Macroscopic and multiple metastases in sentinel lymph node biopsy are respectively associated with poor prognosis in early oral cancer

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Abstract

A multicenter, randomized controlled phase III trial was conducted on sentinel lymph node biopsy (SLNB) and elective neck dissection for T1 (depth of invasion ≥ 4 mm)-T2N0M0 oral cavity squamous cell carcinoma. This study identified factors associated with poor prognosis in patients who underwent SLNB based on a subgroup analysis of this trial.

We analyzed 418 sentinel lymph nodes (SLNs) from 132 patients who underwent SLNB. The metastatic SLNs were classified into three categories based on size—isolated tumor cells: <0.2 mm, micrometastasis: ≥0.2 mm and < 2 mm, and macrometastasis: ≥2 mm. Three groups were formed based on the number of metastatic SLNs: no metastasis, 1 metastatic node, and ≥ 2 metastatic nodes. The size and number of metastatic SLNs on survival was evaluated using Cox proportional hazard models.

Patients with macrometastasis and ≥ 2 metastatic SLNs had worse overall survival (OS) and disease-free survival (DFS) after adjustment for potential confounders (HR for OS: macrometastasis, 4.85; 95% CI: 1.34–17.60; ≥2 metastatic SLN, 3.63; 95% CI: 1.02–12.89; HR for DFS: macrometastasis, 2.94; 95% CI: 1.16–7.44; ≥2 metastatic SLN, 2.97; 95% CI: 1.18–7.51).

In patients who underwent SLNB, a poorer prognosis was associated with macrometastasis or having ≥ 2 metastatic SLNs.

Introduction

Oral cavity squamous cell carcinoma (OCSCC) is the most common type of oral cancer. Although it may be curable after early detection and treatment, there is no international consensus addressing cervical lymph nodes (LNs) in T1-T2N0M0 cases. Therefore, a combination of three strategies is currently used: follow-up, elective neck dissection (END), and sentinel LN biopsy (SLNB). In a large randomized controlled trial, D'Cruz et al. found that overall survival (OS) and disease-free survival (DFS) were significantly increased in the END group compared to those in the follow-up group [1]. Further, in a multicenter, randomized controlled phase III trial, we found that the 3-year OS and 3-year DFS of an SLNB group were not inferior to those of an END group [2]. In a letter to the editor [3], to which we published a response [4], Kaul et al. raised the issue of the predictive value of the presence of isolated tumor cells (ITC) and other pathological findings in the survival data and recurrence rates in this patient population. We considered that more detailed histopathological and prognostic studies were needed, which led to the analyses performed here. This study aimed to perform a subgroup analysis of our multicenter, randomized controlled phase III trial [2] to identify factors associated with poor prognosis from the histopathological characteristics of 132 patients in the SLNB group.

Results

Patient Characteristics

Figure 1 shows the courses of treatment for the 134 patients in the SLNB group in the multicenter, randomized controlled phase III trial [2]. This subgroup analysis included 418 SLNs obtained from 132 patients. This is a mean of 3.2 SLNs per patient among the 132 patients who underwent SLNB. Table 2 shows the number of SLNs for each site and the number of positive metastases in FS. The vertical axis of Table 2 classifies the SLNs in the order of SLNs removed: SLN1, SLN2, SLN3, SLN4, SLN5, and SLN6-8. The horizontal axis is classified by the level of neck lymph nodes. The affected side level II had the highest number of SLNs (173) and metastatic LNs (18). Forty-nine nodes were assessed as metastatic in FS. Four metastatic LNs were found on the healthy side. The positive metastasis rate in FS was 11.7%. The positive metastasis rate was 3.8% for SLN4 and 9.5% for SLN5. However, the four positive cases in SLN4 and SLN5 also had positive LNs in SLN1-3. In the rapid pathological assessments of FS, similar results were obtained from evaluating up to 3 or 8 SLNs when discriminating between SLN-positive and SLN-negative cases. Table 3 shows the number of positive metastases from HE/CK staining of SLNs. Among the 416 SLNs stained with HE/CK, 67 were evaluated as metastatic. Most of them were located on the affected side level II (30 SLNs). Four metastatic LNs were found on the healthy side. The positive metastasis rate in HE/CK staining was 16.1%.

