original reports

Neck Dissections Based on Sentinel Lymph Node Navigation Versus Elective Neck Dissections in Early Oral Cancers: A Randomized, Multicenter, and Noninferiority Trial

Yasuhisa Hasegawa, MD, PhD[1]; Kiyoaki Tsukahara, MD, PhD[2]; Seiichi Yoshimoto, MD, PhD[3]; Kouki Miura, MD, PhD[4]; Junkichi Yokoyama, MD, PhD[5]; Shigeru Hirano, MD, PhD[6]; Hirokazu Uemura, MD, PhD[7]; Masashi Sugasawa, MD, PhD[8]; Tomokazu Yoshizaki, MD, PhD[9]; Akihiro Homma, MD, PhD[10]; Kazuaki Chikamatsu, MD, PhD[11]; Mikio Suzuki, MD, PhD[12]; Akihiro Shiotani, MD, PhD[13]; Takashi Matsuzuka, MD, PhD[1,14]; Naoyuki Kohno, MD, PhD[15]; Masakazu Miyazaki, MD, PhD[16]; Isao Oze, MD, PhD[17]; Keitaro Matsuo, MD, PhD[17]; Shigeru Kosuda, MD, PhD[18]; and Yasushi Yatabe, MD, PhD[3]; for the HNCMM Research Group

abstract

PURPOSE This study aimed to compare patients with early oral cavity squamous cell carcinoma (OCSCC) (tumor category [T] 1-2, node-negative, and no distant metastasis) treated with traditional elective neck dissection (ND) with those managed by sentinel lymph node biopsy (SLNB) using survival and neck function and complications as end points.

METHODS Sixteen institutions in Japan participated in the study (trial registration number: UMIN000006510). Patients of age ≥ 18 years with histologically confirmed, previously untreated OCSCC (Union for International Cancer Control TNM Classification of Malignant Tumors 7th edition T1-2, node-negative no distant metastasis), with ≥ 4 mm (T1) depth of invasion, were randomly assigned to undergo standard selective ND (ND group; n = 137) or SLNB-navigated ND (SLNB group; n = 134). The primary end point was the 3-year overall survival rate, with a 12% noninferiority margin; secondary end points included postoperative neck functionality and complications and 3-year disease-free survival. Sentinel lymph nodes underwent intraoperative multislice frozen section analyses for the diagnosis. Patients with positive sentinel lymph nodes underwent either one-stage or second-look ND.

RESULTS Pathologic metastasis-positive nodes were observed in 24.8% (34 of 137) and 33.6% (46 of 134) of patients in the ND and SLNB groups, respectively ($P = .190$). The 3-year overall survival in the SLNB group (87.9%; lower limit of one-sided 95% CI, 82.4) was noninferior to that in the ND group (86.6%; lower limit 95% CI, 80.9; P for noninferiority $< .001$). The 3-year disease-free survival rate was 78.7% (lower limit 95% CI, 72.1) and 81.3% (75.0) in the SLNB and ND groups, respectively (P for noninferiority $< .001$). The scores of neck functionality in the SLNB group were significantly better than those in the ND group.

CONCLUSION SLNB-navigated ND may replace elective ND without a survival disadvantage and reduce postoperative neck disability in patients with early-stage OCSCC.

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Sharing Statement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 23, 2021 and published at ascopubs.org/journal/jco on April 20, 2021: DOI https://doi.org/10.1200/JCO.20.03637

INTRODUCTION

Cancers of the oral cavity and lip account for 2% of all cancers and are common in Southern Asia.[1] Surgery is generally preferred for early-stage oral cavity squamous cell carcinoma (OCSCC). However, an appropriate management strategy for a clinically node-negative (N0) neck remains controversial; observation, elective neck dissection (ND), and sentinel lymph node (SLN) biopsy (SLNB) have been reported as potential strategies.[2] Sufficient evidence is lacking for the recommendation of a single strategy. Recently, a large-scale randomized controlled trial[3] has reported the superiority of elective ND to observation for early OCSCC.

SLNB has been established as the method for staging patients with clinically N0 breast cancer and cutaneous melanoma and provides useful information of the nodal status.[4] Appropriate ND might be achieved if SLNB is used for treating OCSCC. Since reports of SLNB for OCSCC are limited and detection methods vary, a prospective multi-institutional study with numerous cases constituting unified methodologies is essential for verifying the validity of SLNB. We conducted a randomized, multicenter, noninferiority, phase III trial, comparing SLNB-navigated ND with elective ND in early-stage OCSCC, and studied the postoperative survival rate, safety, and neck function.

CONTEXT

Key Objective

What is the best surgical technique for managing node-negative neck in oral cavity squamous cell carcinoma (OCSCC)? Potential strategies for managing patients with early OCSCC include observation, elective neck dissection, and sentinel lymph node (SLN) biopsy. A large-scale randomized controlled trial reported the superiority of elective neck dissection over observation. However, avoiding unnecessary neck dissection prevents risks and complications, thus reducing surgical intervention and prolonged hospitalization. There is insufficient evidence supporting a single strategy.

Knowledge Generated

In this study, we compared SLN-navigated neck dissection versus elective neck dissection in early OCSCC and showed that SLN-navigated neck dissection was noninferior to elective neck dissection in terms of the survival rate, and superior in terms of neck functionality.

Relevance

Performing SLN biopsy appropriately requires the expertise of a skilled head and neck surgeon, along with the collaborative efforts of a radiologist and a pathologist for pre-, post-, and intraoperative diagnoses.

METHODS

Trial Oversight

This multicenter, randomized, controlled phase III trial involving 16 Japanese centers, evaluating SLNB-navigated ND's noninferiority (SLNB group) compared with elective ND (ND group) in tumor category (T) T1-T2N0 OCSCC, was designed by the Head and Neck Cancer Micrometastasis Research Group and funded by the Japanese Ministry of Health, Labour, and Welfare.

The retrospective and phase II studies[5,6] have been performed before the phase III study.

The study was initiated after ethics committee's approval from each institution (September 2011) and performed under the Safety and Efficacy Evaluation Committee's oversight. Written informed consent was obtained from all participants.

This trial was registered in the UMIN Clinical Trials Registry (UMIN000006510) in November 2011. A stopping rule was built into the Protocol (online only) after an interim analysis that was performed when half of the patients were followed up in 6 months. This was conducted by the Efficiency and Safety Evaluating Committee who were satisfied by the results of the interim analysis.

Study Patients

Patients were recruited between November 2011 and January 2016.

The inclusion criteria were OCSCC (Union for International Cancer Control TNM Classification of Malignant Tumors, 7th edition T1-T2, N0 no distant metastasis) with no cervical lymph node (LN) metastasis on contrast enhanced computed tomography (CT) of the head and neck, no prior treatment, written consent being provided, and age $\geq$ 18 years.

Exclusion criteria included T1 tumors with a depth of invasion (DOI) $<$ 4 mm, recurrence after definitive treatment such as surgical or radiation therapy, a history of radiation therapy to the neck, planned or current pregnancy or lactation, and other disqualifying reasons, as judged by the attending physician.

Patients with OCSCC were randomly assigned to either the SLNB group or the ND group; random assignment was balanced by minimization, according to T classification (T1 or T2) and primary subsite (tongue or others). This was performed by the statistical researcher. Registration and allocation, and subsequent data input were performed through the web enrollment system located in the data center.

