ORIGINAL ARTICLE

PROSPECTIVE RANDOMIZED STUDY OF SELECTIVE NECK DISSECTION VERSUS OBSERVATION FOR N0 NECK OF EARLY TONGUE CARCINOMA

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Abstract: *Background.* There are controversies on the benefits of elective neck dissection (END) for oral tongue carcinoma.

Method. This is a prospective randomized study of elective selective I, II, III neck dissection versus observation for N0 neck of stage I to II oral tongue carcinoma. There were 35 patients on the observation arm and 36 patients on the END arm. The main outcome assessment parameters are node-related mortality and disease-specific survival rate.

Results. There were 11 patients in the observed arm and 2 patients in the END arm who developed nodal recurrence alone without associated local or distant recurrence. All 13 patients were salvaged, and no patient died of nodal recurrence. The 5-year disease-specific survival rate was 87% for the observation arm and was 89% for the END arm; the 2% difference was not significant.

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Conclusion. Observation may be an acceptable alternative to END if strict adherence to a cancer surveillance protocol is followed. © 2009 Wiley Periodicals, Inc. *Head Neck* **31:** 765–772, 2009

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Oral tongue carcinoma is well documented for its propensity of subclinical nodal metastasis in the early stage. 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 of observed radiologic N0 neck is 30% to 40%.[1–4] In view of the high incidence of nodal recurrence of observed neck, prophylactic neck dissection has been advocated as routine management protocol of N0 neck by many surgeons.[5]

There was 1 prospective randomized study in the literature to compare elective ipsilateral radical neck dissection versus observation in the treatment of stage I to II oral tongue carcinoma in India.[6] Another prospective randomized study of T1-3N0M0 of mixed oral tongue and floor of mouth carcinomas was conducted in France comparing observation and elective ipsilateral radical neck dissection.[7] These 2 prospective randomized studies did not show any survival benefit of elective radical neck dissection.

Selective neck dissection is a more acceptable option for elective treatment of the N0 neck with lower shoulder functional morbidity.[8] There was 1 prospective randomized study of selective neck dissection versus observation of stage I to II of a mixed group of oral cancers including tongue and floor of mouth carcinoma in Brazil. The study showed significant benefit of elective selective neck dissection.[9] Despite the common practice of prophylactic selective neck dissection, there is no prospective randomized study comparing selective I, II, III neck dissection (SND) and observation for stage I to II oral tongue carcinoma only in the literature. The aim of this study was to conduct a prospective randomized study to address the unresolved questions of nodal control and survival benefits of elective selective level I, II, III neck dissection compared with observation in the treatment of stage I to II oral tongue carcinoma.

PATIENTS AND METHODS

This is a multicenter prospective randomized study conducted in Queen Mary Hospital, Kwong Wah Hospital, and United Christian Hospital in Hong Kong. Suitable patients were also referred to these 3 hospitals from co-authors of 3 other regional hospitals including Queen Elizabeth Hospital, Ruttonjee Hospital, and Yan Chai Hospital for this study. The study was approved by the research ethnic committee of The University of Hong Kong (reference number EC 807-96). The research protocol was posted to the website of clinical trial public information center of The University of Hong Kong for public access of information in 2005 (http://www.hkclinicaltrials.com, clinical trial registration number HKCTR-17, registration name: prospective randomized study of selective I, II, III neck dissection for stage I and II squamous cell carcinoma of oral tongue). All patients gave written consent for the randomization of treatment.

