Hokkaido J. Dent. Sci., 36 : 128−133, 2016.

ORIGINAL

Management of the N0 Neck in Early Stage Oral Squamous Cell Carcinoma

Mitsunobu Ono, Kazuyo Kuribayashi, Yuichi Ashikaga,
Yoichi Ohiro and Kanchu Tei

ABSTRACT : Management of clinically node negative neck patients with oral squamous cell carcinoma (OSCC) remains controversial. Elective neck dissection (END) is used on an assumption of difficulty in diagnosing subclinical nodal metastases in the neck. This is also the case when early dissection allows better prognosis if nodal metastases actually exist. However, the disadvantage of prophylactic END is that truly N0 neck patients undergo unnecessary neck dissection and have to bear shoulder complaints and dysfunction. Our strategy has been a "wait and see" policy for the management of the neck among patients with T1-2 oral cancer without clinical nodal metastases unless the neck was being opened for reconstruction requirements. The purpose of this study is to assess the outcome of patients who underwent trans-oral tumor excision and "wait-and-see" policy for the N0 neck.

A total of 94 previously untreated patients with T1-2N0 classification were investigated. Elective neck dissection (END) was carried out on 10 patients (10.6%) at the time of treatment of the primary resection with reconstruction (END group), and 84 patients were observed without neck dissection (Observation group).

The 5-year disease specific survival rates were 90.0% for the END group and 95.9% for the observation group. The 5-year over all survival rates were 90.0% in the END group and 88.8% in the observation group. In the observation group of 84 patients, 16 patients (19.0%) had delayed metastasis in the neck subsequently. 15 patients underwent salvage neck dissection. The salvage rate was 86.6% (13/15 patients).

The treatment strategy "wait and see" policy for T1-2N0 OSCC resulted in a good outcome at our institution. Unnecessary neck dissection can be avoided for the truly N0 patients.

Key Words : Oral squamous cell carcinoma, Occult lymph node metastasis, Elective neck dissection, "Wait and see" policy

INTRODUCTION

Regional recurrence is the most common cause of failure after surgical treatment of early stage oral squamous cell carcinoma (SCC). The most important prognostic factor for tumor behavior and outcome in oral SCC is the presence of neck lymph node metastases at diagnosis. Management of the clinically node negative patients with oral SCC remains controversial. Incidence of occult regional lymph node metastasis from such tumors varies 6% to 46%[1]. In 1994, Weiss et al. has established a threshold of a 20% possibility of cervical metastasis as the indication for elective treatment of the neck in SCC of the head and neck[2]. This report supports elective treatment of the neck[3-5]. Elective neck dissection is used on an assumption of difficulty in diagnosing subclinical nodal metastases in the neck and when early dissection allows better prognosis if nodal metastases actually exist. The debate surrounding the value of elective neck dissection in the treatment of early stage oral cancer is an accurate estimate of the incidence of occult lymph node metastasis and whether treatment at the occult stage provide any survival advantage compared with treatment of the neck when lymph node metastasis become clinically apparent.

Our strategy for the management of the neck among patients with cancer of the oral cavity without clinical

Department of Oral and Maxillofacial Surgery, Division of Oral Pathobiological Science, Graduate School of Dental Medicine, Hokkaido University. (Chief : Prof. Kanchu Tei) Kita 13 Nishi 7, Kita-ku, Sapporo, 060-8586, Japan

nodal metastases has been "wait and see" policy unless the neck was being opened for other reasons such as reconstruction requirements. The purpose of this study is to assess the outcome of patients who underwent transoral tumor excision and "wait and see" policy for the N0 neck.

