Is an Elective Neck Dissection Necessary for All Cases of N0 Oral Squamous Cell Carcinoma?

— Elective Neck Dissection may be Performed for Tongue Cancer with Tumor Thickness More than 4 mm —

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We investigated whether neck dissection should be performed to prevent T1-2N0M0 tongue cancer by using the Weiss and colleague's decision tree method. The results showed that preventive neck dissection should not be recommended for T1-2N0M0 tongue cancer. However, preventive neck dissection is a suitable approach when treating tongue cancer tumors with a thickness of ≥ 4 mm.

Key words: N0 oral squamous cell carcinoma, elective neck dissection, tumor thickness

INTRODUCTION

Beneficial radical treatment of oral squamous cell carcinoma (OSCC) includes surgical therapy, radiation therapy, and chemotherapy. However, the type of surgical procedure, irradiation method, or the route of drug administration that should be used for OSCC is at the discretion of the study site, and differences in treatment regimens still exist among the study sites.

It may be true that a small difference in treatment regimens for patients with cervical lymph node metastasis exists among the study sites. Concerning the radical treatment of OSCC with lymph node metastasis, treatment regimens primarily with neck dissection will probably be performed in any study site. Cervical metastasis is a prognostic factor of OSCC [1–3], while extracapsular invasion or multiple lymph node metastasis is the most significant independent prognostic factor [3–5]. Therefore, adjuvant treatment is often performed after neck dissection in these patients [6, 7]. Meanwhile, for OSCCs not associated with cervical metastasis, it is controversial whether to perform neck dissection in addition to resection of the primary lesion. That is, the idea of performing preventive elective neck dissection (END) in the absence of cervical metastasis may be an overtreatment; and one possibility is that observation (wait-and-see) should be performed [8, 9].

In 1994, Weiss *et al*. analyzed data obtained from medical literature using the decision tree and reported about the treatment course for N0 OSCC cases [8]. They recommended performing END when the incidence of occult cervical metastasis is > 20%. When their article was published, the incidence of occult cervical metastasis was high at 25–40% and hence, we concluded that END should be performed. However, the detection rate of occult cervical metastasis has increased due to recent advances in diagnostic imaging, which was earlier considered to be lower. Therefore, we considered it necessary to reexamine the clinical benefit of END.

In the case of OSCC, the most advanced field of analysis on the relationship between the primary site and cervical metastasis is tongue cancer. Several studies have reported that cervical metastasis in tongue cancer correlated with tumor thickness [10, 11]. In addition, the National Comprehensive Cancer Network (NCCN) Guideline Version 2, 2014, states that "For tumors with a depth greater than 4 mm, elective dissection should be strongly considered if RT is not planned," and no clear evidence has been demonstrated [12].

Therefore, we conducted this study to re-investigate the clinical benefit of END in OSCC using T1–2 tongue cancer specimens by the use of the decision tree method as reported by Okura *et al*. in 2009 [9]. In particular, the tumor thickness of ≥ 4 mm by the use of the decision tree method has not been reported so far to the best of our knowledge and is hence studied in this investigation.

PATIENTS AND METHODS

This retrospective review of tongue cancer patients was approved by the institutional review board of Tokai University School of Medicine (Kanagawa, Japan).

This study was conducted in patients with stage I/II tongue squamous cell carcinoma without a previous malignancy, not undergoing neoadjuvant therapy or preoperative radiotherapy, and who received surgery at the Department of Oral and Maxillofacial Surgery, Tokai University Hospital, between 1996 and 2006.