Table 1
Demographic and clinical characteristics of patients

	SLNB (n = 132) No. (%)
Age Median (range) years	63 (21–90)
Sex	
Male	88 (66.7)
Female	44 (33.3)
Site of primary tumor	
Tongue	108 (81.8)
Oral floor	13 (9.8)
Mandibular gingiva	7 (5.3)
Buccal mucosa	4 (3.0)
Clinical T classification	
T1 (DOI ≧ 4 mm)	26 (19.7)
T2	106 (80.3)
Surgical approach and Extent of resection	
Transoral	109 (82.6)
Pull-through	23 (17.4)
Neck Dissection	
None	79 (59.8)
Unilateral	48(36.4)
Bilateral	5 (3.8)
Pathological T classification	
Tis	1 (0.8)
T1	53 (40.2)
T2	69 (52.3)
T3	6 (4.5)
T4a	3 (2.3)
Pathological N classification	
N0	86 (65.2)
N1	22 (16.7)

Clinical T, Pathological T, Pathological N classification: According to UICC TNM classification 7th edition,

CRT: Chemoradiotherapy, DOI: Depth of invasion, RT: Radiotherapy, SLNB: Sentinel lymph node biopsy

	SLNB (n = 132) No. (%)
N2	21 (15.9)
Nx	3 (2.3)
Postoperative therapy	
None	128 (97.0)
RT/CRT	4 (3.0)
Recurrence	
None	105 (79.5)
Locoregional recurrence	25 (18.9)
Distant metastasis	2 (1.5)
Clinical T, Pathological T, Pathological N classification: According to UICC TNM classification 7th edition,	
CRT: Chemoradiotherapy, DOI: Depth of invasion, RT: Radiotherapy, SLNB: Sentinel lymph node biopsy	

Table 2
Number of positive nodes and SLN by the site in frozen specimens

	i-Ⅱa	i-Ⅱb	i-Ⅲ	i-Ⅳ	i-Ⅴ	i-Ⅵ	c-Ⅱ-Ⅳ	Miss	Total	Positive (%)
SLN1	1/7	5/38	7/62	3/14	1/2	1/1	1/6	0/2	19/132	14.4
SLN2	0/6	5/20	6/55	6/30	0/2	0/1	2/5	0/2	19/121	15.7
SLN3	0/1	0/9	5/34	1/24	0/10		1/8		7/86	8.1
SLN4	1/3	0/12	0/15	1/14	0/5		0/3		2/52	3.8
SLN5	0/1	1/3	0/6	1/5	0/1		0/3	0/2	2/21	9.5
SLN6-8	0/1	0/1	0/1					0/3	0/6	0.0
Total	2/19	11/83	18/173	12/87	1/20	1/2	4/25	0/9	49/418	11.7
Positive (%)	10.5	13.2	10.4	13.8	5.0	50.0	16.0	0.0	11.7	
c: contralateral, i: ipsilateral, Miss: missing data, SLN: Sentinel lymph node										

Table 3
Number of positive nodes and SLN by the site in HE/CK staining

	i-Ⅱa	i-Ⅱb	i-Ⅲ	i-Ⅳ	i-Ⅴ	i-Ⅵ	c-Ⅱ-Ⅳ	Miss	Total	Positive (%)
SLN1	1/7	8/38	10/61	4/14	1/2	1/1	1/6	1/2	27/131	20.6
SLN2	0/6	5/20	11/54	7/30	0/2	0/1	2/5	0/2	25/120	20.8
SLN3	0/1	0/9	7/34	1/24	0/10		1/8		9/86	10.5
SLN4	1/3	0/12	2/15	1/14	0/5		0/3		4/52	7.7
SLN5	0/1	1/3	0/6	1/5	0/1		0/3	0/2	2/21	9.5
SLN6-8	0/1	0/1	0/1					0/3	0/6	0.0
Total	2/19	14/83	30/173	14/87	1/20	1/2	4/25	1/9	67/416	16.1
Positive (%)	10.5	16.9	17.3	16.1	5.0	50.0	16.0	11.1	16.1	

c: contralateral, CK: Cytokeratin, HE: Hematoxylin-eosin, i: ipsilateral, Miss: missing data, SLN: Sentinel lymph node

