Elective neck dissection versus observation for cN0 neck of squamous cell carcinoma primarily located in the maxillary gingiva and alveolar ridge: a retrospective study of 129 cases

Zhien Feng, MD, PhD, Jian Nan Li, MD, Chuan Zhen Li, MD, and Chuan Bin Guo, MD, PhD
Peking University, Beijing, China

Objective. The aim of this study was to evaluate the results of elective neck dissection (END) versus those of observation in the treatment of squamous cell carcinoma of the maxillary gingiva.
Study Design. This was a retrospective study of 129 cases.
Results. There were 2 (4.0%) patients in the END group and 19 (24.1%) patients in the observation group who developed nodal recurrence alone. The regional recurrence rate of the observation group was 9.1% for T1 disease, 19.0% for T2, 27.3% for T3, and 40.0% for T4. Patients with stages T2 to T4 who underwent END received more survival benefit than did those in the observation group ($P = .048$). There were no statistical differences for patients with stage T1 disease between the 2 groups ($P = .605$).
Conclusions. This retrospective study suggests that END should be recommended as a preferred management strategy for stage T2 to T4 disease and that observation may be an acceptable alternative to END for stage T1 tumors if strict compliance with a cancer surveillance protocol is followed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:556-561)

Primary squamous cell carcinoma (SCC) located in the maxillary gingiva is relatively uncommon, and the principles of the management of the clinically node negative (cN0) neck lack evidence from large-sample, controlled clinical studies. So the recommendations that guide the management of patients with maxillary SCC of gingival tissue are particularly challenging. The traditional management of patients with maxillary SCCs in the absence of palpable or radiographically suspicious lymph nodes usually involves a widely accepted observation strategy based on the low risk of occult cervical metastases.[1] Recently, many studies have found that maxillary SCCs exhibit aggressive regional metastatic behavior, comparable with that of carcinomas of the tongue, floor of the mouth, and mandibular gingiva, and such studies have recommended elective neck dissection (END) for patients with maxillary SCCs and cN0 neck.[2-8] However, most of the available retrospective studies, which draw conclusions from a small case series or lack a control group, possessed obvious limitations.[5] Currently, there are no prospective, evidence-based studies for these particular tumors, owing to their low incidence rate compared with those of other oral cancer locations. The aim of the present study was to review the results of the surgical treatment of SCC primarily located in the maxillary gingiva alone by comparing END versus observation at our department. Based on a better understanding of the results of different neck management options, a more strategic treatment policy may be adopted in the future.

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Department of Oral and Maxillofacial Surgery, School of Stomatology, Peking University.
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PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the Stomatological Hospital of Peking University. Between August 1998 and September 2011, all inpatients who underwent surgical procedures at the hospital's Department of Oral and Maxillofacial Surgery for pathologically diagnosed maxillary SCC of gingival tissue were screened for the study. Patients' inclusion criteria included the following: (1) a primary tumor located in the maxillary gingiva and alveolar ridge; (2) no evidence of distant metastasis; (3) no previous treatment; and (4) complete medical information and follow-up data. Additionally, patients with tumors originating in the nasal cavity, paranasal sinuses, hard palate, and soft palate were excluded from this study. Identifier data were terminally coded to maintain patient anonymity.

Statement of Clinical Relevance

This study of 129 patients highlights the comparison of prognosis between elective neck dissection and observation in the treatment of squamous cell carcinoma of the maxillary gingiva.

All of the patients were initially treated surgically. The surgical procedure was selected by surgeons according to the tumor site and local practice. Standardized surgery, including radical tumor resection, neck dissection, and the reconstruction of tissue defects (as necessary), was performed. Additionally, postoperative patients were advised to return regularly for visits at intervals of 2 months in the first year, 3 months in the second year, 6 months in the third, fourth, and fifth years, and once every 6 months to 1 year thereafter. A telephone interview for survivors was also completed every 6 months. The aforementioned follow-up policy has been routine practice at our hospitals.