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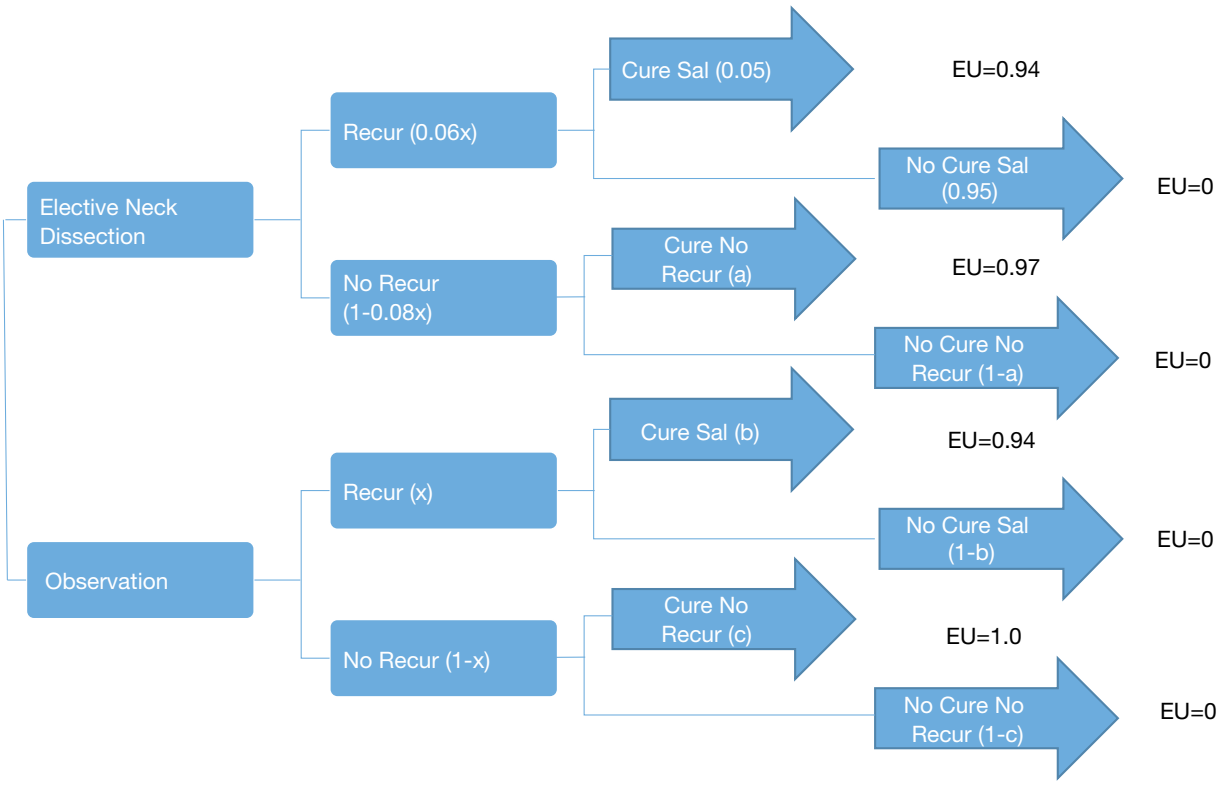

Fig. 1 Decision tree depicting observation and elective neck dissection strategies for N0 neck cancer. See methods for an explanation of the listed items and the analysis. Parentheses indicate the probability of each event. x: probability of occult metastasis; EU: expected utility; a–c: probabilities of being cured.

Patients with T3/T4 were excluded because most of them underwent concomitant reconstructive surgery using a free flap, and in such cases, neck dissection was performed for the purpose of convenience. Several studies have reported that patients with stage I/II tongue squamous cell carcinoma with tumor thickness > 4 mm are at an increased risk for subsequent cervical metastasis [10, 11]. Therefore, a detailed analysis was performed by categorizing patients based on tumor thickness more than and less than 4 mm. The tumor thickness of the tongue was measured transorally, primarily using ultrasonography with 7.5- to 10-MHz linear array transducers.

Method to analyze the clinical benefit of END according to Okura *et al.* As mentioned earlier, Weiss *et al.* had reported about a treatment strategy for cervical lymph nodes in patients with N0 OSCC of the head and neck, based upon their analysis of data using the decision tree (Fig. 1) [8]. This strategy is as follows. The probability of occult metastasis is a variable x, and END is recommended if this probability is > 20% and the wait-and-see approach is recommended if it is < 20%. However, there are several issues to be discussed regarding the determination of the treatment threshold (Rx) when the probability of occult metastasis is 20%, as demonstrated by Weiss *et al.* For example, such issues include the following the success rate of salvage treatment for neck recurrence is assumed to be 50% and the survival rate of N0 patients is assumed to be 60%. Furthermore, the success rate of salvage treatment, survival rate, and probability of occult metastasis vary among the study sites, and when this aspect is taken into account, the Rx based on the study site should be different. In this context, Okura *et al.*, by taking this aspect into account, has suggested a calculation formula to determine the Rx based on the study site [9].