Patients had AJCC stage I to II squamous cell carcinoma of oral tongue. All patients had preoperative ultrasonic scanning of neck, and also had ultrasonic-guided aspiration for cytology if necessary to rule out nodal metastasis. All patients had no prior surgery, chemotherapy, or radiotherapy treatment of the oral tongue carcinoma. Oral cavity carcinoma of other subsites and tongue base carcinoma were not included in this study. Two sets of sealed envelopes, 1 set for T1 patients and another set for T2 patients, were used for the randomization of patients to either observation or elective neck dissection. The patients were stratified into T1 and T2 for randomization in order to ensure comparable number of T1 and T2 patients in both arms. The sample size estimation was based on the published data of our previous retrospective study of 63 patients which demonstrated significant reduction of node-related mortality from 23% of observation to 3% after selective neck dissection.[4] With type I error of 0.05 and power of 0.70, the minimum sample size required is 69. A sample size of 72 patients was planned to see if our previous retrospective study results could be verified in a prospective randomized study. The sample size could demonstrate statistically significant difference of 15% between the 2 arms. The patients were recruited in the period between 1996 and 2004.

All patients had transoral glossectomy with 1.5-cm resection margin according to the recommendation in our previous study.[10] Those patients who were randomized to elective neck dissection had ipsilateral selective level I, II, III neck dissection (SND). All pathologic specimens were serially sectioned in 3-mm interval in Queen Mary Hospital using our previous reported method.[1] The histologic slides were examined by the co-author pathologists KY Lam, WF Yuen, or NJ Trendell-Smith.

Of those patients with pN+ neck, postoperative radiotherapy (RT) to the neck was advised to the patients. All patients were followed up regularly with interval of 1 month in the first year, 2 months in the second year, 3 months in the third year, 4 months in the fourth and fifth year, and thereafter once every 6 months to 1 year. This policy of follow-up interval has been routine practice for all head and neck cancer patients in our hospitals and is not solely designed for this study. Of those patients on the observation arm, ultrasonographic examination of the neck was done every 3 months for the first 3 years.

Of those patients who had nodal recurrence, radical or modified radical neck dissection would be performed depending on the status of nodal recurrence and oncologic safety to preserve the functional structures. Radiotherapy to the neck after salvage radical neck dissection would be given to all pN2-3 nodal recurrence or in the presence of extracapsular spread. Adjuvant postoperative radiotherapy was not given to patients with pN1 neck without extracapsular spread.

If a patient did not have previous RT, pN+ neck of electively dissected neck and therapeutically dissected neck for nodal recurrence were treated similarly. The dose of postoperative RT differed depending on whether the area was considered high risk or low risk. High-risk areas were those sites with positive resection margin, multiple nodal metastases, extracapsular spread and lymphovascular permeation. For high-risk areas, the dose would be 64 to 66 Gy. For the low risk areas, the dose would be 60 Gy. For some patients, different parts of the neck might receive different doses (eg, the upper neck was usually the site of nodal recurrence and would have 64 to 66 Gy, and the posterior and lower neck might have no nodal metastasis and would have 60 Gy). The oral cavity was considered at risk and was also in close proximity with the upper neck, it would be irradiated together with the neck in case of nodal recurrence even if the primary appeared to be in disease control.

The data were evaluated by using SPSS version 13.0 software (SPSS Inc., Chicago). The baseline demographic data between the 2 arms were compared by chi-square test or Fisher's test 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 or distant metastasis. The secondary outcome assessment parameter was the 5-year tumor-specific survival rate. The disease-specific survival (DFS) was calculated from the time of first operation to the time of death or the last follow-up. The Kaplan-Meier curve of DFS was generated for each arm and compared using the log-rank test.

Table 1. Demographic data.

	Observation, 35 patients	SND, 36 patients	Statistics
Sex			
Male	22	21	Chi-square test
Female	13	15	$p = .702$
Age	Mean = 58 y, (29–81 y)	Mean = 56 y, (30–77 y)	*t* test, $p = .517$
T classification			
T1	21	22	Chi-square test
T2	14	14	$p = .925$
Tumor			
Well	19	14	Chi-square test
Moderate	12	18	$p = .405$
Poor	4	4	

RESULTS

There were 72 patients recruited into the study. One clinically T2 patient who was randomized to the observation arm was found to have pathologic T3 and therefore was excluded. The demographic data of the 71 patients are shown in Table 1. There were no significant differences in sex, age, T classification, and tumor grade between the 2 arms.