Outcomes

The primary end point was the 3-year overall survival (OS) rate, and secondary end points were postoperative neck function and adverse events and 3-year disease-free survival (DFS) rate. Full analysis set (FAS) was used for case analysis. The flow diagram for study enrollment is shown in Figure 1.

Intervention

N0 diagnostic criteria. For diagnostic imaging of LN metastasis, CT was used as initial examination, which was supplemented by US examination when necessary. Diagnostic criteria were established for both examinations, and magnetic resonance and positron emission tomography and/or CT were added at the discretion of each institution. Detailed criteria are shown in Appendix Table A1 (online only).

SLN identification and biopsy. The basic procedures have been reported in detail in our previous phase II study[5]; briefly, ^{99m}Tc phytate was used as radiopharmaceutical. The day before the surgery, 74 MBq of ^{99m}Tc phytate (2 mCi, 1 mL total) was administered equally into four sites in the peritumoral mucosa using a 27 gauge needle. On the

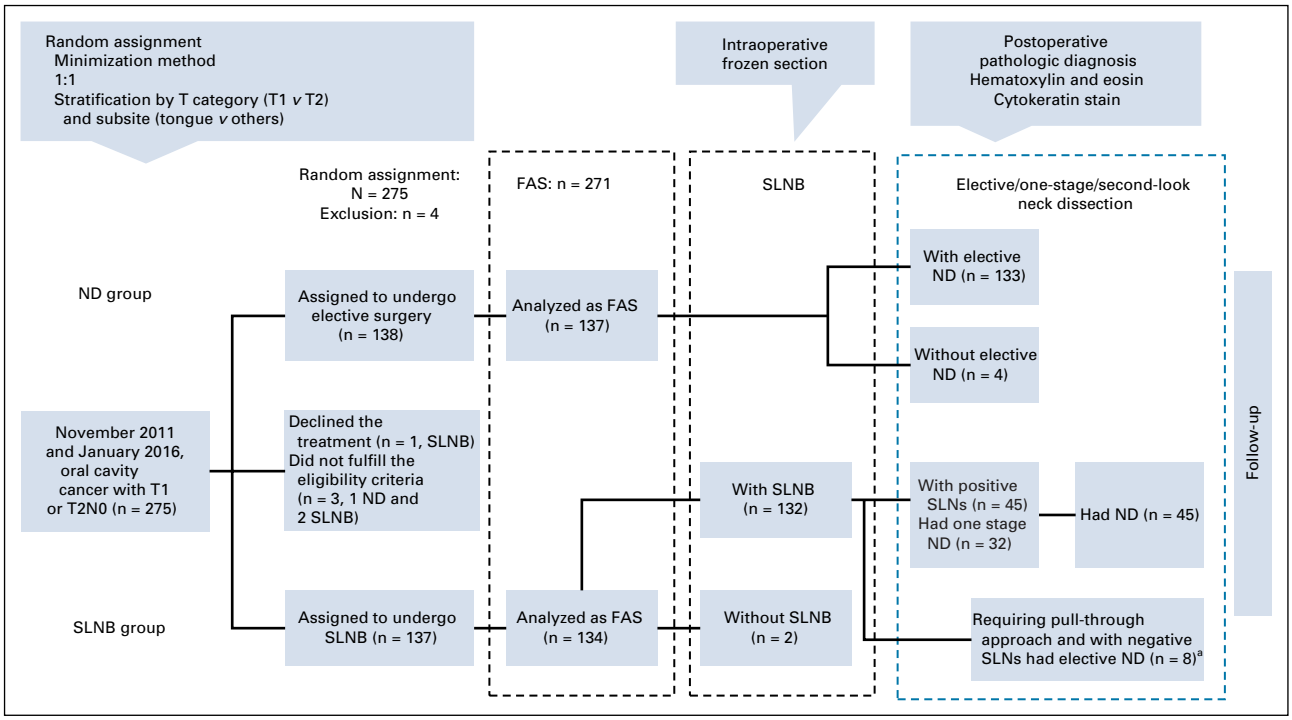

FIG 1. Flow diagram of the procedures for study enrollment. [a]One case with SLN-negative and non-SLN–positive is included. FAS, full analysis set; N0, node-negative; ND, neck dissection; SLN, sentinel lymph node; SLNB, SLN biopsy; T category, tumor category.

surgery day, the SLN was sought; a gamma probe was used for the search using lymphoscintigraphy with or without single-photon emission CT.

Histopathologic diagnosis of SLN and dissected tissue. The analysis of the SLN was a two-stage process. During surgery, 2-mm-thick blocks of rapid frozen specimen (FS) were obtained. If negative, these blocks were paraffin embedded for a more detailed evaluation using two 4-μm-thin sections from each cutout surface of the specimen blocks subjected to hematoxylin and eosin (HE) staining and cytokeratin immunostaining; non-SLN in both arms of the study was evaluated by traditional HE staining of a slice through the center of the node. Immunostaining was performed using an anti-cytokeratin primary antibody (AE1/3; Signet Laboratories, Dedham, MA) and streptavidin-biotin labeling. The Union for International Cancer Control TNM Classification of Malignant Tumors (6th edition) and the report of Hermanek et al[7] were used for classifying maximum metastasis size.

At the time of planning this study, the relationship between isolated tumor cells (ITCs) and prognosis of head and neck cancer had remained unexamined. In breast cancer, a report[8] examining the correlation among micrometastasis (mi), regional LNs (pN1mi), ITCs, and prognosis has concluded that postoperative adjuvant therapy improves survival in the presence of pN1mi/ITC+, which affects the survival rate. Therefore, in this study, ITCs were treated as metastasis-positive, in consideration of patient safety.

ND. The ND group underwent supraomohyoid ND (SOHND).[9] In the SLNB group, SLN detection and tumor resection were performed; patients with metastasis-positive nodes, proven by frozen section diagnosis, underwent therapeutic ND as a one-stage procedure. If postoperative diagnosis using HE and cytokeratin staining revealed metastasis-positive nodes, therapeutic ND was performed as a second-look surgery within 6 weeks of the first surgery.

In the SLNB group, if no metastasis was detected on intraoperative frozen pathologic diagnosis, only SLNB was performed; however, in cases requiring pull-through resection of the primary site, SOHND was performed. If metastases were intraoperatively observed in the SLN, therapeutic ND of the affected neck was performed at levels I-IV or I-V, as appropriate. Additionally, the patients with negative SLN on the contralateral side of the neck received a limited node dissection of the SLN region (ie, SLN basin dissection).[5] To prevent the shine-through effect, the primary excision preceded SLNB, when possible.

Postoperative adjuvant treatment. As an adjuvant treatment, the Protocol stipulated that patients with extracapsular spread of LN metastases should receive radiotherapy within 6 weeks of surgery. Concomitant chemotherapy was left at the discretion of each institution.

Additionally, for patients with positive tumor margins, reoperation or radiotherapy with or without chemotherapy was performed according to judgment of each institution.

Functional analysis. The arm abduction test (AAT) and the neck disability quality-of-life (QOL) questionnaire (Appendix Table A2, online only) were performed at 1, 3, 6, and 12 months after ND.

Follow-Up

Follow-up of all enrolled patients was performed at 6, 12, 18, 24, 30, and 36 months postoperatively. Local recurrence, cervical LN recurrence, distant metastases, and the basis and date of diagnosis for each were recorded.