PATIENTS AND METHODS

Study design ; Retrospective cohort study.
Primary outcome : Overall survival (OS).
Secondary outcome : Probability of neck recurrence, disease specific survival (DSS).
Inclusion : From a database of the patients with histologically proven SCC of the oral cavity treated at Oral surgery of Hokkaido University Hospital between 2000 and 2013, a total of 130 patients with SCC of the oral cavity defined as T1 or T2, N0. The preoperative nodal staging was based on US, CT, MRI and FDG-PET. The medical records, operative details, and histopathological reports were retrospectively analyzed.
Exclusion : We excluded the patients who had recurrence of primary cancer or who had second primary cancer in oral cavity. Nine patients with synchronous second primary lesions and 20 patients whose primary cancer had recurred during the follow-up period were excluded. A minimum follow-up of 18 months or until death were identified and included in this study. Seven patients who were followed-up under 18 months were excluded. A total 94 patients were investigated for this study.

Follow-up time was calculated from the date of operation until the date of death or last contact. Survival curves were constructed using the Kaplan-Meier method.

Our policy for management of the clinically negative neck in early stage cancer has been a wait-and-see policy unless the neck was being opened for other reasons such as for the better access to the primary tumor, reconstruction requirements. Observation of N0 patient involves regular careful examination of the neck for evidence of regional disease. Therapeutic neck dissection was performed for patients with clinical evidence of metastases on follow-up. The mean follow-up was 50 months from the initial treatment. Patients were reviewed monthly in the first year, 2 monthly in the second year, 3 monthly in the third year. After this time, patients were reviewed every 6 months.

RESULTS

There were 52 male and 42 females, with a median age of 66.5-years (range, 19-89). Primary tumor location was as follows : 57 tongue, 7 floor of the mouth, 16 buccal mucosa, 11 lower alveolar, 3 upper alveolar (Table 1). The 94 primary tumors were staged T1 in 40 and T2 in 54 cases. Of the 94 patients, 75 had a primary resection alone, the 14 patients had undergone previous chemotherapy with S-1 for 2 weeks, and one patient had intra-arterial infusion chemotherapy with CDDP. Two patients were performed pre-operative radiotherapy, and 2 patients received pre-operative chemo- radiotherapy.

Elective neck dissection (END) was carried out in 10 patients (10.6%) at the time of treatment of the primary resection with reconstruction (END group), and 84 patients were observed without neck dissection (Observation group). END was performed following sequence: supra-omohyoid neck dissection in 6 cases, modified radical neck dissection in 4 cases. Out of the 10 patients who received END, pathological metastatic

Table 1 Baseline patients clinical characteristics

		Total	Observation group	END group
Sex	Male	52	46	6
	Female	42	38	4
Age (years)	Median	65.5	66	62
	Range	19–89	19–89	31–81
Site	Tongue	57	49	8
	Buccal mucosa	16	16	
	Lower alveolar	11	10	1
	Floor of the mouth	7	6	1
	Upper alveolar	3	3	
T stage	T1	40	40	
	T2	54	44	10

nodes were found in 4 patients. After END, one patient developed parapharyngeal node recurrence and he died of nodal recurrence.

In the observation group 84 patients, 16 patients (19.0%) had delayed metastasis in the neck subsequently. The neck metastases in the observation group were detected within 3-months in 8 cases, 6-months in 5 cases, 1-year in 2 cases and 2-years in 1 case, at the median of 4 months (Fig. 1). Of these 16 patients, 15 patients underwent salvage neck dissection, 3 patients received post-operative radiotherapy, and 4 patients received adjuvant chemotherapy with S-1. Most metastases were detected at level I and II (Table 2). Thirteen patients could have surgical salvage and two patients developed ipsilateral nodal recurrence, and they died of nodal recurrence. The salvage rate by delayed neck dissection or combination therapy was 86.6% (13/15 patients). Another patient received chemotherapy with S-1 and radiotherapy. This patient remained alive without tumor 5 years after nodal recurrence.

The 5-year disease specific survival rates were 90.0% for END group and 95.9% for observation group (Fig. 2). The 5-year over all survival rates were 90.0% in the END group and 88.8% in the observation group (Fig. 3). In the 16 patients who had neck recurrence in the observation group, the 5-year disease specific survival rates were 80.0%, and the over all survival rates were 72.0% (Fig. 4, 5).