Kaplan–Meier curves of OS and DFS

Figure 2 shows Kaplan–Meier curves of OS and DFS according to the size of the largest metastatic sentinel lymph node. Patients with no metastasis and ITC had better OS and DFS compared to those with micro- or macro metastasis [3-year OS: 90.9% (95% CI, 82.6–95.3) for no metastasis vs 100% for ITC vs 75.0% (95% CI, 40.8–91.2) for micro metastasis vs 79.8% (95% CI, 58.1–91.1) for macro metastasis, p = 0.166; 3-year DFS: 83.5% (95% CI, 73.7–89.9) for no metastasis vs 83.3% (95% CI, 27.3–97.5) for ITC vs 66.7% (95% CI, 33.7–86.0) for micro metastasis vs 67.8% (95% CI, 45.7–82.4) for macro metastasis, p = 0.174]. Figure 3 shows Kaplan–Meier curves of OS and DFS according to the number of metastatic sentinel lymph nodes. Patients with no metastasis had better OS and DFS compared to those with 1 or more than 2 metastases [3-year OS: 90.9% (95% CI, 82.6–95.3) for no metastasis vs 84.0% (95% CI, 62.8–93.7) for 1 metastasis vs 77.8% (95% CI, 51.1–91.0) for more than 2 metastases, p = 0.246; 3-year DFS: 83.5% (95% CI, 73.7–89.9) for no metastasis vs 76.3% (95% CI, 54.6–88.6) for 1 metastasis vs 60.6% (95% CI, 34.6–79.0) for more than 2 metastases, p = 0.068].

Prognostic impact of size and number of metastatic SLNs

Table 4 shows the results of the Cox proportional hazard models. In the univariate analysis, DFS was significantly lower in cases with ≥ 2 metastases than those with no metastases (HR = 2.79, p = 0.027). In the multivariate analysis, both OS and DFS were significantly lower in cases with macrometastasis (OS: HR = 4.85, p = 0.016 and DFS: HR = 2.94, p = 0.023, respectively) and ≥ 2 metastases (OS: HR = 3.63, p = 0.046 and DFS: HR = 2.97, p = 0.021, respectively), respectively compared to those with no metastases. Additionally, a significant interaction between size and number of metastatic SLNs on OS and DFS was not found (Supplementary Table S1).

Table 4
Cox proportional hazard models of the relationship between the size of the largest metastatic sentinel lymph node and the number of metastases with overall survival and disease-free survival, corrected for age, sex, primary lesion, resection method, and pathological T classification

		Univariate analysis						Multivariate analysis					
		Overall survival			Disease-free survival			Overall survival			Disease-free survival		
	n	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Size													
No metastasis	88	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
ITC	6	NE	-	-	1.00	0.13–7.64	0.996	NE	-	-	0.92	0.11–7.41	0.936
Micro	13	3.07	0.81–11.59	0.097	2.18	0.72–6.62	0.170	4.47	1.06–18.91	0.042	2.22	0.71–6.92	0.171
Macro	25	2.33	0.76–7.11	0.139	2.38	1.00–5.67	0.051	4.85	1.34–17.60	0.016	2.94	1.16–7.44	0.023
Number													
0	88	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
1	26	1.87	0.56–6.23	0.305	1.63	0.63–4.24	0.318	1.53	0.44–5.37	0.507	1.78	0.66–4.82	0.257
≥ 2	18	2.56	0.77–8.49	0.125	2.79	1.12–6.91	0.027	3.63	1.02–12.89	0.046	2.97	1.18–7.51	0.021
*Adjustment by age, sex, primary site, resection method, and pathological T classification													
CI: confidence interval, HR: hazard ratio, ITC: isolated tumor cell, Macro: macrometastasis, Micro: micrometastasis, NE: not evaluated													

Metastatic SLN size (ITC, micrometastasis, macrometastasis) assessed with FS (n = 418) and HE/CK staining (n = 416)

Positive SLNB metastases were found in 49/418 (11.7%) in FS and 67/416 (16.1%) in HE/CK staining. Table 5 shows the number and rate of positive SLNs in FS and HE/CK staining for ITC, micrometastasis, and macrometastasis. The detection rate of ITC was significantly higher with HE/CK staining than with FS (p = 0.020). However, the detection rate of macrometastasis was almost the same for HE/CK staining and FS.