Statistical Analysis

The 3-year OS rate of both the SLNB and ND groups was reportedly 85% (hazard rate = 0.055). The clinically acceptable difference in the 3-year OS between the groups was set at 12% (73%, hazard rate = 0.105), with a one-sided α of .05, a power of 80%, an accrual period of 2.5 years, and a follow-up period of 3 years. To prove noninferiority,[10] 130 patients per group were required. Assuming a loss of 5%, 274 patients were included.

For the interim analyses, the patients' OS time was evaluated using stratified log-rank test that considered stratification factors for random assignment. OS time was defined as the duration between the dates of registration and death or the last follow-up. DFS time was defined as the duration between the dates of registration and relapse, death, or last follow-up. Log-rank test for noninferiority was used for the evaluation.[10] Kaplan-Meier survival curves were used to calculate survival rates. Based on the method proposed by O'Brien-Fleming,[11] the significance levels of the interim and final analyses were 0.0056 and 0.0483, respectively.

The difference in the postoperative QOL and AAT scores between the two groups at 1, 3, 6, and 12 months postoperatively was tested using the Mann-Whitney *U* test. *P* values $< .0125$ were considered statistically significant for QOL and AAT scores to correct multiple testing.

The survival analysis and Mann-Whitney *U* test were performed using STATA version 15.1 (STATA Corporation, College Station, TX), and EZR version 1.37 (Jichi Medical University, Saitama, Japan)[12] on R commander was used for the χ^2 and *t* tests.

RESULTS

Interim Analysis

To avoid inconveniencing the study participants, an interim analysis was conducted after registering half of the patients. The analysis was conducted on November 2013, during which the survival, false-negative, and SLN nonidentification rates were within the acceptable range; thus, the trial continued.

Patients

From 2011 to 2016, 275 patients were enrolled and randomly assigned. The ND and SLNB groups included 138 and 137 patients, respectively. Four patients were excluded because of postregistration deviations from the eligibility criteria. Finally, 271 patients were included in the FAS, with 137 and 134 patients assigned to the ND and SLNB groups, respectively (Fig 1). ND was performed in 97.1% (133 of 137) of patients in the ND group and 39.5% (53 of 134) in the SLNB group, after one-stage or second-look surgery.

Patient characteristics are shown in Table 1. Among all patients, the median age was 63 years, the number of males was 66.1% (179 of 271) and 82.3% (223 of 271) with primary site being tongue, and 81.2% (220 of 271) were T2. There were no differences between the groups on the basis of age, sex, primary subsite, T classification, surgical approach, surgery, pathologic node (pN) metastasis, postoperative therapy, or median follow-up.

SLN Metastatic Status

Pathologic positive-nodal status was confirmed in 24.8% (34 of 137) and 34.3% (46 of 134) of patients in the ND and SLNB groups, respectively; it was not significantly different on the χ^2 test (Table 1). Overall, 418 SLNs were identified in 132 of 134 patients in the SLNB group, averaging 3.2 SLNs per patient with a 98.5% detection rate. According to metastasis size, we classified nodal metastatic status into three groups: ITC, micrometastasis, and macrometastasis. Among FSs, a total 37 cases at three metastatic node groups were metastasis-positive, whereas postoperative pathologic examination revealed 54 cases as metastatic-positive; the evaluation sensitivity of FS was 68.5% (37 of 54; Table 2).

OS and DFS

The curves of 3-year OS and DFS are shown in Figure 2. The median follow-up period was 3.1 years. Among 271 patients in the FAS, 33 patients (12.2%) were censored with a follow-up of < 3 years. In the SLNB group, the 3-year OS was 87.9% (lower limit of one-sided 95% CI, 82.4); in the ND group, it was 86.6% (lower limit 95% CI, 80.9; *P* for noninferiority $< .001$). Since the noninferiority margin was set to 12%, the 3-year OS in the SLNB group was not inferior to that of the ND group. The 3-year DFS was 78.7% (lower limit 95% CI, 72.1) in the SLNB group and 81.3% (lower limit 95% CI, 75.0) in the ND group (*P* for noninferiority $< .001$).

Functional Analyses

The mean scores of neck functionality tests at 1, 3, 6, and 12 months after surgery are shown in Table 3. Neck stiffness was worst at 1 month postoperatively and improved over time; its scores at 1, 3, 6, and 12 months in the SLNB group were significantly better than those in the ND group. Other functionality scores (constriction, pain, numbness, shoulder-drop, reach-above, neck appearance, and AAT) showed similar trends.

Pattern of Recurrence

During follow-up, recurrence was observed in 18.2% (25 of 137) and 21.6% (29 of 134) of patients in the ND and SLNB groups, respectively (Table 4). Recurrence was

TABLE 1. Characteristics of the Patients at Baseline

Characteristic	Elective ND Group (n = 137) No. (%)	SLNB Group (n = 134) No. (%)	All Patients (N = 271) No. (%)	Chi-Square and *t* test, *P*
Median age (range), years	63 (85-28)	63 (90-21)	63 (90-21)	.84
Sex				
Male	90 (65.7)	89 (66.4)	179 (66.1)	.90
Female	47 (34.3)	45 (33.6)	92 (33.9)	
Site of primary tumor				
Tongue	114 (83.2)	109 (81.3)	223 (82.3)	.87
Floor of mouth	14 (10.2)	13 (9.7)	27 (10.0)	
Lower gingiva	6 (4.4)	7 (5.2)	13 (4.8)	
Buccal mucosa	3 (2.2)	5 (3.7)	8 (3.0)	
T category				
T1 (DOI ≥ 4 mm)	25 (18.2)	26 (19.4)	51 (18.8)	.81
T2	112 (81.8)	108 (80.6)	220 (81.2)	
Surgical approach and extent of resection for primary tumor				
Transoral	112 (81.8)	111 (82.8)	223 (82.3)	.82
Partial	111	111	222 (99.6)	
Hemi	1	0	1 (0.4)	
Pull-through	25 (18.2)	23 (17.2)	48 (17.7)	
Partial	8	9	17 (35.4)	
Hemi	11	13	24 (50.0)	
Subtotal	6	1	7 (14.6)	
ND				
None	4[a] (2.9)	81 (60.4)	85 (31.4)	
Unilateral	128 (93.4)	48 (35.8)	176 (64.9)	
		41[b] (30.6)		
		7[c]		
Bilateral	5 (3.6)	5 (3.7)	10 (3.7)	
		4[b]		
		1[d]		
Operation				
Median time (range), minutes	207 (69-583)	166 (61-667)	195 (61-667)	.12
Median blood loss (range), g	70 (5-740)	30 (0-600)	50 (0-740)	.10
Unknown cases[e]	2	1	3	
pN metastasis				
pN–	99 (72.3)	86 (64.2)	185 (68.3)	.19
pN+	34 (24.8)	46[d] (34.3)	80 (29.5)	
pNx	4 (2.9)	2 (1.5)	6 (2.2)	
Postoperative therapy				
None	131 (95.6)	130 (97.0)	261 (96.3)	.52
Radiation and/or chemoradiation[f]	3/3 (4.4)	4/0 (3.0)	7/3 (3.7)	
Median follow-up, months	37 (IQR, 38-36)	37 (IQR, 39-36)	37 (IQR, 39-36)	

Abbreviations: DOI, depth of invasion; IQR, interquartile range; ND, neck dissection; pN, pathologic node metastasis; pNx, no data of nodal status; SLNB, sentinel lymph node biopsy; T category, tumor category.