Of those 36 patients with SND, there were 22% (8/36) pN+ neck including 6 pN1 and 2 pN2b. None of the subclinical metastatic node had extracapsular spread. Of these 8 pN+ patients, 7(88%) patients accepted the advice to proceed to postoperative adjuvant radiotherapy treatment of the nodal metastasis. The median total radiotherapy dose was 60 Gy (range, 60–66 Gy).

The sites of recurrence of the 2 groups of patients are shown in Table 2. Nodal recurrence was found in a median follow-up of 7 months (range, 6 weeks to 16 months). Of the 36 patients with SND, nodal recurrence occurred in 4% (1 of 28) of pN0 patients and 13% (1 of 8) of pN+ patients. The site of nodal recurrence was in the contralateral neck of the pN0 patient and was in the ipsilateral neck within the field of SND for the patient with pN+ neck. There

Table 2. Sites of recurrences and their treatment results.

Site of recurrence	Observation group			Elective neck dissection group		
	Patient	Treatment	Success salvage	Patient	Treatment	Success salvage
Local	2	1 op + RT 1 op	100%, (2/2)	4	1 op, 1 op + RT, 1 op + CTRT, 1 CTRT	25%, (1/4)
Local + node	1	1 op + RT	0%, (0/1)	0		
Node	11	4 op, 5 op + RT, 2 op + CTRT	100% (11/11), *1 died of distant metastasis	2	1 op + RT, 1 multiple op + CTRT	100% (2/2), *1 died of distant, metastasis
Node + distant	1	0	0%, (0/1)	0		
distant	1	1 RT	0%, (0/1)	0		

Abbreviations: op, operation; RT, radiotherapy; CTRT, concurrent chemoradiotherapy.
**Patient with distant metastasis had nodal control.*

were 37% (13 of 35) patients of the observed arm who developed nodal metastasis, of which 31% (11 of 35) patients had nodal recurrence alone without associated local or distant recurrence. Of these 11 patients, 10 nodal recurrences were in the ipsilateral neck and 1 in the contralateral neck. There was significant reduction of nodal recurrence rate from 37% (13 of 35) of observed neck to 6% (2 of 36) after elective SND (chi-square test, $p = .001$).

Of the 11 patients with nodal recurrence alone without local or distant metastasis on the observation arm, only 1 patient did not comply with our follow-up protocol and was found to have a 5-cm node on follow-up. All 11 patients had salvage neck dissection, including 8 radical neck dissections, 2 modified radical neck dissections with preservation of accessory nerve, and 1 modified radical neck dissection with preservation of accessory nerve, sternomastoid muscle, and internal jugular vein. The median size of nodal recurrence was 1.5 cm (range, 1.0–5.0 cm). The pathologic nodal classification of nodal recurrences of these 11 patients were 5 pN1, 1 pN2a, and 5 pN2b. There were 45% (5 of 11) of specimens with extracapsular spread. There was a higher incidence of extracapsular spread of observed neck compared with electively dissected neck (Fisher's test, $p = .045$). On the basis of the pathologic findings of pN2 or extracapsular spread, 7 patients accepted the advice to proceed to postoperative adjuvant radiotherapy treatment of the neck. The median dose was 60 Gy, 1 patient who had prior radiotherapy 11 years ago for neck lymphoma received 50 Gy, the other patients received total dose 60–66 Gy. The other 4 patients with pN1 without extracapsular spread did not have postoperative radiotherapy.