Table 5
Frozen specimen and HE/CK staining results for isolated tumor cells, micrometastasis, and macrometastasis per sentinel lymph node

	Frozen section (n = 418)	HE/CK stain (n = 416)	Chi-Square Test
Isolated tumor cells (%)	**2 (0.5)**	**10 (2.4)**	p **= 0.020**
Micrometastasis (%)	**13 (3.1)**	**23 (5.5)**	p **= 0.086**
Macrometastasis (%)	**34 (8.1)**	**34 (8.2)**	p **= 0.984**
CK: Cytokeratin, HE: Hematoxylin-eosin			

Discussion

The first SLNB for oral cancer was reported in 1996 [7]. SLNB aims to reduce complications from unnecessary ND by identifying cases in which this procedure can be omitted. A review by de Bree et al. [8] described studies demonstrating the efficacy of SLNB, which included fewer complications, less cervical, and shoulder dysfunction, lower costs, and shorter hospital stays in SLNB groups compared to those in the END groups. They concluded that SLNB is a better option than END for OCSCC, excluding floor of mouth cancer, which is prone to the "shine-through" phenomenon. In our phase III trial, postoperative neck function was better in the SLNB group [2]. The present subgroup analysis showed that having larger macrometastases and ≥ 2 metastases are associated with poorer prognosis in both OS and DFS. Considering this, we suggest that the case criteria for SLNB can be further defined.

A relationship between ITC and lower survival rates has been reported for breast cancer [9, 10]. During the planning of this study, the clinical significance of ITC in head and neck cancer was unclear. An association between ITC and prognosis was later reported in head and neck cancer as well [11–13]. Broglie et al. [11] found that 38% of 111 patients with early oral and oropharyngeal squamous cell carcinoma were positive for SLN metastasis, and 20% had ITC. Moreover, they reported that the disease-specific survival rate was significantly lower in the ITC-positive group than in the SLN-negative group. The SENT trial [12] reported statistically significant differences in survival between ITC, micrometastasis, and macrometastasis in early-stage OCSCC. Pedersen et al. [13] also reported that in OCSCC, disease-specific survival was lower in patients with ITC or micrometastasis than in SLN-negative cases. These reports [11–13] suggest that in patients with OCSCC, OS differs between patients with SLN metastasis negative, ITC, micrometastases, and macrometastases, although the magnitude of the differences varied between studies. In our analysis, OS and DFS studies did not reveal significant differences, although a trend was observed. Moreover, the multivariate Cox regression analysis showed a significantly poorer prognosis in the macrometastasis group than in the no-metastasis group for both OS and DFS. However, there was no difference in prognosis between the ITC and no-metastasis groups. The French Senti-MERORL trial [14] is a multicenter, randomized, open-label prospective equivalence study on SLNB vs. END. This trial showed that patients with ITCs had a better OS than the patients with micro and macro metastasis. A global consensus has not been reached on the relationship between ITC and prognosis. Therefore, further research is needed on the relationship between ITC and survival rates. Meanwhile, for the relationship between the number of metastases and survival rate, we compared 3 groups—no metastases, 1 metastasis, ≥ 2 metastases—and found that prognosis was significantly associated with the number of metastases, which is similar to the results of the SENT trial [12]. Thus, OS and DFS were significantly poorer in patients with ≥ 2 metastases in both the univariate and multivariate analyses.

Chone et al. [15] reported that it is useful to add immunostaining to the assessments of SLNs. In their study, CK staining was performed on negative SLNs in HE staining, which additionally identified metastatic SLNs in 3.8% of the samples. They concluded that CK and other types of immunostaining are important tools for reducing false-negative results. In the present study, 390 SLNs underwent CK staining. The positive rate of ITC was significantly higher with HE/CK staining than with FS ($p = 0.020$). Consequently, ITC should be evaluated perioperatively with FS and postoperatively with HE/CK staining. In contrast, the positive rate for macrometastasis was similar between FS and HE/CK staining (8.1% and 8.2%, respectively). This indicates that for relatively large lesions (≥ 2 mm), which were evaluated as negative during surgery, the probability of a diagnosis changing to metastasis in postoperative HE/CK staining is low. Based on this, the clinical question should be, "Should additional ND be performed when ITC is positive in postoperative HE/CK staining?" In the French Senti-MERORL trial [14], neck node and locoregional recurrence rates were not different in the ITC group compared to those of the no-metastasis group. Therefore, it suggested that ITC does not seem to require ND. Den Toom et al. [16] reported that metastases to non-SLN were found in 31% of SLN-positive cases. Metastasis to non-SLN was observed in 13% of ITC, 20% of micrometastasis, and 40% of macrometastasis. Their report concludes that it is important to classify ITC, micrometastasis, and macrometastasis. In the future, a randomized controlled trial with an additional ND group and a follow-up group should be performed to examine patients with positive ITC identified after surgery.