[a]NDs were not performed because of poor general condition in two, rejection in one, and unknown reason in one.

[b]ND for cases of positive sentinel lymph node.

[c]Including seven selective ND for pull-through resections with negative sentinel lymph node.

[d]One case of sentinel lymph node–negative and nonsentinel lymph node–positive is included.

[e]Missing data.

[f]The combination of chemotherapy and the agents depended on the policy of each institution.

TABLE 2. Metastatic Status of Sentinel Lymph Nodes

	Node[a] Group Level				Patient Level
	ITC[b]	Micrometastasis[b]	Macrometastasis[b]	Total	Positive Cases
Method of Multislice Analysis	No. of Cases (%)	No. of Cases (%)	No. of Cases (%)	No. of Cases	No. of Cases (%)
Frozen section	2 (1.5)	10 (7.6)	25 (18.9)	37	32 (24.2)
HE and/or CK stain	9 (6.8)	20 (15.2)	25 (18.9)	54	45 (34.1)

Abbreviations: CK, cytokeratin; HE, hematoxylin and eosin; ITC, isolated tumor cell.

[a]Total detected sentinel lymph nodes = 418 nodes/132 pts, average value of detected sentinel lymph node/patient = 3.2, and sentinel lymph node detection rate = 98.5% (132 of 134 patients).

[b]ITC < 0.2 mm, micrometastasis 0.2-2 mm, and macrometastasis ≥ 2 mm in maximum size.

mostly local and/or regional, with no between-group differences in distribution.

False negative (FN) was defined as neck recurrence after a negative SLN or pN, as previously reported.[13,14] Among regional recurrences, four cases were pN-negative in the ND group, and seven were SLN-negative in the SLNB group. Additionally, one case in the SLNB group was SLN-negative and non-SLN–positive (FN) each; the FN rates of metastasis in the ND and SLNB group were calculated to be 10.5% and 15.1%, respectively.

Adverse Events

Adverse events were identified in 20 (14.6%) of 137 patients in the ND group and in 12 (9%) of 134 patients in the SLNB group. No significant difference was observed between the two groups (Table 4). One postoperative death (grade 5) because of myocardial infarction was observed in the ND group and one because of pneumonia in the SLNB group.

DISCUSSION

In this study, we compared SLN-navigated ND versus elective ND in early-stage OCSCC and showed that SLN-navigated ND was noninferior to elective ND regarding survival rate and superior regarding neck functionality.

Our study was characterized by the following three points, which were designed to enhance the clinical utility of SLNB: (1) DOI as an exclusion criterion for T1; (2) adaptability to pull-through resection; and (3) application of frozen section diagnosis to intraoperative pathology.

DOI is an independent predictor of OS and disease-specific survival.[15,16] T classification with a low rate of occult node metastasis may not be appropriate for studies with OS as the primary end point. Therefore, we considered excluding cases that were predicted to have a low potential for LN metastasis. The cutoff value was set at DOI ≥ 4 mm, based on previous reports.[15,17]

Pull-through resection is indicated to some extent in invasive tumors of early OCSCC and has been reported to be oncologically safer than peroral resection, especially for T2.[18,19] In this study, pull-through resection was performed at about the same rate in both groups: 25 of 137 (18.2%) in the ND group and 23 of 134 (17.2%) in the SLNB group, all of which were T2. Furthermore, 24 of 48 (50%) of the patients underwent hemiresection, and 43 of 48 (90%) underwent combined resection of the floor of the mouth, base of the tongue, and mandibular margin; however, no patients underwent segmental mandibulectomy.

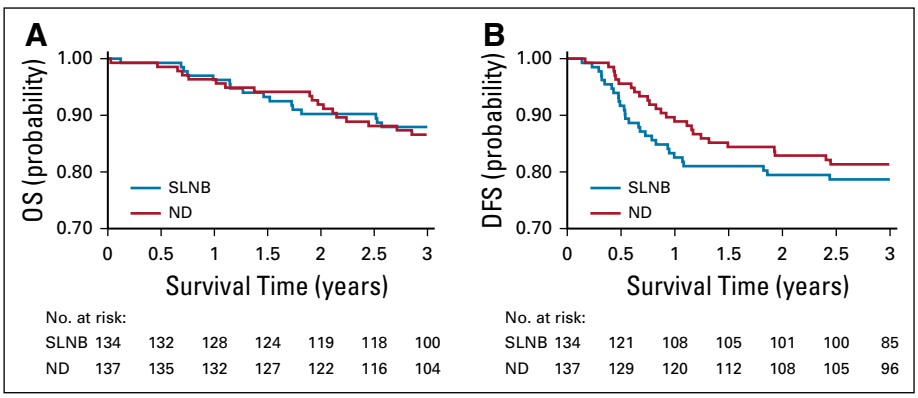

FIG 2. Kaplan-Meier plots of (A) OS rate and No. at risk and (B) DFS rate and No. at risk. DFS, disease-free survival; ND, neck dissection; OS, overall survival; SLNB, sentinel lymph node biopsy.

TABLE 3. Result of Neck Dissection QOL Questionnaire and AAT of the Affected Site (QOL and AAT Score[a] Trend During 12 Months After Surgery)

		Months After Surgery							
		1		3		6		12	
QOL Item	Score	No.	%	No.	%	No.	%	No.	%
Stiffness									
ND	1	12	9.52	9	6.87	1	0.78	3	2.50
	2	32	25.40	32	24.43	24	18.75	15	12.50
	3	44	34.92	46	35.11	37	28.91	34	28.33
	4	11	8.73	17	12.98	29	22.66	35	29.17
	5	27	21.43	27	20.61	37	28.91	33	27.50
SLNB	1	5	4.00	1	0.80	0	0.00	1	0.93
	2	16	12.80	16	12.80	14	11.38	7	6.48
	3	35	28.00	29	23.20	23	18.70	22	20.37
	4	25	20.00	22	17.60	28	22.76	26	24.07
	5	44	35.20	57	45.60	58	47.15	52	48.15
P		< .001		< .001		.00105		.00108	
Constriction									
ND	1	9	7.20	4	3.05	1	0.78	4	3.33
	2	23	18.40	25	19.08	15	11.72	11	9.17
	3	40	32.00	41	31.30	42	32.81	31	25.83
	4	23	18.40	24	18.32	26	20.31	31	25.83
	5	30	24.00	37	28.24	44	34.38	43	35.83
SLNB	1	5	4.00	2	1.60	0	0.00	1	0.93
	2	8	6.40	6	4.80	8	6.50	7	6.48
	3	27	21.60	28	22.40	16	13.01	16	14.81
	4	27	21.60	23	18.40	28	22.76	23	21.30
	5	58	46.40	66	52.80	71	57.72	61	56.48
P		< .001		< .001		< .001		.00133	
Pain									
ND	1	4	3.17	2	1.54	1	0.78	2	1.67
	2	21	16.67	11	8.46	6	4.69	4	3.33
	3	36	28.57	41	31.54	32	25.00	32	26.67
	4	25	19.84	35	26.92	34	26.56	30	25.00
	5	40	31.75	41	31.54	55	42.97	52	43.33
SLNB	1	3	2.40	0	0.00	0	0.00	1	0.93
	2	7	5.60	8	6.40	7	5.69	6	5.56
	3	28	22.40	23	18.40	20	16.26	19	17.59
	4	27	21.60	30	24.00	21	17.07	20	18.52
	5	60	48.00	64	51.20	75	60.98	62	57.41
P		.00117		.00086		.01172		.06394	
Numbness									
ND	1	5	3.97	3	2.29	3	2.34	4	3.33
	2	21	16.67	12	9.16	12	9.38	9	7.50
	3	33	26.19	42	32.06	35	27.34	32	26.67
	4	22	17.46	27	20.61	21	16.41	26	21.67