$$Rx = (c-0.97a)/(0.00376-0.0776a-0.94b+c)$$

a = the curable probability (5-year overall survival rate) of patients receiving END with no neck recurrence.

b = the curable probability of observed patients with late neck metastasis.

c = the curable probability of observed patients with no neck recurrence.

Therefore, the curable probabilities a, b, and c were determined using eligible patients in this study based on the Kaplan-Meier method. The statistical analyses were performed using SPSS version 23 for Windows (Chicago, IL, USA). Based on the calculated a, b, and c, the Rx was determined and the clinical benefit of END was investigated.

Furthermore, univariate analysis was performed using the log rank test, and multivariate analysis was performed using the Cox proportional hazards model.

RESULTS

Patients

There were 162 patients (97 males, 65 females) with stage I/II tongue SCC without a previous malignancy and not undergoing neoadjuvant therapy or preoperative radiotherapy. Based on the International Union Against Cancer TNM classification, there were 94 patients with stage T1 tumor and 68 patients with stage T2 tumor. Among these patients, END was performed in 26 patients and observation (wait-and-see) in 136 patients. Among the 26 patients undergoing END, pathological lymph node metastases were observed

Table 1 Characteristics of patients with tongue squamous cell carcinoma (n = 162)

Characteristics			END (n = 26)		Observation (N = 136)		
		total	No of patients	(%)	No of patients	(%)	P-value
Gender	Male	97	17	65.4	80	58.8	0.532
	Female	65	9	34.6	56	41.2	
Age		61.1 +/- 15.2	60.4 +/- 14.6		61.2 +/- 15.4		0.789
Performance status	0	153	23	88.5	130	95.6	0.219
	1	8	3	11.5	5	3.7	
	2	1	0	0	1	0.7	
T classification	1	94	1	3.8	93	68.4	< 0.001
	2	68	25	96.2	43	31.6	
Tumor thickness		4.3 +/- 3.6	8.1 +/- 4.6		3.6 +/- 2.9		< 0.001
Histology	well differentiated	133	21	80.8	112	82.4	0.712
	Moderatery differentiated	26	3	11.5	22	16.2	
	poorly differentiated	4	2	7.7	2	1.4	

END: Elective neck dissection

Table 2 Characteristics of patients with tongue squamous cell carcinoma (≥ 4 mm) (n = 75)

Characteristics			END (n = 21)		Observation (N = 54)		
		total	No of patients	(%)	No of patients	(%)	P-value
Gender	Male	49	14	66.7	35	64.8	0.88
	Female	26	7	33.3	19	35.2	
Age		60.3 +/- 14.4	57.1 +/- 13.0		61.6 +/- 14.8		0.235
Performance status	0	70	18	85.7	52	96.3	0.099
	1	5	3	14.3	2	3.7	
	2						
T classification	1	24	1	4.8	33	61.1	< 0.001
	2	41	20	95.2	21	38.9	
Tumor thickness		7.27 +/- 3.4	9.57 +/- 3.8		6.37 +/- 2.8		< 0.001
Histology	well differentiated	66	18	85.7	48	88.9	0.93
	Moderatery differentiated	6	2	9.5	4	7.4	
	poorly differentiated	3	1	4.8	2	3.7	

END: Elective neck dissection

in 5 patients. Among the 136 observed patients, neck recurrence was observed in 30 patients. Therefore, occult metastasis was observed in 35 of 162 patients (probability of occult metastasis: 21.6%) (Table 1). Out of 30 patients with neck recurrence in the OBS group, neck dissection was performed in 18 patients, neck dissection and radiotherapy in 10 patients, and best supportive care was provided to 2 patients. Best supportive care was provided to 3 patients with neck recurrence in the END group.