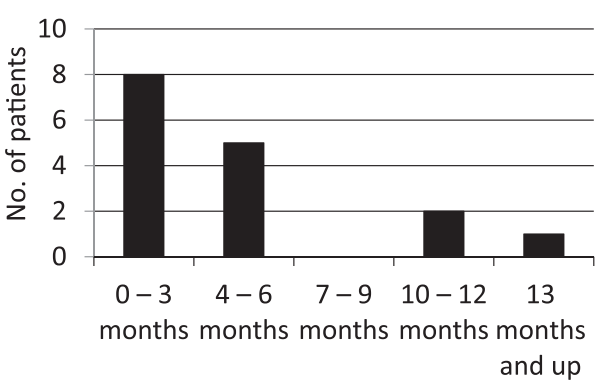

Fig. 1 Interval between excision of the primary tumor and neck metastasis in 16 patients

Table 2 Distribution by level of occult metastasis

Level	Total	Observation group	END group
I	8	6	2
II	5	5	
III	3	2	1
IV	2	1	1
V	1	1	

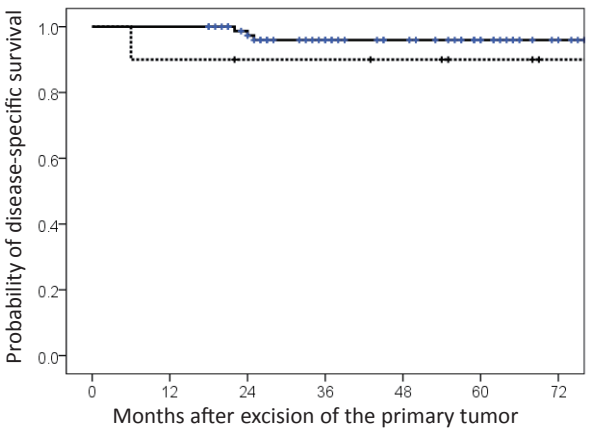

Fig. 2 Disease-specific survival curves of the END group (dotted line) versus the observation group (solid line)

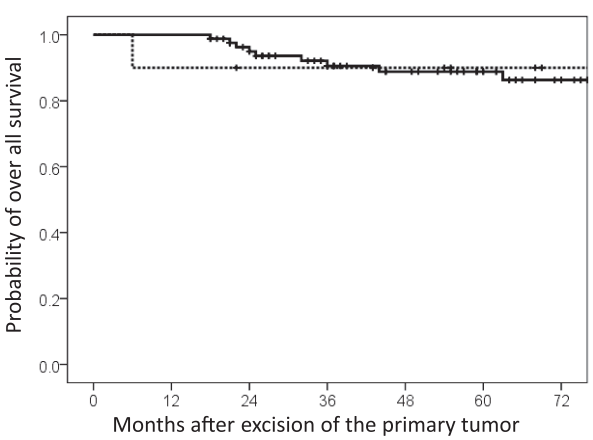

Fig. 3 Over all survival curves of the END group (dotted line) versus the observation group (solid line)

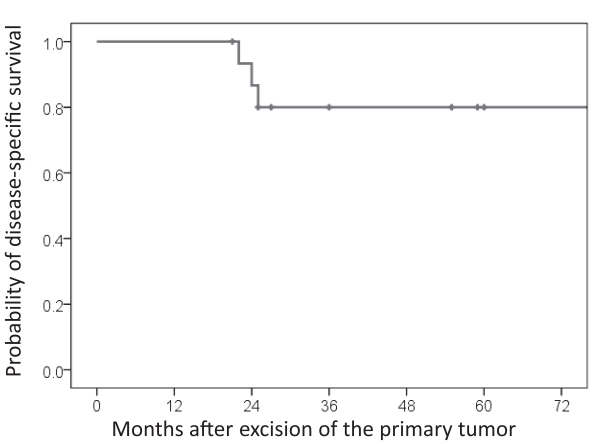

Fig. 4 Disease-specific survival curve of the 16 patients who had neck metastasis in the observation group