(continued on following page)

TABLE 3. Result of Neck Dissection QOL Questionnaire and AAT of the Affected Site (QOL and AAT Score[a] Trend During 12 Months After Surgery) (continued)

		Months After Surgery							
		1		3		6		12	
QOL Item	Score	No.	%	No.	%	No.	%	No.	%
	5	45	35.71	47	35.88	57	44.53	49	40.83
SLNB	1	1	0.81	1	0.80	0	0.00	1	0.93
	2	9	7.26	4	3.20	4	3.25	2	1.85
	3	28	22.58	23	18.40	20	16.26	16	14.81
	4	32	25.81	25	20.00	23	18.70	21	19.44
	5	54	43.55	72	57.60	76	61.79	68	62.96
P		.01345		< .001		.00077		< .001	
Shoulder drop									
ND	1	0	0.00	0	0.00	0	0.00	3	2.52
	2	4	3.17	9	6.87	6	4.69	2	1.68
	3	31	24.60	29	22.14	22	17.19	10	8.40
	4	29	23.02	28	21.37	30	23.44	38	31.93
	5	62	49.21	65	49.62	70	54.69	66	55.46
SLNB	1	1	0.80	1	0.80	0	0.00	1	0.93
	2	2	1.60	4	3.20	0	0.00	0	0.00
	3	12	9.60	9	7.20	9	7.32	7	6.48
	4	23	18.40	22	17.60	29	23.58	27	25.00
	5	87	69.60	89	71.20	85	69.11	73	67.59
P		< .001		< .001		.004		.04873	
Reach above									
ND	1	4	3.17	5	3.85	5	3.91	5	4.17
	2	22	17.46	19	14.62	4	3.13	4	3.33
	3	36	28.57	32	24.62	26	20.31	19	15.83
	4	19	15.08	25	19.23	27	21.09	32	26.67
	5	45	35.71	49	37.69	66	51.56	60	50.00
SLNB	1	4	3.23	4	3.20	2	1.63	1	0.93
	2	13	10.48	5	4.00	4	3.25	3	2.78
	3	16	12.90	20	16.00	16	13.01	16	14.81
	4	12	9.68	13	10.40	23	18.70	22	20.37
	5	79	63.71	83	66.40	78	63.41	66	61.11
P		< .001		< .001		.04327		.09578	
Neck appearance									
ND	1	9	7.20	3	2.29	5	3.91	5	4.17
	2	13	10.40	15	11.45	8	6.25	4	3.33
	3	43	34.40	41	31.30	30	23.44	27	22.50
	4	22	17.60	29	22.14	25	19.53	30	25.00
	5	38	30.40	43	32.82	60	46.88	54	45.00
SLNB	1	5	4.00	2	1.60	1	0.81	2	1.85
	2	11	8.80	9	7.20	7	5.69	2	1.85
	3	19	15.20	21	16.80	16	13.01	19	17.59

(continued on following page)

TABLE 3. Result of Neck Dissection QOL Questionnaire and AAT of the Affected Site (QOL and AAT Score[a] Trend During 12 Months After Surgery) (continued)

		Months After Surgery							
		1		3		6		12	
QOL Item	Score	No.	%	No.	%	No.	%	No.	%
	4	26	20.80	20	16.00	26	21.14	23	21.30
	5	64	51.20	73	58.40	73	59.35	62	57.41
P		< .001		< .001		.01852		.04795	
AAT									
ND	0	3	4.41	2	2.74	2	4.88	0	0.00
	1	3	4.41	2	2.74	2	4.88	0	0.00
	2	9	13.24	18	24.66	5	12.20	5	16.13
	3	13	19.12	15	20.55	7	17.07	6	19.35
	4	19	27.94	13	17.81	8	19.51	3	9.68
	5	21	30.88	23	31.51	17	41.46	17	54.84
SLNB	0	3	7.89	3	9.09	1	3.85	1	5.26
	1	3	7.89	3	9.09	1	3.85	1	5.26
	2	9	23.68	4	12.12	4	15.38	2	10.53
	3	5	13.16	4	12.12	1	3.85	2	10.53
	4	4	10.53	7	21.21	8	30.77	4	21.05
	5	14	36.84	12	36.36	11	42.31	9	47.37
P		< .001		< .001		.06219		.099	

NOTE. Scores at 1, 3, 6, and 12 months after surgery in the ND group and the SLNB group were tested by Mann-Whitney *U* test. Threshold of significance of the difference was set as $P < .0125$ by Bonferroni correction.

Abbreviations: AAT, arm abduction test; ND, neck dissection; QOL, quality of life; SLNB, sentinel lymph node biopsy.

[a]A higher score indicates a better QOL.

Given that pull-through resection is usually combined with SOHND as a selective dissection technique, SLNB has rarely been reportedly indicated. However, we believe that it has several advantages. First, it can deal with skip metastasis, which potentially causes late metastasis. Cervical LN metastasis in OCSCC mainly involves levels I-III, according to Lindberg.[20] Crean et al[21] performed an extended SOHND, which involves dissections of levels I-IV, on N0 OCSCC cases, reporting 10% of potential metastasis to level IV outside the elective dissection level. Our phase II trial also reported 10% of SLN metastases on the contralateral side of the neck.

Second, the procedure can be changed to pull-through resection to obtain oncologic safety in patients in whom intraoperative metastasis becomes apparent.

In this light, SLNB is a more individualized and precise solution for pull-through resection.

We performed intraoperative pathologic diagnosis of multiple surfaces of the rapid FSs.[22] In our experience, multislice frozen section analysis surpasses imprint cytology in terms of intraoperative diagnosis of SLNB.[23] A follow-up study[24] using intraoperative pathologic diagnosis of multislice rapid FSs showed that the indication for ND might be based on these results. In contrast, step-serial sections may be more accurate; however, they require more time, effort, and costs. Furthermore, intraoperative diagnosis of all nodal metastasis is impossible; thus, a second-look procedure may be needed. Two surgeries may put additional burden on the patient.[25] Therefore, since we predominantly performed one-stage surgery, we used the 2-mm multislice method to produce rapid FSs. Notably, not all cases could be diagnosed using frozen specimen examination, and of 32 of 46 metastasis-positive cases, 70.0% underwent one-stage surgery.