Among the eligible patients, tumor thickness ≥ 4 mm was observed in 75 patients (49 males, 26 females). Among these patients, END was performed in 21 patients, and pathological lymph node metastases were observed in 5 patients. Observation was performed in 54 patients, of whom 16 patients had neck recurrence. Therefore, occult metastasis was observed in 21 of 75 patients with stage I/II tongue SCC with thickness ≥ 4 mm (probability of occult metastasis 28.0%) (Table 2). Out of 16 patients with neck recurrence in the OBS group, neck dissection was performed in 7 patients, neck dissection and radiotherapy in 7 patients, and best supportive care was provided to 2 patients. Best supportive care was provided to 2 patients with neck recurrence in the END group.

Furthermore, multivariate analysis using the Cox proportional hazards model showed that age and T factor were significant prognostic factors in all patients; however, no significant prognostic factor was observed in patients with a tumor thickness of ≥ 4 mm (Table 3, 4).

Calculation of treatment threshold

The Kaplan–Meier analysis method resulted in 78.3%, 46.7%, and 87.7% threshold probabilities a, b, and c, respectively, for stage I/II tongue SCC (Fig. 2). When these were plugged into the equation of Okura *et al.*, the Rx of stage I/II tongue SCC was 30.8%. The probability of occult metastasis was 21.6%, which was exceeded by Rx, and therefore, END was not recommended for the overall stage I/II tongue SCCs.

Meanwhile, when the target is limited to tumor thickness > 4 mm, the probabilities a, b, and c were 84.2%, 50.0%, and 86.8%, respectively, and the Rx was 15.2% (Fig. 3). In this case, the probability of occult metastasis was 28.0%, and the Rx fell below this.

Table 3 Univariate and multivariate analysis for survival with tongue squamous cell carcinoma (n = 162)

		Univariate		Multivariate	
		Overall survival	P-value	HR (95%CI)	P-value
Gender	Male	78.5	0.736	-	-
	Female	76.3			
Age	60 ≦	84.5	0.044	10.5 (1.019-1.082)	0.001
	< 60	77.2			
Performance status	0	77.8	0.293	-	-
	1	750			
	2	0			
T classification	1	83	0.045	2.223 (1.024-4.824)	0.043
	2	69.1			
Tumor depth	4 ≦	79.3	0.451	-	-
	< 4	74.7			
Histology	well differentiated	76.7	0.659	-	-
	Moderatery differentiated	76.9			
	poorly differentiated	100			
Treatment	END	78.7	0.233	-	-
	observasion	69.2			

END: Elective neck dissection

Table 4 Univariate analysis for survival with tongue squamous cell carcinoma (≥ 4 mm) (n = 75)

		Univariate	
		Overall survival	P-value
Gender	Male	75.5	0.802
	Female	73.1	
Age	60 ≦	80.6	0.345
	< 60	70.5	
Performance status	0	75.7	0.559
	1	60	
T classification	1	82.4	0.141
	2	68.3	
Histology	well differentiated	72.7	0.516
	Moderatery differentiated	83.3	
	poorly differentiated	100	
Treatment	END	76.2	0.836
	observasion	74.1	

Therefore, END was recommended.

DISCUSSION

Weiss *et al.* conducted an analysis on the treatment guidelines for N0 OSCC using a decision tree and as a result recommended END if the probability of occult cervical lymph node metastasis is > 20% [8]. Before 1994, several studies had reported that the probability of occult cervical lymph node metastasis was 25–49% and that there was a tendency to recommend END [13–18]. In contrast, in 2009, Okura *et al.* conducted the same analysis as that of Weiss *et al.* and concluded that if the probability of occult cervical lymph node metastasis is > 44.4%, END should be recommended [9]. It has also been reported that if this probability was 20%, END is not recommended. An increasing number of studies in recent years reported that the probability of occult cervical lymph node metastasis is < 20% [9–21]. Therefore, there is a tendency that END is not recommended for OSCC at present.

In this study, we conducted the same investigation on the treatment course for T1–2 N0 tongue cancer in our facility. The results showed that when the probability of occult lymph node metastasis was > 30.8%, END was thus recommended, whereas when the probability was 21.6%, END was not recommended.