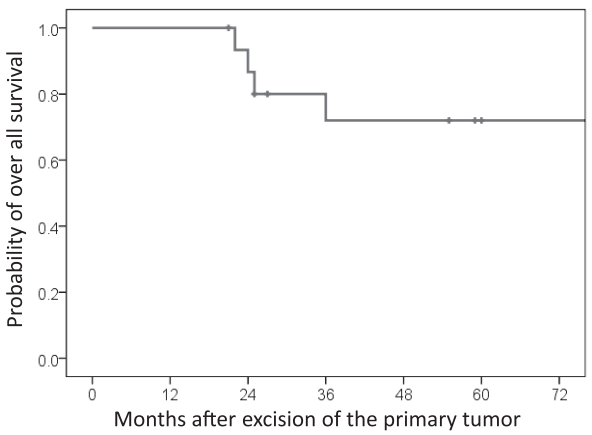

Fig. 5 Over all survival curves of the 16 patients who had neck metastasis in the observation group

DISCUSSION

The treatment of patients with early stage oral cancer is usually performed surgery via the per-oral route. Elective neck dissection at the time of the excision of the primary tumor is an additional procedure. Elective neck dissection for the patients with early stage oral cancer remains a controversial topic. There are two policies for the patients with early stage N0 oral cancer, elective neck treatment or wait-and-see policy as observing the neck without neck treatment. There have been many retrospective studies, most of which have shown an advantage of elective neck treatment. But these studies were not randomized studies. Four randomized prospective studies[6–9] have been performed. All of the studies showed lower disease-specific death rate in the END group compared to the observation group, but only in the study by Kligerman[7] the significance was reached. Most of these studies have small sample size. In a meta-analysis[10] of four prospective, randomized trials comparing elective and therapeutic neck dissection, there was significant reduction in the disease-specific rate of death in the END group compared to the observation group. The current guidelines recommend END when the probability of occult metastasis is greater than 20%. On the other hand, some studies disclosed meticulous observation was a safety option for the management of the N0 neck in patients with early oral cancers[11, 12]. Recently, D'Cruz reported that elective neck dissection at the time of resection of the primary tumor improve an overall survival benefit in 500 patients with early-stage, clinical N0 oral SCC[13].

It has been our neck treatment strategy that patients with early stage N0 oral cancer should not be treated with END at the time of primary resection, and perform therapeutic neck dissection after nodal relapse. Careful observation can reduce an unnecessary surgical invasion of the neck and make it possible to offer better QOL for patients who do not actually have nodal metastases[14]. There are risks of shoulder morbidities including neck pain, keloid, reduced shoulder mobility and power, despite of the preservation of functional structures during neck dissection[15]. Even if the spinal accessory nerve is preserved, shoulder complaints and dysfunction may occur. The disadvantage of END is that about 80% of truly N0 neck patients will undergo unnecessary neck dissection. These patients have to bear the additional cost of treatment, additional risk of operative mortality and morbidity[9]. Symptoms occur in 18% to 77% of patients after modified radical neck dissection, and in 29% to 39% of patients after selective neck dissection[16, 17]. The low rate of occult metastases and high salvage rate in case of neck recurrences warrant further use of "wait and see" policy. Estimating the incidence of occult metastases in the patients with N0 OSCC has been the focus of many clinical investigations. Analyses by Weiss[2] suggested that N0 head and neck cancer should be observed without END if probability of occult metastasis is less than 20%. On the other hand, Okura[11] suggested the threshold at 44% of occult metastasis as cut off in the decision to perform END or observe.