Various methods have been reported for detecting micrometastases and determining ND indication; however, it is difficult to detect occult metastases by CT, magnetic resonance imaging, or ultrasound.[26] Detection of micrometastases by adding immunohistochemistry to conventional HE staining ranges around 15%-20% among pN0 cases.[26-28] We believe that SLNB using HE staining and immunohistochemistry may detect micrometastasis

TABLE 4. Pattern of Recurrence and Postoperative Complications

Pattern of Recurrence

Site of Recurrence	Elective ND Group (n = 137) pN (–) (n = 99)	pN (+) (n = 34)	pNx (n = 4)	Total No. (%)	SLNB Group (n = 134) SLN (–) (n = 87)	SLN (+) (n = 45)	SLNx (n = 2)	Total No. (%)	All Patients (N = 271) Total No. (%)	Chi-Square, *P*
Local	3	2	0	5 (3.6)	6[a]	2	0	9 (6.7)	14 (5.2)	.48
Regional	4	9	0	13 (9.5)	7	8	0	15 (11.2)	28 (10.3)	
Locoregional	2	0	0	2 (1.5)	0	3	0	3 (2.2)	5 (1.8)	
Distant	2	3	0	5 (3.6)	1	1	0	2 (1.5)	7 (2.6)	
Total	11	14	0	25 (18.2)	14	14	0	29 (21.6)	54 (19.9)	

Postoperative Complications

Complication	Elective ND Group (n = 137) No. (%)	SLNB Group (n = 134) No. (%)	All Patients (N = 271) No. (%)	Chi-Square, *P*
None	115 (83.9)	121 (90.3)	236 (87.1)	.29
Yes	20 (14.6)	12 (9.0)	32 (11.8)	
Grades[b] 1-2	11	8		
Grades 3-4	6	2		
Grade 5	1	1		
Not graded	2	1		
Unknown cases[c]	2 (1.5)	1 (0.7)	3 (1.1)	

Abbreviations: (–), nodal metastasis–negative; (+), nodal metastasis–positive; ND, neck dissection; pN, pathologic node metastasis; pNx, no data of nodal status; SLN, sentinel lymph node; SLNB, SLN biopsy; SLNx, no data of SLN.

[a]One case had negative SLN and positive non-SLN as false negative.

[b]Grading score by CTCAE. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0.

[c]Missing data.

better than conventional methods. In the SLNB group, we observed nine ITCs and 20 micrometastases (53.7%, 29 of 54) in the 54 metastasis-positive cases. With ITC, reduced breast cancer–specific survival has been reported,[29] in addition to the studies previously reported. Other studies[30] on patients with head and neck cancer support this consideration. Several ITCs and micrometastases were observed in this study. In such cases, especially with ITC, further study is needed to confirm whether selective ND is required or SLNB may be sufficient. If SLNB alone can be followed up, it may be a less invasive treatment.

In a retrospective cohort study,[31] SLNB for stage I-II OCSCC was associated with reduced length of hospital stay and equivalent OS, compared with elective ND; moreover, other reports have described the functional superiority and lower complication rate of SLNB compared with those of elective ND,[32,33] assessed using the Neck Dissection Impairment Index questionnaire. The results of neck function superiority observed in our study were consistent with those of the aforementioned studies.

Similar to the results of our study, Garrel et al[34] have also reported the effectiveness of SLNB. Despite some differences between the two studies regarding the research methods, such as the primary end point of the study, the target cancer including the oropharynx and all T1 OCSCC, and the response to ITC, the findings of the aforementioned study support the validity of our study.

The strength of our study was that it clarified the efficacy of our treatment strategy based on SLNB navigation as an appropriate modality for targeting oral cancer in aspects of OS and neck functionality.

The limitation of our study was the noninferiority margin of 12%. A smaller margin might have been better at proving the noninferiority of prognosis in SLNB group; however, adverse events associated with ND,[32,33] physical and financial burden associated with reoperation, and anxiety of recurrence might be reduced with SLNB. The expected difference in the 3-year survival rate between ND and nondissection was 20%-35%.[35,36] Taking these results and the improved prognosis into consideration, the noninferiority margin of 12% in the 3-year survival rate might be a clinically acceptable difference.

In conclusion, SLNB-navigated ND is noninferior and less invasive than elective ND. The results of this study may promote a widespread use of SLNB (for early-stage OCSCC) worldwide.

AFFILIATIONS

[1]Asahi University Hospital, Gifu, Japan
[2]Tokyo Medical University, Tokyo, Japan
[3]National Cancer Center Hospital, Tokyo, Japan
[4]International University of Health and Welfare, Mita Hospital, Tokyo, Japan
[5]Nadogaya Hospital, Kashiwa, Japan
[6]Kyoto Prefectural University of Medicine, Kyoto, Japan
[7]Nara Medical University, Nara, Japan
[8]Saitama Medical University International Medical Center, Hidaka, Japan
[9]Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan
[10]Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
[11]Gunma University School of Medicine, Maebashi, Japan
[12]University of the Ryukyus Faculty of Medicine, Okinawa, Japan
[13]National Defense Medical College, Tokorozawa, Japan
[14]Fukushima Medical University, Fukushima, Japan
[15]Kyorin University School of Medicine, Mitaka, Japan
[16]National Cancer Center Hospital East, Kashiwa, Japan
[17]Aichi Cancer Center Research Institute, Nagoya, Japan
[18]Kouseikai General Clinic and Hospital, Kawagoe, Japan

CORRESPONDING AUTHOR

Yasuhisa Hasegawa, MD, PhD, Asahi University Hospital, 3-23 Hashimotocho, Gifu 500-8523, Japan; e-mail: yhasegawa@hosp.asahi-u.ac.jp.

PRIOR PRESENTATION

Presented at the 2019 ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2019.

SUPPORT

Supported by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H21-Gannrinshou-Ippan-016 and H24-Gannrinshou-Ippan-006) from the Ministry of Health, Labour and Welfare in Japan.

CLINICAL TRIAL INFORMATION

UMIN000006510

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03637.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.20.03637.

AUTHOR CONTRIBUTIONS

Conception and design: Yasuhisa Hasegawa, Kiyoaki Tsukahara, Seiichi Yoshimoto, Kouki Miura, Junkichi Yokoyama, Shigeru Hirano, Akihiro Homma, Naoyuki Kohno, Keitaro Matsuo, Shigeru Kosuda
Financial support: Yasuhisa Hasegawa
Administrative support: Yasuhisa Hasegawa, Isao Oze, Shigeru Kosuda
Provision of study materials or patients: Yasuhisa Hasegawa, Seiichi Yoshimoto, Junkichi Yokoyama, Shigeru Hirano, Hirokazu Uemura, Masashi Sugasawa, Akihiro Homma, Kazuaki Chikamatsu, Mikio Suzuki, Naoyuki Kohno, Masakazu Miyazaki
Collection and assembly of data: Yasuhisa Hasegawa, Kiyoaki Tsukahara, Seiichi Yoshimoto, Kouki Miura, Junkichi Yokoyama, Shigeru Hirano, Hirokazu Uemura, Masashi Sugasawa, Tomokazu Yoshizaki, Akihiro Homma, Kazuaki Chikamatsu, Mikio Suzuki, Akihiro Shiotani, Takashi Matsuzuka, Naoyuki Kohno, Masakazu Miyazaki, Yasushi Yatabe
Data analysis and interpretation: Yasuhisa Hasegawa, Kiyoaki Tsukahara, Seiichi Yoshimoto, Kouki Miura, Junkichi Yokoyama, Tomokazu Yoshizaki, Akihiro Homma, Naoyuki Kohno, Isao Oze, Keitaro Matsuo, Yasushi Yatabe
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients and their families for participation in the trial. We also thank the physicians, nurses, medical technicians, and research staff at the participating institutions, especially Dr Daisuke Kawakita.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Monroe MM, Gross ND: Evidence-based practice: Management of the clinical node-negative neck in early-stage oral cavity squamous cell carcinoma. Otolaryngol Clin North Am 45:1181-1193, 2012
3. D'Cruz AK, Vaish R, Kapre N, et al: Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 373:521-529, 2015
4. Dogan NU, Dogan S, Favero G, et al: The basics of sentinel lymph node biopsy: Anatomical and pathophysiological considerations and clinical aspects. J Oncol 2019:3415630, 2019
5. Miura K, Hirakawa H, Uemura H, et al: Sentinel node biopsy for oral cancer: A prospective multicenter phase II trial. Auris Nasus Larynx 44:319-326, 2017
6. Yoshimoto S, Hasegawa Y, Matsuzuka T, et al: Sentinel node biopsy for oral and laryngopharyngeal squamous cell carcinoma: A retrospective study of 177 patients in Japan. Auris Nasus Larynx 39:65-70, 2012
7. Hermanek P, Hutter RV, Sobin LH, et al: International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. Cancer 86:2668-2673, 1999
8. de Boer M, van Deurzen CH, van Dijck JA, et al: Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med 361:653-663, 2009
9. Robbins KT, Clayman G, Levine PA, et al: Neck dissection classification update: Revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 128:751-758, 2002
10. Jung SH, Kang SJ, McCall LM, et al: Sample size computation for two-sample noninferiority log-rank test. Biopharm Stat 15:969-979, 2005
11. Piantadosi S: Clinical Trials: A Methodologic Perspective (ed 2). Hoboken, NJ, John Wiley and Sons, 2005
12. Kanda Y: Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transpl 48:452-458, 2013
13. Holden AM, Sharma D, Schilling C, et al: Biopsy of the sentinel lymph node in oral squamous cell carcinoma: Analysis of error in 100 consecutive cases. Br J Oral Maxillofac Surg 56:615-620, 2018