There were 2 patients with nodal recurrence after elective SND. The first patient had pN0 neck and developed contralateral neck recurrence of 3.5 cm at the time of detection. Pathologic examination of specimen showed multiple nodal metastasis with extracapsular spread (pN2b) on the contralateral neck. This patient died of lung metastasis after successful surgical salvage and radiotherapy treatment of contralateral neck recurrences. The second patient had pN1 without extracapsular spread. He also received post-operative radiotherapy to the neck. He had ipsilateral level I neck recurrence of 2 cm with extracapsular spread to involve the skin. The patient had salvage neck dissection and deltopectoral flap reconstruction of neck skin. He developed ipsilateral nodal recurrence again and had further resection. He again developed ipsilateral nodal recurrence with infiltration to larynx, and eventually underwent laryngectomy. He again developed contralateral neck nodal recurrence and was salvaged by radical neck dissection and chemoradiotherapy. This patient remained alive without tumor 8 years after the fourth surgical salvage.

The treatment results of recurrences are summarized in Table 2. Of the 20 patients with local and/or nodal recurrences, 19 (95%) had surgical salvage. Radiotherapy and/or chemoradiotherapy were also given after surgical salvage in 74% (14 of 19) patients. All nodal recurrences were successfully salvaged in both arms, and there was no patient who died of nodal recurrence alone. The node-related mortality rate was 0% in both arms. There was 1 patient in each group who died of lung metastasis after successful salvage of neck recurrence, overall 15% (2 of 13) died of distant metastasis despite successful treatment of neck recurrence.

There were 4 patients in each arm who died of tumor recurrence in the period between 14 and 34 months of follow-up. There were 10

patients who died of other diseases without tumor recurrence. Of the other 53 patients who were still alive, none of them had tumor at the last follow-up; the minimum follow-up duration of these 53 patients was 34 months (mean, 86 months; longest, 122 months). The median follow-up duration of patients was 92 months on observation arm and was 93 months for neck dissection arm. The actuarial 5-year disease-specific survival rates were 87% for observation and 89% for elective neck dissection as shown in Figure 1 (log rank test, $p = .89$).

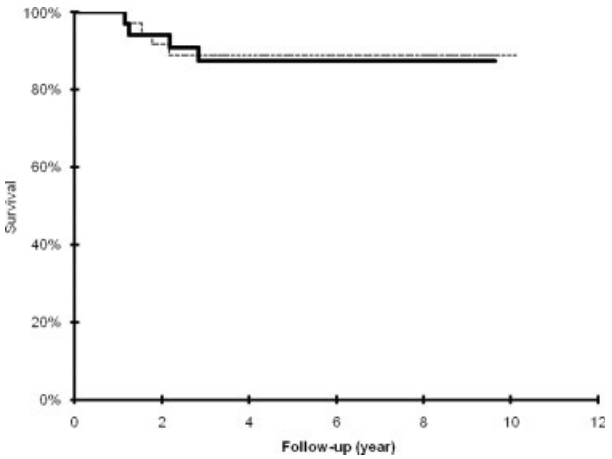

FIGURE 1. Kaplan-Meier disease-specific survival curves of selective neck dissection (dotted line) versus observation (solid line).

DISCUSSION

There was a 37% nodal recurrence of observed necks after ultrasonic assessment. Subclinical nodal metastasis missed by radiologic evaluation continued to be a clinical management problem of early oral tongue carcinoma. Nodal micrometastasis may be missed in histologic sections. We could identify 22% nodal metastasis in ultrasonic N0 neck in this study. Compared with the 37% nodal recurrence rate of observed neck, we might have missed 15% micrometastasis on histologic examination. Although 15% pN0 neck might be pN+, this subgroup of patients had a very low risk of nodal recurrence after SND without further radiotherapy. No patient with pN0 neck developed ipsilateral nodal recurrence in this study, and the result is consistent with our previous report.[4] SND alone is therefore an adequate treatment for those patients with pN0 neck even when nodal micrometastasis might be missed histologically.

Although SND is an adequate treatment in pN0 in which nodal micrometastasis may be missed histologically, it is still controversial whether it is an adequate treatment of pN+ neck. We considered level I, II, III SND to be inadequate treatment of pN+ neck; therefore, all patients with pN+ neck were advised to proceed to radiotherapy for possible better nodal control.