Okura *et al.* pointed out that the probability of occult cervical lymph node metastasis is decreasing due to the improvement of diagnostic imaging techniques such as CT/MRI/FDG-PET and the salvage rate of secondary lymph node metastasis is improving due to the improvement of treatment techniques, due to which END was no longer recommended for N0 OSCC [9]. At present, the wait-and-see approach is the common treatment course for the N0 neck in OSCC.

Meanwhile, tumor thickness of ≥ 4 to 5 mm has conventionally been associated with increased risk for occult cervical lymph node metastasis in tongue cancer, and Fukano *et al.* and Shintani *et al.* had reported that lymph node metastasis significantly increases with a cut-off point for tumor thickness of > 4 mm and 5 mm, respectively [10, 11, 22]. Furthermore, according

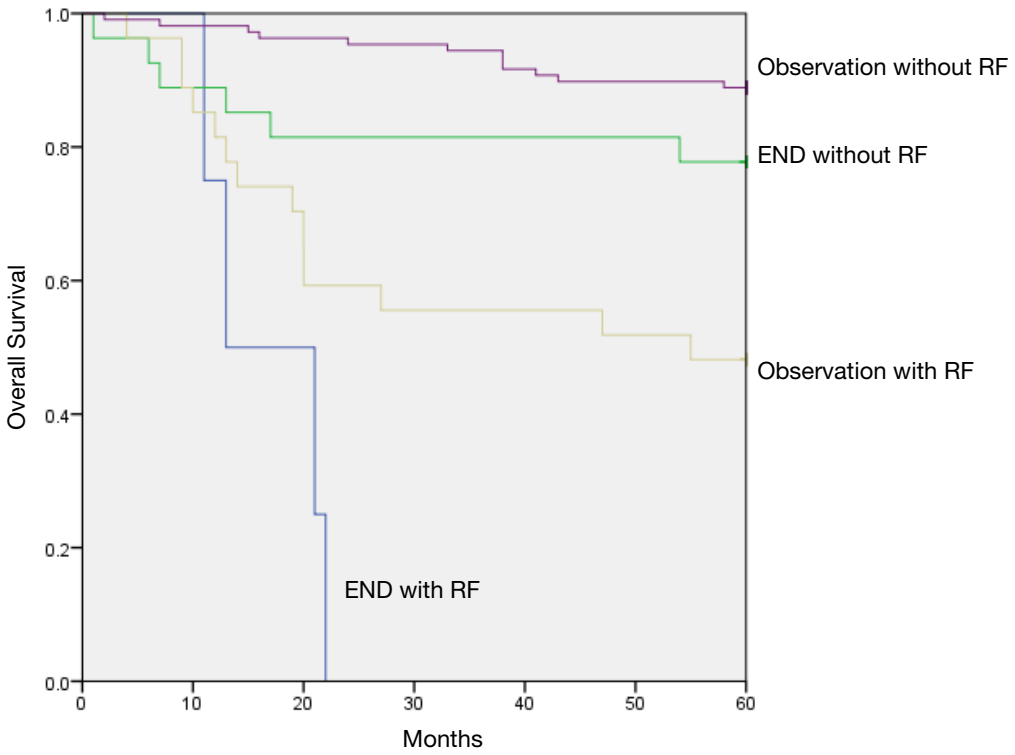

Fig. 2 Tongue squamous cell carcinoma.
Overall survival according to neck treatment with or without regional failure (RF).
END: Elective neck dissection