The baseline demographic data between the 2 groups were compared by a χ^2 test as appropriate for categorical variables and by a *t* test for continuous variables. A rate of node recurrence exceeding 15% defined a tumor with high metastasis risk. The main outcome assessment parameter was node-related mortality rate, as described by Yuen et al.,[9] which was defined as the percentage of patients whose mortality resulted from nodal metastasis but was not associated with local recurrence or distant metastasis. The secondary outcome assessment parameter was the 5-year disease-specific survival (DSS), which included only patients who underwent treatment for the first time 5 years previously. The 5-year DSS was calculated from the time of the first surgical procedure to the time of death or last follow-up. The Kaplan-Meier curve of DSS was generated for each group and compared using the log-rank test. Values of $P < .05$ were considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 17.0; SPSS Inc, Chicago, IL, USA).

RESULTS

Patient characteristics

Ultimately, 129 eligible patients were enrolled in this study: 50 patients in the END group and 79 patients in the observation group. There were 65 male patients and 64 female patients, and the mean age was 64.2 years (range, 5-82 years). The demographic data of the 129 patients are shown in Table I. Additionally, the patients were well matched between the 2 groups regarding age, gender, T stage, pathologic grade, growth pattern, and tobacco and alcohol use. In these patients' data, the cutoff date of follow-up was April 1, 2013, for survivors. The median follow-up for surviving patients was 62 months (interquartile range, 49 to 96) for the END group and 61 months (interquartile range, 44.5 to 92.5) for the observation group.

Treatment outcome

All primary tumors were completely excised, and the margins were found to be negative. Patients in the END group received one of several types of END, including unilateral supraomohyoid neck dissection (SOND, level I, II, or III) or extended supraomohyoid neck dissection (ESOND, level I, II, III, or IV) in 39 cases, unilateral or modified radical neck dissection (RND) in 10 cases, and bilateral SOND in 1 case. There was no statistically significant difference in the regional recurrence rate between RND and SOND/ESOND (1/10 vs 1/40, χ^2 test, $P = .857$). Tissue reconstruction using free-flap transfer was performed in 29 cases, including radial forearm flap in 16 cases, fibular flap in 6 cases, lateral arm flap in 3 cases, radical forearm plus fibular flap in 1 case, anterolateral thigh flap in 1 case, deep inferior epigastric perforator flap in 1 case, and transverse rectus abdominis myocutaneous flap in 1 case. For those patients with pN+ neck, postoperative radiotherapy to the neck was advised.

Table I. Baseline demographics of the 129 patients who participated in the study

	END group (n = 50)		*Observation group (n = 79)*		
Variable	*No.*	*%*	*No.*	*%*	*P*
Age (y), mean ± SD	62.3 ± 10.6		65.4 ± 12.7		.162
Gender					
Male	23	46.0	42	53.2	.473
Female	27	54.0	37	46.8	
cTNM stage					
I	5	10.0	22	27.8	.100
II	18	36.0	21	26.7	
III	10	20.0	11	13.9	
IV	17	34.0	25	31.6	
Pathologic grade					
I	26	52.0	40	50.6	.426
II	18	36.0	29	36.7	
III	5	10.0	3	3.8	
Missing	1	2.0	7	8.9	
Growth pattern					
Exophytic	27	54.0	48	60.8	.874
Ulcerative	15	30.0	24	30.4	
Infiltrative	4	8.0	5	6.3	
Missing	4	8.0	2	2.5	
Smoking history					
Smoker	11	22.0	24	30.4	.415
Nonsmoker	37	74.0	54	68.4	
Missing	2	4.0	1	1.2	
Alcohol history					
Drinker	9	18.0	9	11.4	.300
Nondrinker	39	78.0	69	87.3	
Missing	2	4.0	1	1.3	

END group, elective neck dissection group; *SD*, standard deviation; *cTNM stage*, clinical TNM stage.