The benefits of elective level I, II, III SND on nodal control and survival published in our previous retrospective study could not be verified in this prospective randomized study. The most remarkable change was the improvement of nodal salvage rate from 50% in our previous retrospective study to 100% in the present prospective randomized study.[4] In our previous retrospective study, patients were not closely followed up after glossectomy, many patients were found to have advanced nodal recurrence and had poor salvage results. Although we performed ultrasonographic surveillance of observed neck every 3 months, we did not find any nonpalpable nodal recurrence. If ultrasonic surveillance is to be useful, it has to be performed more frequently. Close follow-up with clinical palpation was however adequate, the median size of nodal recurrence was 1.5 cm in this study.

Although the nodal recurrence of observed neck had higher risk of extracapsular spread compared with the subclinical nodal metastasis of elective SND, the salvage rate could be as high as 100%. Apart from the presence of extracapsular spread, we hypothesize that the extent of extracapsular spread is also an important prognostic factor, and the extent of extracapsular spread correlates with the size of metastatic lymph node. Smaller nodes would have less extensive extracapsular spread compared with larger size nodes. Although we do not have pathologic data of the extent of extracapsular spread of those patients in our retrospective study for comparison, we hypothesize that the lymph nodes in this prospective study were smaller in size with less extensive extracapsular spread compared with those in our previous retrospective study, and therefore would be more likely to be salvaged successfully. The detection of small nodes with less extensive extracapsular spread with close surveillance protocol is essential. Therefore, risk of nodal recurrence with extracapsular spread of observed neck is not adequate reason to reject observation as an acceptable treatment option. Successful salvage could be achieved with radical or

modified radical neck dissection alone without radiotherapy in 32% of patients with early pN1 nodal recurrence without extracapsular spread. This is 1 of the advantages of observation in which salvage neck dissection without radiotherapy of early nodal recurrence is an adequate curative treatment, and could avoid the additional cost and side effects of radiotherapy. These patients would otherwise need radiotherapy if they were treated by prophylactic level I, II, III SND. Radiotherapy was necessary for pN2 or pN1 with extracapsular spread. Further research is necessary, however, to verify that high salvage rate is achievable for nodal recurrences with extracapsular spread. The salvage result in relation to the extent of extracapsular spread should also be further studied.

There are only a few studies with available published details on salvage results of nodal recurrence comparing elective neck dissection and observation as shown in Table 3. Klingerman et al showed a low salvage rate of only 27% for nodal recurrence of observed neck, and their results demonstrated survival benefit of elective neck dissection.[11] Fakih et al showed a low (30%) salvage rate of nodal recurrence of observed neck.[6] However, their study also had exceptionally high (23%) node-related mortality even after prophylactic radical neck dissection of the N0 neck. Despite the low salvage rate of observed neck, their study did not demonstrate any survival benefit of prophylactic radical neck dissection. The study of Vandenbrouck et al showed a high salvage rate of 84%, and therefore, their results showed no survival benefit of elective neck dissection.[7] Nieuwenhuis et al in The Netherlands also showed a high salvage rate of 79% of nodal recurrence of observed neck of oral cavity carcinomas.[12] The wide range of salvage rates from 27% to 100% in different countries may be due to the differences of follow-up protocol, compliance of follow-up and salvage treatment algorithm in these institutes. However, patients on observation can be reassured that high nodal salvage rate and equally high survival rate compared with prophylactic neck dissection could be achieved on our recommended follow-up protocol and salvage treatment algorithm. There is limitation of sample size in this prospective study because of the difficulty of recruitment of patients, and the same problem applies to the other published data in the literature. Although there is lack of large-scale prospective randomized study on this

Table 3. Literature review of elective neck dissection versus observation of oral tongue carcinoma.