The neck metastasis rate in the observation group in this study was 19.0%. This result is very lower than the incidence of occult metastases quoted in the literature for patients treated with trans-oral tumor excision and a "wait and see" follow-up strategy for the neck[3–5, 9, 13, 18]. On the other hand, the probability of occult metastasis in the END group (40%) was significantly higher compared to that in the observation group. The reason why the difference of two results in our study occurred was considered that the difference of the tumor depth between in the END group and in the observation group. In this study, association between the tumor depth and occult metastases was not assessed. Several articles have reported that the tumor depth is conjectured as an important factor of lymph node metastasis[19–22]. It must be kept in mind that our study is retrospective study and it is not designed as randomized controlled trial. Retrospective data are not sufficient to conclusively state that the END group was higher incidence of occult metastases compared to that in the observation group.

This is important to consider the difference of the tumor stage between the END group and the observation group. It was expected that the depth of the tumor invasion in the patients with END was larger than the depth of the patients in observation group, because all the patients of the END group need reconstructive surgery.

Salvage rates after neck metastases in the patients who have not undergone END in this study were not poor. Thirteen of 15 patients (86.6%) who developed neck metastasis were alive at the end of the follow-up period, and the 5-year over all survival rates of the 16 patients who had neck recurrence were 72.0%. The salvage rate was higher compared to those reports[2, 12, 13, 23], because we have detected delayed neck metastases earlier. Our early detection of metastasis (median, 4 months) leads to produce the highly salvage rate in this study. On the other hand, END is recommended in the institute where delayed metastasis can not be early detected.

One of the problems of therapeutic neck dissection for delayed neck metastasis after primary tumor resection is lingual node metastasis. In the 1938, Rouvierre[24] first described the presence of lymph nodes in the floor of mouth and reffered to them as the median and lateral lingual nodes. In patients with early stage cancer, neck dissection and resection of primary tumors are usually performed separately due to the limited tumor extent. It should be noted, however, that some metastatic foci in lingual lymph nodes may remain with this methodology[18]. In this study, no patient developed lingual node metastasis in the observation group.

An important issue for the prognostic impact of a wait-and-see policy is the salvage rate in the case of delayed neck metastases. The reported salvage rate for observed patients after regional recurrence varied from 27% to 82% (average, 50%)[12]. In our study, salvage rate of the patient who undergone late therapeutic neck dissection is 86.6%. The higher curable probability of patients was attributed to early detection of the lymph node recurrence at the median of 4 months after primary resection. As if the nodal relapse were not detected earlier, those patients may have more advanced nodal stage and higher incidence of extracapsular spread.

In our study, both groups of patients had similar acceptable survival rate. These results suggest that wait-and-see policy is advisable for T1-2 oral cancer patients with no clinical nodal metastasis.

CONCLUSION

The treatment strategy "wait and see" policy for T1-2N0 OSCC was recommended. Unnecessary neck dissection can be avoided for the truly N0 patients.

REFERENCES

1) Capote A, Escorial V, Munoz-Guerra FM, Rodriguez-Campo JF, Gamallo C, Naval L : Elective neck dissection in early-stage oral squamous cell carcinoma–does it influence recurrence and survival? Head Neck 29 : 3–11, 2007.
2) Weiss MH, Harrison LB, Isaacs RS : Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 120 : 699-702, 1994.
3) Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG : Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 21 : 517-525, 1999.
4) Ho CM, Lam KH, Wei WI, Lau SK, Lam LK : Occult lymph node metastasis in small oral tongue cancers. Head Neck 14 : 359-363, 1992.
5) Lydiatt DD, Robbins KT, Byers RM, Wolf PF : Treatment of stage I and II oral tongue cancer. Head Neck 15 : 308-312, 1993.
6) Fakih AR, Rao RS, Borges AM, Patel AR : Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. Am J Surg 158 : 309-313, 1989.
7) Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, Olivatto LO : Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg 168 : 391-394, 1994.
8) Vandenbrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C : Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer 46 : 386-390, 1980.
9) Yuen AP, Ho CM, Chow TL, Tang LC, Cheung WY, Ng RW, Wei WI, Kong CK, Book KS, Yuen WC, Lam AK, Yuen WC, Trendell-Smith NJ, Chan YW, Wong BY, Li GK, Ho AC, Ho WK, Wong SY, Yao TJ : Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head Neck 31 : 765-772, 2009.
10) Fasunla AJ, Greene BH, Timmesfeld N, Wiegand

S, Werner JA, Sesterhenn AM : A metaanalysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol 47 : 320-324, 2011.