Specimen characteristics of neck dissection

During the histopathologic assessment of the surgically removed neck preparation, the lymph nodes were analyzed separately from the primary tumor in the END group. In unilateral SOND, 669 lymph nodes in

39 patients (mean, 17.2; range, 4-45) were found. In unilateral RND, 355 lymph nodes in 10 patients (mean, 35.5; range, 18-53) were found. In bilateral SOND, 39 lymph nodes in 1 patient were found. Of those 50 patients with END, occult lymph node metastases were detected in 12 cases (24.0%), including 8 pN1 and 4 pN2b. The nodal histologic characteristics of the surgical specimens are listed in Table II. There was no statistical significance regarding the occult metastasis rate between different T stages ($P = .771$). None of the subclinical metastatic nodes showed extracapsular spread.

Table II. The nodal histologic characteristics of surgical specimens in the END group

	END group (n = 50)			
N status	*T1 (n = 5)*	*T2 (n = 18)*	*T3 (n = 10)*	*T4 (n = 17)*
N0	3 (60.0%)	15 (83.3%)	8 (80.0%)	12 (70.6%)
N1	1 (20.0%)	2 (11.1%)	1 (10.0%)	4 (23.5%)
N2b	1 (20.0%)	1 (5.6%)	1 (10.0%)	1 (5.9%)
P		.771		

END, elective neck dissection.

END decreases node-related mortality by reducing the regional recurrence rate

During the follow-up period, 56 (43.4%) of the 129 patients died (END group, 18 deaths; observation group, 38 deaths). Three patients died as a result of causes unrelated to cancer: 1 person in the END group and 2 persons in the observation group, including 2 patients who died of cardiac failure and 1 patient who died of respiratory failure. The sites of first recurrence and the treatment results of the 2 groups are shown in Table III. There were 2 (4.0%) patients in the END group and 19 (24.1%) patients in the observation group who developed nodal recurrence alone without associated local recurrence or distant metastasis. Additionally, the node-related mortality rate was 4.0% (2/50) for the END group and 13.9% (11/79) for the observation group (χ^2 test, $P = .127$). Nodal recurrence was found during the median follow-up of 6 months (range, 1 to 28 months). Regarding the 2 patients with regional recurrence in the END group, the site of nodal recurrence was in the contralateral neck of the pT3N0 and pT4N0 patients.

Stage T1 had low risk of node metastasis, whereas stages T2 to T4 had high risk

Of those 19 patients who developed nodal recurrence alone in the observation group, 16 cases of nodal recurrence were found in the ipsilateral neck, 2 cases were found in the contralateral neck, and 1 case was found in the bilateral neck. The total regional recurrence rate of untreated N0 neck was 24.1%, and the rates by stage were as follows: stage T1, 2/22 (9.1%); stage T2, 4/21 (19.0%); stage T3, 3/11 (27.3%); and stage T4, 10/25 (40.0%). These rates reflect that stage T1 tumor has low metastasis risk, whereas stage T2 to T4 tumors have high metastasis risk. Additionally, 94.7% of nodal recurrence cases occurred in the early postoperative period (within 2 years). Of these 19 patients, 11 patients did not comply with our follow-up protocol and were found to have multinode metastasis or extracapsular invasion. Ultimately, 17 patients received therapeutic neck dissection ± adjuvant radiotherapy; however, only 8 patients had successful salvage. Additionally, further analysis found that the success rates of cervical salvage for patients with and without regular return visits were 100.0% (8/8) and 27.3% (3/11), respectively. The poor success rate of cervical salvage for the patients in the observation group is associated with noncompliance with the regular return visit protocol.