		Observation			Elective neck dissection			
Author	Tumor stage and subsites	Node-recur	Success salvage	Node-related mortality	Node-recur	Success salvage	Node-related mortality	Survival benefit
Fakih et al 1989[6]	T1-2, tongue	58%, (23/40)	30%, (7/23)	40%, (16/40)	30%, (9/30)	22%, (2/9)	23%, (7/30)	No
Vandenbrouck et al 1980[7]	T1-3, tongue, and FOM	53%, (19/36)	84%, (16/19)	8%, (3/36)	9%, (3 /32)	0%, (0/3)	9%, (3/32)	No
Kligerman et al 1994[11]	T1-2 tongue and FOM	33%, (11/33)	27%, (3/11)	24%, (8/33)	12%, (4/34)	25%, (1/4)	9%, (3/34)	Yes
Yuen et al 1997[4]	T1-2, tongue	47%, (14/30)	50%, (7/14)	23%, (7/30)	9%, (3/33)	67%, (2/3)	3%, (1/33)	Yes
Present study	T1-2, tongue	31%, (11/35)	100%, (11/11)	0%, (0/35)	6%, (2/36)	100%, (0/2)	0%, (0/36)	No

Abbreviations: FOM, floor of mouth.

controversial issue, the highly successful salvage results achievable in Hong Kong, France, and The Netherlands are encouraging. We believe that the same result can also be achieved in many other head and neck cancer centers worldwide. Having said that, commitment to our recommended follow-up protocol should be emphasized to the patient.

There is a common misconception that patients with elective neck dissection have received adequate neck treatment and they do not need close follow-up. In fact, 17% patients of the neck dissection arm developed local and/or nodal recurrence, and these patients had a high chance of successful salvage only if they were followed up closely. Close follow-up is a prerequisite of early diagnosis and successful salvage. Close follow-up is therefore equally essential for patients who opt for elective neck dissection. Patients should be advised clearly of the importance of close follow-up monitoring with the same protocol of those on observation. The high surgical salvage rate of local and/or nodal recurrence had major contribution in achieving high survival rates of nearly 90% in patients with elective neck dissection.

Although elective SND is commonly performed worldwide because of the high nodal recurrence rate of observed neck, there are risks of shoulder morbidities including neck pain, keloid, reduced shoulder mobility, and power despite preservation of functional structures during selective neck dissection.[13] The patient should always be clearly informed of the risks of additional mortality and morbidity of prophylactic selective neck dissection. The disadvantage of prophylactic elective neck dissection is that about 70% of truly N0 neck patients will undergo unnecessary neck dissection, and these patients have to bear the additional cost of treatment, additional risk of operative mortality and morbidity. There is, however, 1 major advantage of prophylactic neck dissection, selective neck dissection has less surgical morbidity compared with salvage radical or modified radical neck dissection for nodal recurrence.

The advantage of observation is that only 30% to 40% patients who have truly subclinical nodal metastasis require treatment. Unnecessary neck dissection can be avoided for the truly node-negative neck. Observation also has 1 major disadvantage, most patients need radical or modified radical neck dissection for salvage of recurrence and have more shoulder morbidity.

Because there were no differences in node-related mortality and survival, observation and elective neck dissection should be offered to the patients, with a clear explanation of the advantages and disadvantages of each treatment. In our recent experiences, most patients prefer observation. Some patients might consider the 30% to 40% risk of subclinical nodal metastasis psychologically stressful and would prefer prophylactive neck dissection. Of those patients who are unable to be followed up closely after operation or in those centers with poor salvage track record, we still prefer the recommendation of elective selective neck dissection.

In conclusion, close follow-up is essential for detection of early salvageable local or nodal recurrences irrespective to the choice of observation or prophylactic neck dissection treatment of the N0 neck. For those patients who can be followed-up closely, both elective neck dissection and observation have similar treatment results. The advantages and disadvantages of both observation and elective neck dissection should be clearly explained to the patient, and the decision of treatment should be judged individually by the patient.

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