14. Schilling C, Stoeckli SJ, Vigili MG, et al: Surgical consensus guidelines on sentinel node biopsy (SLNB) in patients with oral cancer. Head Neck 41:2655-2664, 2019
15. Kligerman J, Lima RA, Soares JR, et al: Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg 168: 391-394, 1994
16. Tam S, Amit M, Zafereo M, et al: Depth of invasion as a predictor of nodal disease and survival in patients with oral tongue squamous cell carcinoma. Head Neck 41:177-184, 2019
17. Fukano H, Matsuura H, Hasegawa Y, et al: Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. Head Neck 19: 205-210, 1997
18. Lim Y, Choi E: Unilateral, clinically T2N0, squamous cell carcinoma of the tongue: Surgical outcome analysis. Int J Oral Maxill Surg 36:610-614, 2007
19. Baserer N, Damar M: Pull-through resection and peroral resection in early-stage (T1 and T2) tongue and floor of the mouth cancers: A comparison of two techniques [in Turkish]. Kulak Burun Bogaz Ihtis Derg 21:305-311, 2011
20. Lindberg R: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446-1449, 1972
21. Crean SJ, Hoffman A, Potts J, et al: Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck 25: 758-762, 2003
22. Terada A, Hasegawa Y, Goto M, et al: Sentinel lymph node radiolocalization in clinically negative neck oral cancer. Head Neck 28:114-120, 2006
23. Terada A, Hasegawa Y, Yatabe Y, et al: Intraoperative diagnosis of cancer metastasis in sentinel lymph node of oral cancer patients. Oral Oncol 44:838-843, 2008
24. Terada A, Hasegawa Y, Yatabe Y, et al: Follow-up after intraoperative sentinel node biopsy of N0 neck oral cancer patients. Eur Arch Otorhinolaryngol 268: 429-435, 2011
25. Sloan P: Head and neck sentinel lymph node biopsy: Current state of the art. Head Neck Pathol 3:231-237, 2009
26. Nieuwenhuis EJ, Leemans CR, Kummer JA, et al: Assessment and clinical significance of micrometastases in lymph nodes of head and neck cancer patients detected by E48 (Ly-6D) quantitative reverse transcription-polymerase chain reaction. Lab Invest 83:1233-1240, 2003
27. Rinaldo A, Devaney KO, Ferlito A: Immunohistochemical studies in the identification of lymph node micrometastases in patients with squamous cell carcinoma of the head and neck. ORL J Otorhinolaryngol Relat Spec 66:38-41, 2004
28. Hamakawa H, Fukizumi M, Bao Y, et al: Genetic diagnosis of micrometastasis based on SCC antigen mRNA in cervical lymph nodes of head and neck cancer. Clin Exp Metastasis 17:593-599, 1999
29. Leidenius MH, Vironen JH, Heikkila PS, et al: Influence of isolated tumor cells in sentinel nodes on outcome in small, node-negative (pT1N0M0) breast cancer. Ann Surg Oncol 17:254-262, 2010
30. Broglie MA, Haile SR, Stoeckli SJ: Long-term experience in sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Ann Surg Oncol 18: 2732-2738, 2011
31. Cramer JD, Sridharan S, Ferris RL, et al: Sentinel lymph node biopsy versus elective neck dissection for stage I to II oral cavity cancer. Laryngoscope 129: 162-169, 2019
32. Murer K, Huber GF, Haile SR, et al: Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. Head Neck 33:1260-1264, 2011
33. Schiefke F, Akdemir M, Weber A, et al: Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck 31:503-512, 2009
34. Garrel R, Poissonnet G, Moya Plana A, et al: Equivalence randomized trial to compare treatment on the basis of sentinel node biopsy versus neck node dissection in operable T1-T2N0 oral and oropharyngeal cancer. J Clin Oncol 38:4010-4018, 2020
35. Haddadin KJ, Soutar DS, Oliver RJ, et al: Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 21:517-525, 1999
36. Capote A, Escorial V, Munoz-Guerra MF, et al: Elective neck dissection in early-stage oral squamous cell carcinoma—Does it influence recurrence and survival? Head Neck 29:3-11, 2007

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neck Dissections Based on Sentinel Lymph Node Navigation Versus Elective Neck Dissections in Early Oral Cancers: A Randomized, Multicenter, and Noninferiority Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Akihiro Homma
Research Funding: Taiho Pharmaceutical, Ono Pharmaceutical, Eisai Co, Ltd, Eisai Co, Ltd

Akihiro Shiotani
Honoraria: Kyorin, Mitsubishi Tanabe Pharma
Research Funding: Taiho Pharmaceutical, Shionogi, Mitsubishi Tanabe Pharma, Daiichi Sankyo/UCB Japan, Teijin Pharma, Takeda

Yasushi Yatabe
Consulting or Advisory Role: MSD K.K, Chugai Pharma, AstraZeneca, Novartis, Amgen, Archer, Takeda, Daiichi Sankyo/UCB Japan
Speakers' Bureau: MSD K.K, Chugai Pharma, AstraZeneca, Novartis, Amgen, Archer, Pfizer, Ventana Medical Systems, Agilent, Thermo Fisher Scientific

No other potential conflicts of interest were reported.

