	64	41.0	27	37.0	
III	5	3.2	2	2.7	
Growth pattern					
Exophytic	40	25.6	23	31.5	0.139
Ulcerative	57	36.6	30	41.1	
Infiltrative	59	37.8	20	27.4	
Smoking history					
Smoker	48	30.8	24	32.9	0.749
Nonsmoker	108	69.2	49	67.1	
Alcohol history					
Drinker	111	71.2	18	24.7	0.587
Nondrinker	45	28.8	55	75.3	

Abbreviations: END group: elective neck dissection group; SD: standard deviation.

3.2. Treatment outcome

All primary tumours were completely excided and margins were negative. The patients of END group received elective neck dissection including unilateral supraomohyoidal neck dissection (SOND, level I, II, III with or without) in 108 cases, unilateral radical/modified radical neck dissection (RND) in 43 cases and bilateral SOND in 5 cases. All tumours were resected in continuity. There was no significant statistical difference in regional recurrence rate between unilateral RND and unilateral SOND (4/43 vs. 11/108, Fisher exact test, $p > 0.999$). All 5 patients underwent bilateral neck dissection without delayed nodal recurrence. Tissue reconstruction using free-flap transfer was performed in 73 cases including radical forearm flap in 68 cases, lateral arm flap in 3 cases, fibular flap in 1 case and anterolateral thigh flap in 1 case. Of those patients with pN+ neck, postoperative radiotherapy (RT) to the neck was given to the patients.

3.3. Specimen characteristics of neck dissection

During the histopathological assessment of the surgically removed neck preparation, the lymph nodes were analysed separately from the primary tumour in END group. In unilateral SOND, 2320 lymph nodes in 108 patients (mean: 21.5, range: 4–47) were found. In unilateral RND, 1400 lymph nodes in 43 patients (mean: 32.6, range: 12–53) were found. In bilateral SOND, altogether 144 lymph nodes in 5 patients (mean: 28.8, range: 19–48) were found. Of those 156 patients with END, occult lymph node metastases were detected in 40 cases (25.6%) including 19 pN1, 15 pN2b and 6 skip metastasis. These occult metastases were found more frequently in T2 compared to T1 tumours though no statistical difference was seen (30.5% (29/95) vs. 18.0% (11/61), $p = 0.081$). None of the subclinical metastatic node had extracapsular spread.

3.4. END decreases node-related mortality by reducing regional recurrence rate

During the follow-up period, 61 (26.6%) of the 229 patients had died (END group: 31 cases and observation group: 30 cases). Five

patients died as a result of causes unrelated to cancer, two cases in END group and three cases in observation group, including three patients who died of cardiac failure and brain stroke, one patient died of uncontrolled lung infection and one patient died of uncertain cause. The sites of recurrence of the two groups of patients are shown in Table 2. There were 15 (9.6%) patients in the END group and 14 (19.2%) patients in the observation group who developed nodal recurrence alone without associated local recurrence or distant metastasis. Node-related mortality rate was 5.1% (8/156) for END and 12.3% (9/73) for observation, respectively (chi-square test, $p = 0.053$). Nodal recurrence was found in a median follow-up of 7 months (range, 1–34 months).

Of the 156 patients with END, nodal recurrence occurred in 9.5% (11 of 116) of pN0 patients and 10.0% (4 of 40) of pN+ patients. The site of nodal recurrence was the contralateral neck in 4 cases and the ipsilateral neck in 3 cases in the pN0 patient. There were 4 cases in the contralateral neck and 2 cases in the ipsilateral neck within the field of END for the patient with pN+ neck. Irregular metastasis followed by neck dissection occurred in 3 cases involved in pharyngeal, anterior cervical and inferior parotid lymph nodes. The above 2 of 3 patients died of uncontrolled lymph node metastasis.

Of those 14 patients who developed nodal recurrence alone in the observation group, 13 nodal recurrences were in the ipsilateral neck and 1 in the contralateral neck. Of these 14 patients, 7 patients did not comply with our follow-up protocol and were found to have multi-node metastasis even involving the carotid artery in 2/7 patients. 12 patients had salvage neck dissection, including 8 radical neck dissections, 4 modified radical neck dissections with preservation of accessory nerve, sternomastoid muscle, and internal jugular vein. The median size of nodal recurrence was 2.5 cm (range, 2.0–6.0 cm). The pathologic nodal classification of nodal recurrences was 2 pN1, 9 pN2b and 1 pN2c. There was a higher incidence of extracapsular spread in the observed neck (8/14) compared with electively dissected neck (2/15) ($p = 0.021$). On the basis of guideline of pN+ neck management, 10 patients accepted postoperative adjuvant radiotherapy and 2 patients did not. The minimum recommended dose was 60 Gy in patients who could tolerate radiotherapy.