11) Okura M, Aikawa T, Sawai Y N, Iida S, Kogo M : Decision analysis and treatment threshold in a management for the N0 neck of the oral cavity carcinoma. Oral Oncol 45 : 908-911, 2009.

12) van den Brekel MW, Castelijns JA, Reitsma LC, Leemans CR, van der Waal I, Snow GB : Outcome of observing the N0 neck using ultrasonographic-guided cytology for follow-up. Arch Otolaryngol Head Neck Surg 125 : 153-156, 1999.

13) D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, Agarwal JP, Pantvaidya G, Chaukar D, Deshmukh A, Kane S, Arya S, Ghosh-Laskar S, Chaturvedi P, Pai P, Nair S, Nair D, Badwe R : Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 373 : 521-529, 2015.

14) Kaneko S, Yoshimura T, Ikemura K, Shirasuna K, Kusukawa J, Ohishi M, Shiba R, Sunakawa H, Tominaga K, Sugihara K, Shinohara M, Katsuki T, Yanagisawa S, Kurokawa H, Mimura T, Ikeda H, Yamabe S, Ozeki S : Primary neck management among patients with cancer of the oral cavity without clinical nodal metastases: A decision and sensitivity analysis. Head Neck 24 : 582-590, 2002.

15) El Ghani F, Van Den Brekel MW, De Goede CJ, Kuik J, Leemans CR, Smeele LE : Shoulder function and patient well-being after various types of neck dissections. Clin Otolaryngol Allied Sci 27 : 403-408, 2002.

16) Leipzig B, Suen JY, English JL, Barnes J, Hooper M : Functional evaluation of the spinal accessory nerve after neck dissection. Am J Surg 146 : 526-530, 1983.

17) Dijkstra PU, van Wilgen PC, Buijs RP, Brendeke W, de Goede CJ, Kerst A, Koolstra M, Marinus J, Schoppink EM, Stuiver MM, van de Velde CF, Roodenburg JL : Incidence of shoulder pain after neck dissection: a clinical explorative study for risk factors. Head Neck 23 : 947-953, 2001.

18) Huang SF, Kang CJ, Lin CY, Fan KH, Yen TC, Wang HM, Chen IH, Liao CT, Cheng AJ, Chang JT : Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. Cancer 112 : 1066-1075, 2008.

19) Fukano H, Matsuura H, Hasegawa Y, Nakamura S : Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. Head Neck 19 : 205-210, 1997.

20) Yuen AP, Lam KY, Wei WI, Lam KY, Ho CM, Chow TL, Yuen WF : A comparison of the prognostic significance of tumor diameter, length, width, thickness, area, volume, and clinicopathological features of oral tongue carcinoma. Am J Surg 180 : 139–143, 2000.

21) Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, Yuen WF, Wei WI : Prognostic factors of clinically stage I and II oral tongue carcinoma-A comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez-Gimeno score, and pathologic features. Head Neck 24 : 513-520, 2002.

22) Asakage T, Yokose T, Mukai K, Tsugane S, Tsubono Y, Asai M, Ebihara S : Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. Cancer 82 : 1443-1448, 1998.

23) D'Cruz AK, Siddachari RC, Walvekar RR, Pantvaidya GH, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P : Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue : need for a randomized controlled trial. Head Neck 31 : 618-624, 2009.

24) Rouvière H : Anatomy of the Human Lymphatic System. English edition, Edward Brothers, Inc., Ann Arbor, Michigan, 5-51, 1938