END significantly improved the 5-year DSS for patients with stages T2 to T4

At the cutoff date of the follow-up, 76 patients who underwent their first treatments in the previous 5 years were included in the survival analysis of 5-year DSS. The END group had 25 of these patients (T1, 2 cases; T2, 9 cases; T3, 6 cases; and T4, 8 cases), and the other 51 patients were in the observation group (T1, 16 cases; T2, 13 cases; T3, 7 cases; and T4, 15 cases). Interestingly, there was no significant difference between the END and observation groups concerning the 5-year DSS, although the END group had a higher 5-year DSS (72.0% vs 56.9%, $P = .191$; Figure 1). Further analysis of subgroups found that patients with stage T1 disease in the END group had a similar 5-year DSS compared with those in the observation group (100.0% vs 87.5%, $P = .605$; Figure 2). It was noteworthy that patients with stage T2 to T4 disease in the END group received more survival benefit than did those in the observation group (5-year DSS rate, 69.6% vs 40.0%, $P = .048$; Figure 3).

DISCUSSION

Most tumors in oral cavity subsites have a comparably high propensity to metastasize to regional lymph nodes in the neck.[10] Recent studies seem to refute the traditional belief that maxillary SCCs have a lower rate of metastasis to the neck.[2,11,12] It is widely accepted that the presence of regional neck metastases is a major determinant of both prognosis and treatment decisions in patients with oral SCC.[13] However, the low sensitivity of currently available diagnostic modalities is a problem, because a high proportion (>30%) of lymph node metastases is left undetected in this population.

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

	END group (n = 47)			*Observation group (n = 68)*		
Site of recurrence	*Patient*	*Treatment*	*Success rate of operative salvage*	*Patient*	*Treatment*	*Success rate of operative salvage*
Local	12	10 op; 2 RT	30.0%, 3/10	14	9 op; 5 RT	22.2%, 2/9
Local+node	1	1 op+RT	0%, 0/1	2	1 RT; 1 op+RT	0%, 0/1
Node only	2	1 op+RT; 1 RT	0%, 0/1	19	9 op; 8 op+RT; 2 RT	47.1%, 8/17
Node+distant	1	1 chemo	—	1	1 quit	—
Distant	1	1 quit	—	0	—	—
SPM	0	—	—	3	1 op; 1 CRCT; 1 quit	100.0%, 1/1

SPM, second primary malignancy; *op*, surgical procedure; *RT*, radiotherapy; *chemo*, chemotherapy; *CRCT*, concurrent chemoradiotherapy.

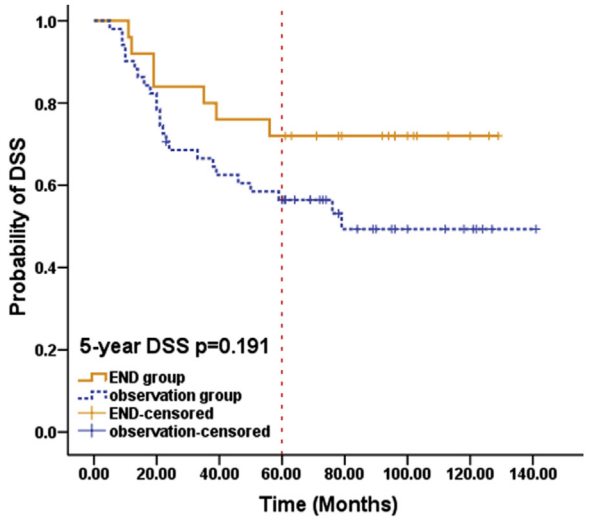

Fig. 1. Kaplan-Meier survival curves of disease-specific survival (DSS) for the elective neck dissection (END) group vs the observation group (5-year DSS for END group vs observation group, 72.0% vs 56.9%, respectively; log-rank $P = .191$).