APPENDIX

APPENDIX 1. HNCMM Research Group and the List of 16 Participating Institutions

Name	Research Affiliation and City
Yasuhisa Hasegawa	Aichi Cancer Center Hospital, Nagoya
Yasushi Yatabe	Aichi Cancer Center Hospital, Nagoya
Yoshiko Murakami	Aichi Cancer Center Hospital, Nagoya
Nobuhiro Hanai	Aichi Cancer Center Hospital, Nagoya
Yusuke Koide	Aichi Cancer Center Hospital, Nagoya
Isao Oze	Aichi Cancer Center Research Institute, Nagoya
Keitaro Matsuo	Aichi Cancer Center Research Institute, Nagoya
Daisuke Kawakita	Aichi Cancer Center Research Institute, Nagoya
Akihiro Homma	Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo
Tomohiro Sakashita	Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo
Takatsugu Mizumachi	Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo
Takashi Matsuzuka	Fukushima Medical University, Fukushima
Tomokazu Yoshizaki	Graduate School of Medical Science, Kanazawa University, Kanazawa
Kazuhira Endo	Graduate School of Medical Science, Kanazawa University, Kanazawa
Naohiro Wakisaka	Graduate School of Medical Science, Kanazawa University, Kanazawa
Shigeru Hirano	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Morimasa Kitamura	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Chiaki Suzuki	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Takehiro Iki	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Nao Hiwatashi	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Ichirou Tateya	Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto
Kazuaki Chikamatsu	Gunma University School of Medicine, Maebashi
Minoru Toyoda	Gunma University School of Medicine, Maebashi
Kouki Miura	International University of Health and Welfare, Mita Hospital, Tokyo
Junkichi Yokoyama	Juntendo University Graduate School of Medicine, Tokyo
Shinichi Ohba	Juntendo University Graduate School of Medicine, Tokyo
Shigeru Kosuda	Koseikai Hospital, Kawagoe
Naoyuki Kohno	Kyorin University School of Medicine, Mitaka
Dai Sato	Kyorin University School of Medicine, Mitaka
Yasunao Kogashiwa	Kyorin University School of Medicine, Mitaka
Masakazu Miyazaki	National Cancer Center Hospital East, Kashiwa
Takashi Maruo	National Cancer Center Hospital East, Kashiwa
Takeshi Shinozaki	National Cancer Center Hospital East, Kashiwa
Akihiro Shiotani	National Defense Medical Collage, Tokorozawa
Masayuki Tomifuji	National Defense Medical Collage, Tokorozawa

(continued on following page)

APPENDIX 1. HNCMM Research Group and the List of 16 Participating Institutions (continued)

Name	Research Affiliation and City
Koji Araki	National Defense Medical Collage, Tokorozawa
Hirokazu Uemura	Osaka International Cancer Institute, Osaka
Motoyuki Suzuki	Osaka International Cancer Institute, Osaka
Shinji Otozai	Osaka International Cancer Institute, Osaka
Masashi Sugasawa	Saitama Medical University International Medical Center, Hidaka
Yuichiro Enoki	Saitama Medical University International Medical Center, Hidaka
Yoshie Sano	Saitama Medical University International Medical Center, Hidaka
Seiichi Yoshimoto	National Cancer Center Hospital, Tokyo
Fumihiko Matsumoto	National Cancer Center Hospital, Tokyo
Kenya Kobayashi	National Cancer Center Hospital, Tokyo
Kiyoaki Tsukahara	Tokyo Medical University Hachioji Medical Center, Hachioji
Takahito Kondo	Tokyo Medical University Hachioji Medical Center, Hachioji
Mikio Suzuki	University of the Ryukyus Faculty of Medicine, Okinawa
Shinya Agena	University of the Ryukyus Faculty of Medicine, Okinawa

NOTE. The list of 16 participating institutions from north to south in Japan is as follows: (1) Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; (2) Fukushima Medical University Hospital, Fukushima, Japan; (3) Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan; (4) Saitama Medical University International Medical Center, Hidaka, Japan; (5) Gunma University Hospital, Maebashi, Japan; (6) National Defense Medical College, Tokorozawa, Japan; (7) National Cancer Center Hospital East, Kashiwa, Japan; (8) International University of Health and Welfare Mita Hospital, Minato, Japan; (9) Juntendo University Hospital, Bunkyo, Japan; (10) National Cancer Center Hospital, Tokyo, Japan; (11) Tokyo Medical University, Tokyo, Japan; (12) Kyorin University School of Medicine, Mitaka, Japan; (13) Aichi Cancer Center Hospital and Research Institute, Nagoya, Japan; (14) Osaka International Cancer Institute, Osaka, Japan; (15) Faculty of Medicine, Kyoto University, Kyoto, Japan; and (16) Faculty of Medicine, University of the Ryukyus, Ginowan, Japan.

TABLE A1. N0 Diagnostic Criteria

The maximum diameter (transverse image) was ≥ 15 mm for superior internal deep cervical and/or submandibular LNs and ≥ 10 mm for others. The minimum diameter (transverse image) was ≥ 11 mm for superior internal deep cervical LN and ≥ 10 mm for other LNs. The diameter of retropharyngeal LNs was ≥ 8 mm.
In terms of imaging findings, diagnosis involved a local defect showing central necrosis and an unclear boundary showing extranodal extension, fusion of ≥ 3 LNs, and asymmetry with the maximum diameter on the affected side more than twice that on the healthy side.
Ultrasound was used as an adjunctive diagnostic tool, based on the following criteria for metastatic nodes: Regardless of the LN location, some LNs in the neck have a thickness of ≥ 6 mm. Even if the thickness is < 6 mm, some LNs have a thickness or major axis > 0.5, and the nodal hilus is absent.

NOTE. Computed tomography was mandatory for N0 judgment. The following diagnostic criteria for metastatic nodes were used, and a comprehensive judgment was made by the addition of physical and ultrasound findings.

Abbreviations: LN, lymph node; N0, node-negative.

TABLE A2. Neck Dissection Quality-of-Life Questionnaire and Arm Abduction Test[a,b]

As a Result of the Cancer Treatment, How Much Have You Been Bothered by the Following?		
ND QOL Questionnaire		
0.	First of all, which is your dominant arm?	
	Right[c]	Left
1.	Are you bothered by neck or shoulder stiffness?	
	Right[d]	Left[d]
2.	Are you bothered by constriction of your neck?	
	Right[d]	Left[d]
3.	Are you bothered by neck or shoulder pain?	
	Right[d]	Left[d]
4.	Are you bothered by numbness of your neck?	
	Right[d]	Left[d]
5.	Do you think your shoulders have dropped?	
	Right[d]	Left[d]
6.	Have you been limited in your ability to reach above your head for objects because of your shoulder or neck?	
	Right[d]	Left[d]
7.	Are you bothered by the appearance of your neck?	
	Right[d]	Left[d]

AAT Score	Evaluation
5	Up to 180° without pain or effort
4	Up to 181° with pain or effort
3	Up to more than 150° but < 180°
2	Up to more than 90° but < 150°
1	Up to around 90°
0	Up to < 90°

Abbreviations: AAT, arm abduction test; ND, neck dissection; QOL, quality-of-life.

[a]Inoue H, Nibu K, Saito M, et al: Quality of life after neck dissection. Arch Otolaryngol Head Neck Surg 132:662-666, 2006.

[b]Nibu K, Ebihara Y, Ebihara M, et al: Quality of life after neck dissection: A multicenter longitudinal study by the Japanese Clinical Study Group on standardization of treatment for lymph node metastasis of head and neck cancer. Int J Clin Oncol 15:33-38, 2010.

[c]Right and left refer to the right and left sides of the neck.

[d]Scoring was achieved by rating response items from 1 to 5, with 5 representing best QOL and 1 representing worst QOL.