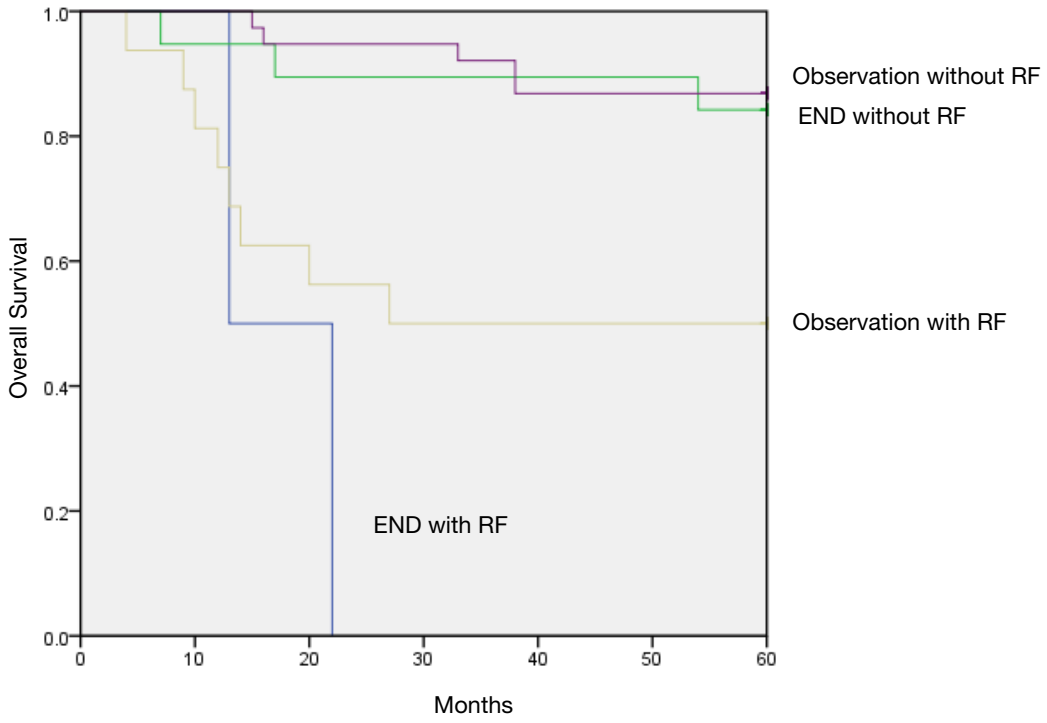

Fig. 3 Tongue squamous cell carcinoma (≥ 4 mm).
Overall survival according to neck treatment with or without regional failure (RF).
END: Elective neck dissection

to the 2014 NCCN guidelines, tumor thickness is considered as a risk factor and END is necessary if the tumor thickness is larger [12]. This indicates that it is not sufficient to represent the stage of tongue cancer progression based on only T classification. It was therefore necessary to reexamine whether the determination of treatment course with tumor thickness was appropriate.

However, it is often necessary to perform reconstructive surgery in patients with T3 or higher even if the stage of tongue cancer is N0. As for reconstructive surgery, END is often performed conveniently even if the stage of tongue cancer is N0. Therefore, it is difficult to analyze the clinical benefit of END in patients with tumors of grade T3 or higher, and it is necessary to limit to patients with T1–2. Furthermore, in reality, it is often unclear whether END should be performed for T1–2 tongue cancer or observation (wait-and-see) should be performed. Therefore, we reexamined whether END should be performed in patients based on tumor thickness in T1–2 tongue cancer.

Consequently and remarkably, END was recommended for T1–2 N0 tongue cancer with tumor thickness of ≥ 4 mm.

This was considered because the incidence of occult cervical lymph node metastasis was higher with T1–2 N0 tongue cancer with tumor thickness of ≥ 4 mm than with that of < 4 mm and the survival rate of patients with no recurrence after END was favorable. In all the patients, the multivariate analysis revealed that tumor thickness was not a significant prognostic factor, while T factor and age were significant prognostic factors; however, no significant prognostic factor was identified in patients with a tumor thickness of ≥ 4 mm. This may be because almost no END was performed in patients with a tumor thickness of < 4 mm in clinical practice, and the bias was reduced by limiting the target to a tumor thickness of ≥ 4 mm.

In addition, according to the analysis method of Weiss *et al.*, the patients quality of life factors may also affect the outcome, and ultimately END was recommended for T1–2N0 tongue cancer with a tumor thickness of ≥ 4 mm [8]. However, in the strict sense, no randomized controlled study has been conducted, and therefore, it is necessary to perform a prospective review to determine whether END can improve the prognosis.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to be reported.

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