3.5. *END significantly improved 5-year DSS of stage T2 OSCC*

Elective neck dissection significantly improved 5-year DSS compared with the observation group (79.2% vs. 61.9%, Log-rank $p = 0.040$, shown in Fig. 1). Through the analysis of T stage and prognosis in END group, we found that, compared to the T2 subgroup the T1 subgroup had a better 5-year DSS, which were 87.2% and 74.2% but there was no statistical difference (Log-rank $p = 0.113$). A significant survival benefit (T1 vs. T2) was seen in the patients in the observation group, which were 76.0% and 41.2% for T1 subgroup and T2 subgroup, respectively (Log-rank $p = 0.006$). Further analysis for subgroups of stage T1 showed that the patients from END group have a better 5-year DSS than those from the observation group, although there was no statistically significant difference (87.2% vs. 76.0%, Log-rank $p = 0.282$). END compared with observation for patients with stage T2 had a better 5-year DSS (74.2% vs. 41.2%, Log-rank $p = 0.008$) (shown in Fig. 2).

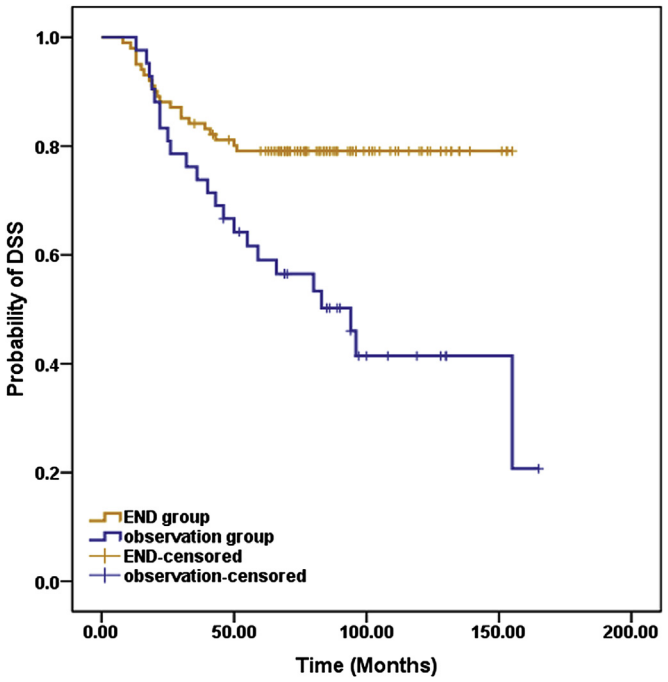

Fig. 1. Kaplan–Meier survival curves of DSS between END group and observation group (5-year DSS for "END group" vs. "observation group": 79.2% vs. 61.9%, Log-rank $p = 0.040$).

4. Discussion

The presence or absence of lymph node metastasis is a major prognostic factor for survival in patients with negative cervical lymph nodes (Sparano et al., 2004). Therefore, elective treatment of the cervical nodes is widely accepted in such patients when the risk of metastases exceeds 15–20% (Beltramini et al., 2012; Haddadin et al., 1999; Pitman, 2000; Yao et al., 2007). In this study, the total regional recurrence rate of the untreated N0 neck was found to be 19.2% for stage T1 (8/48, 16.7%) and stage T2 (6/25, 24.0%), respectively. 92.9% of them occurred in the early postoperative period (within 2 years). Of these regional recurrences, only 41.7% patients were successful salvaged due to advanced neck disease.

In our department, observation policy for clinically N0 neck was more common in patients with the stage T1 tumours, so that the

Table 2
The sites of first recurrence and treatment results of the two groups of patients.

Site of recurrence	END group (n = 156)			Observation group ($n = 73$)		
	Patient	Treatment	Success rate of operative salvage	Patient	Treatment	Success rate of operative salvage
Local	13	6 op; 4 RT; 3 quit	50.0%, 3/6	14	13op; 1 RT	53.8%, 7/13
Local + node	1	1 op + RT	0%, 0/1	3	2 op + RT; 1 op	50.0%, 1/2
Node only	15	7 op; 5 op + RT; 3 RT	58.3%, 7/12	14	10 op + RT; 2 op; 2 RT	41.7%, 5/12
Node + distant	2	1 CT	–	4	2 CT; 2 quit	–
Distant	6	4 CT; 1 CTRT; 1 quit	–	1	1 quit	–
SPM	7	4 op; 2 CTRT; 1 CT	100.0%, 4/4	8	5 op; 2 op + RT; 1 RT	57.1%, 4/7

Abbreviations: SPM: second primary malignancy; op: operation; RT: radiotherapy; CT: chemotherapy; CTRT: concurrent chemoradiotherapy.