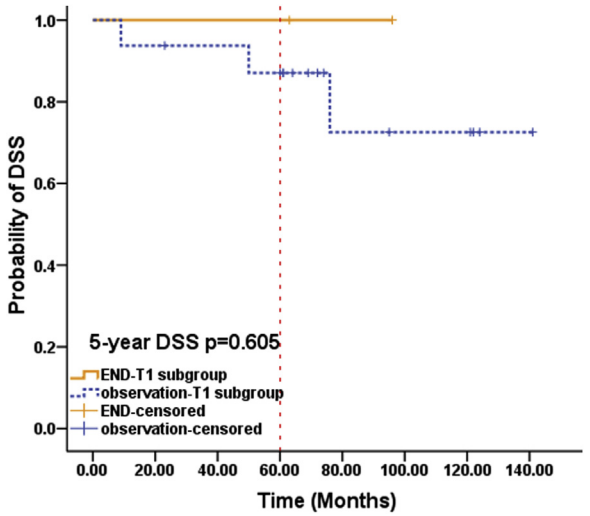

Fig. 2. Kaplan-Meier survival curves of disease-specific survival (DSS) for stage T1 between the elective neck dissection (END) group and the observation group (5-year DSS, 100.0% vs 87.5%; log-rank $P = .605$).

These metastases will develop into overt neck disease during follow-up.[10]

In our study, the occult metastasis risk of the END group predictably increased with the elevation of the T stage; however, a surprising exception was T1 tumors, with the highest metastasis rate of 40.0% (2/5). The most likely cause of this phenomenon was that the small sample size—only 5 cases in the END-T1 tumor subgroup—easily produced discrete values in the statistical analysis. Concerning this study, the actual metastasis rate of T1 tumors should refer to the delayed metastasis rate of untreated N0 neck in the observation group, which was only 9.1% (2/22). Through further analysis of the observation group, stage T2, T3, and T4 SCCs had an obviously high delayed cervical nodal metastasis rate of 19.0% to 40.0%. Therefore, the results explicitly show that intermediate-stage and advanced-stage SCCs of the maxillary gingiva have more aggressive behavior than do oral cancers of other locations.

The prognosis of patients with delayed nodal metastasis of maxillary SCC of gingival tissue is poor. Of those patients with regional recurrence in the observation group, only 47.1% had successful salvage, because most patients did not comply with our follow-up protocol. However, it was noteworthy that early detection of regional recurrence could lead to a 100% cervical salvage rate irrespective of T stage; otherwise, the salvage rate was <30.0%. Therefore, the follow-up compliance of patient populations was the vital factor to adopting the observation strategy for the cN0 neck.

The results from our study show that END can significantly improve long-term survival for patients with stage T2 to T4 SCC of the maxillary gingiva, compared with observation. Therefore, END should be recommended as the first-line management for all intermediate- and advanced-stage patients. A solitary exception is made for patients with stage T1 tumors, who have a low risk of nodal metastasis of <10.0% and for whom observation may be an acceptable alternative to END if the patients strictly comply with a cancer surveillance protocol.

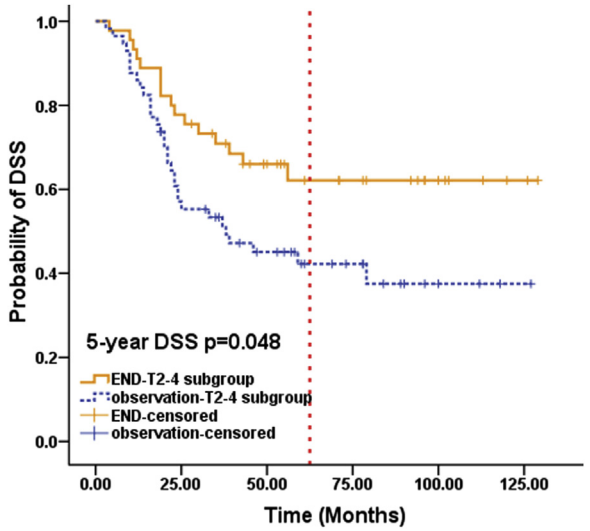

Fig. 3. Kaplan-Meier survival curves of disease-specific survival (DSS) for stages T2 to T4 between the elective neck dissection (END) group and the observation group (5-year DSS, 69.6% vs 40.0%; log-rank $P = .048$).