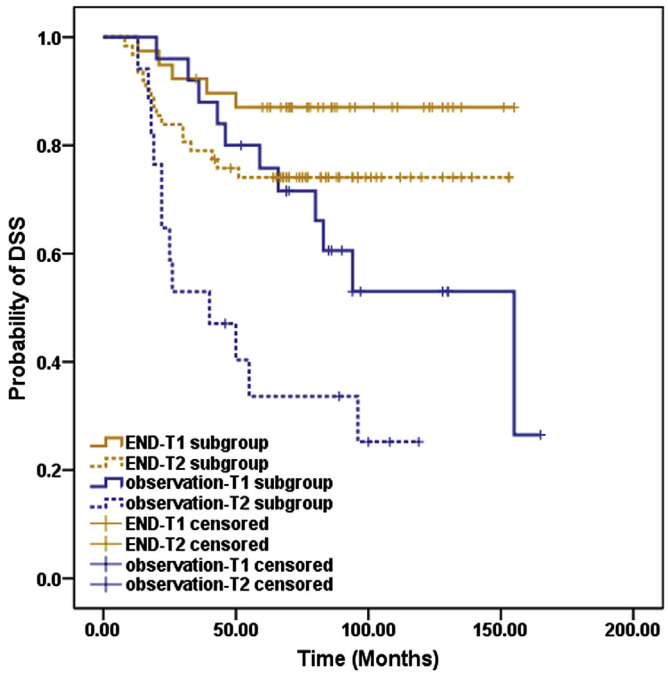

Fig. 2. Kaplan–Meier survival curves of DSS for T1/T2 subgroups between END group and observation group (5-year DSS for "END-T1 subgroup" vs. "END-T2 subgroup": $p = 0.113$; "observation-T1 subgroup" vs. "observation-T2 subgroup": $p = 0.006$; "END-T1 subgroup" vs. "observation-T1 subgroup": $p = 0.282$; "END-T2 subgroup" vs. "observation-T1 subgroup": $p = 0.008$).

T1/T2 ratio for the randomized controlled study was unbalanced (T1/T2 ratio in "END vs. observation": 0.6 vs. 1.9). Although the patients from the observation group had a higher proportion of stage T1, We found that the patients from END group exhibited significantly better DSS rates than those from observation group. We further analysed the prognosis of subgroups (T1/T2) in each group, the results showed that the patients from the END group with stage T2 tumours had a higher survival rate than those from the observation group.

Besides the influence of intrinsic metastasis regularity and management plan, the compliance of patients for regular return visit is crucial for the prognosis. In this study, the high incidence of extracapsular spread (57.1%) for region recurrence leads to an unsatisfactory success rate (41.7%) of operative salvage. Therefore, observation policy on the clinically N0 neck should be especially cautious for the patients with poor health awareness and who might find return visits difficult. More importantly, most patients in the observation group need radical or modified radical neck dissection for salvage of regional recurrence and have more shoulder morbidity (Yuen et al., 2009). Due to its high efficiency and minor morbidity, elective SOND has gained increasing popularity as a definitive therapeutic approach in the treatment of OSCC (Cheng and Schmidt, 2008).

Currently, the neck is staged by palpation and different imaging techniques, including ultrasound, CT, and MRI, which are more accurate than palpation alone (de Bondt et al., 2007; Martínez-Gimeno et al., 2011; Ng et al., 2006). However, up to one-third of nodal metastases in patients with oral SCCs are smaller than 3 mm, which is a detection threshold that limits the sensitivity of available imaging techniques (Buckley and MacLennan, 2000; Liao et al., 2012). The PET/CT, which is generally recognized as the most sensitivity imaging technique (Lonneux et al., 2010), is still not able to serve as a conventional diagnostic technique due to high cost in developing countries.

The actual metastasis rate is often underestimated because only 1–2 sections are analysed in the pathological examination of each postoperative cervical lymph node. Our previous study used immunohistochemical (IHC) staining with cytokeratin combining semi-serial sections to detect 1638 lymph nodes of 26 patients with cN+ neck (Guo et al., 2007). We found that 5 patients who were diagnosed as pN0 by HE staining were found to have lymph node metastasis by cytokeratin staining, indicating 19.2% micrometastasis rate. These findings supported our aggressive policy for neck management rather than observation in view of high potential risk of metastasis.

Recently, a preoperative minimally-invasive surgical approach called "sentinel lymph node biopsy" has been investigated in many cancer centres (O'Connor et al., 2013). Some authors postulate that sentinel lymph node biopsy might replace elective neck dissection in the treatment of early, node-negative OSCC (Alkureishi et al., 2009; Stoeckli et al., 2009). Other studies, however, do not find such a high sensitivity for sentinel lymph node biopsy, suggesting that this approach should primarily be considered for patients with T1 tumours and a low risk of occult metastases (Keski-Säntti et al., 2008a, 2008b; Thiele et al., 2012). In the future, we believe that sentinel lymph node biopsy will play a vital role in classification for patients with T1 tumours who would benefit from END. Nevertheless, before further prospective studies confirm that sentinel lymph node biopsy can actually replace END for T2 tumours, simultaneous neck dissection is still the most preferred recommended neck management choice for UICC stage II OSCC.

This study is retrospective and may be restricted to patient subsets with clinicopathological data. We aimed to exclude the selection bias, and consecutive patients who met all inclusion criteria were enrolled in the study. All of the factors were used for survival analysis between the T1/T2 subgroups was well matched, so, the results from the study are reliable.

5. Conclusion

In view of the high incidence of nodal recurrence and poor prognosis in the neck of T2 OSCC, END for these tumours is strongly proposed by our department. A prospective randomized study would be worthwhile to further evaluate the benefit of END, informed by sentinel lymph node biopsy in the treatment of early stage tongue carcinoma.

Conflicts of interest

None declared.

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