Elective SOND/ESOND has gained increasing popularity as a definitive therapeutic approach in the treatment of oral SCC, owing to its high efficiency and minor morbidity.[14] The other advantage of neck dissection is its convenience in reconstructing the surgical defect by free or pedicle flaps; most head and neck surgeons will usually opt for END.[15,16] The observation strategy increases the probability of second salvage surgery, and therapeutic neck dissection adds the risk of more shoulder morbidity.[9]

Currently, the neck is staged by palpation and various imaging techniques, including ultrasound, computed tomography (CT), and magnetic resonance imaging, which are more accurate than palpation alone.[17,18] 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.[19,20] Another cause to lead to the actual metastasis rate being often underestimated is that only 1 or 2 sections are analyzed in the pathologic diagnosis procedure per postoperative specimen of cervical lymph node. Our previous study applied immunohistochemical stain with cytokeratin, combining semi-serial sections to detect 1638 lymph nodes of 26 patients with cN+ neck.[21] It was found that all 26 patients (162 nodes) were positive, including micrometastasis, by immunohistochemical staining, but traditional cytomorphologic detection (with hematoxylin-eosin staining) only found 21 patients (52 nodes) positive. And 5 patients who were diagnosed as pN0 by hematoxylin-eosin staining were found to have lymph node metastasis by cytokeratin staining, indicating a 19.2% micrometastasis rate. Our experience supported an aggressive policy for neck management rather than observation, in view of high potential risk of metastasis.

It has been suggested that positron emission tomography and computed tomography with ^{18}F-fludeoxyglucose (^{18}F-FDG PET/CT imaging) might be more accurate than CT or magnetic resonance imaging in identifying cervical lymph node metastases in head and neck SCC,[22] and in one study the diagnostic sensitivity and specificity for regional recurrence were 90% and 91%, respectively.[23] Our previous study found that single-photon emission computed tomography (SPECT) with a complex of technetium 99m (V) meso-2,3-dimercaptosuccinic acid (^{99m}Tc (V)-DMSA SPECT imaging) has fairly high affinity with metastatic lymph nodes in the neck, especially in the cN0 patients, and is helpful for designing proper neck dissection. The sensitivity, specificity, and accuracy of ^{99m}Tc(V)-DMSA imaging for detecting metastatic lymph nodes have been reported at 75.0%, 90.0%, and 84.4%, respectively.[24] Therefore, we believe that PET/CT and SPECT imaging may be promising techniques for screening the patients with occult lymph node metastasis.

Recently, a new approach, sentinel lymph node biopsy (SNB), has been investigated as one of the most promising techniques for the personalized management of the cN0 neck.[10] Some authors have postulated that SNB might replace END in the treatment of early, node-negative oral SCC.[25,26] However, other studies have found a poor sensitivity of SNB, particularly for tumors on the floor of the mouth, suggesting that this approach may possess some limitations. A conservative standpoint confirms that SNB should primarily be considered for patients with T1 tumors and a low risk of occult metastases.[27-30] Nevertheless, a prospective study of maxillary SCC is very difficult to conduct because of the tumor's rarity. The conclusion that SNB can replace END in patients with SCC of the maxillary gingiva may remain unsettled for a long time.

CONCLUSIONS

Stage T1 SCC of the maxillary gingiva has a low risk of nodal metastases, whereas stage T2 to T4 tumors have an obvious propensity for early nodal metastases. END should be recommended as the preferred management for stage T2 to T4 SCCs of the maxillary gingiva. Observation with a careful monitoring strategy may be an acceptable alternative to END for cN0 neck of T1 tumors. In the future, a prospective randomized study will be worthwhile to further evaluate the benefit of neck management in the treatment of early SCC of the maxillary gingiva.

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Reprint requests:

Chuan Bin Guo, MD, PhD
Department of Oral and Maxillofacial Surgery
School of Stomatology
Peking University, No. 22 Zhong-Guan-Cun South Road
Hai-Dian District, Beijing 100081
China
guodazuo@sina.com