This subgroup analysis was based on data from a multicenter, randomized controlled phase III trial of 16 institutions in Japan, which provides a very high level of evidence. However, only 45 patients were SLN positive, and ITC was only found in 2.4% of the total number of SLNs, even when using HE/CK staining, which represents an insufficient number of cases to provide reliable evidence. The 2014 revision to the NCCN guidelines added SLNB to diagnose stage I/II oral cancer [17]. In Japan, SLNB is covered by health insurance for breast cancer and malignant melanoma. SLNB may be incorporated into standard treatment regimens once more evidence of early-stage oral cancer becomes available worldwide.

In conclusion, poor prognosis is a factor in patients with OCSCC receiving SLNB, including the presence of macrometastasis or having more than two metastases. The assessment of ITC in these patients requires assessing perioperative FS and performing postoperative HE/CK staining.

Methods

Patients

Patients were enrolled from November 2011 to January 2016. The inclusion criteria were T1-T2N0M0 OCSCC (UICC TNM classification 7th edition), no prior treatment, written consent, and ≥ 18 years old. The exclusion criteria were patients with T1 < 4 mm depth of invasion (DOI), history of radiation therapy to the neck, currently pregnant/breastfeeding or planning to conceive, or otherwise deemed ineligible by a physician. In the phase III trial, the patients were randomly assigned to an SLNB group (n = 134) or an END group (n = 137). This subgroup analysis targeted the 132 patients of the SLNB group who underwent SLNB (Table 1).

Sentinel lymph node (SLN) identification

Details are given in phase II [5] and phase III trial protocols [2]. 99mTc-phytate was used as the radiopharmaceutical. The day before surgery, a total of 1 mL 74 MBq (2mCi) 99mTc-phytate was evenly administered to four sites in the mucosa around the tumor using a 27G needle. Lymphoscintigraphy was performed 1–2 hours after administration. Whenever possible, single-photon emission computed tomography (SPECT) was performed to create fusion SPECT and CT images. A gamma probe was used to search for SLNs while referencing the lymphoscintigraphy results on the day of surgery.

Histopathologic diagnosis of SLNs

Details are given in phase II [5] and phase III trial protocols [2]. The SLN analysis was performed in two stages. First, 2-mm blocks were created as rapid intraoperative frozen specimens (FS). These blocks were embedded in paraffin, and two 4-μm slices were prepared from each of the block's cut surfaces, which underwent hematoxylin-eosin (HE) and cytokeratin (CK) staining. CK immunostaining was performed using an anti-CK primary antibody (AE1/3; Signet Laboratories, Dedham, MA) and streptavidin-biotin labeling. Metastatic LN size was classified into three groups [6]: ITC (size < 0.2 mm), micrometastasis (size ≥ 0.2 mm and < 2 mm), and macrometastasis (size ≥ 2 mm). In this study, ITC was considered positive for metastasis to avoid disadvantaging the subjects.

Rapid intraoperative diagnosis of FS of SLNs and postoperative response

SLN detection, SLN resection, and intraoperative pathological diagnosis of FS were performed. In patients with metastatic SLNs, neck dissection (ND) was performed in one stage, either level I-IV or I-V. If there were no metastatic SLNs in the intraoperative pathological diagnosis of the FS, only SLNB was performed. Moreover, supraomohyoid neck dissection (level I-III) was performed in cases requiring pull-through resection of the primary tumor. When the intraoperative pathological

diagnosis of the FS indicated no metastasis and postoperative HE or CK staining did, ND was performed in two stages within 6 weeks of the initial surgery.

Postoperative adjuvant treatment

In patients with extranodal invasion of metastatic LNs, chemoradiation (radiation therapy) was given as adjuvant therapy within 6 weeks of surgery. Whether to administer chemotherapy was left to the discretion of each institution. In patients with positive resection margins, reoperation, chemoradiation, or radiotherapy was performed at the institution's discretion.

Size and number of metastatic SLNs

The largest metastatic SLNs were categorized into four groups and analyzed: no metastasis, ITC, micrometastasis, and macrometastasis. The number of metastases was classified into three groups: no metastasis, 1 metastasis, and ≥ 2 metastases. The differences in the assessments of metastatic SLN size between FS and HE/CK staining were also investigated. Positive rates of ITC, micrometastasis, and macrometastasis were compared between FS and HE/CK staining. FS and HE/CK staining were evaluated for the SLNB. We also evaluated the largest metastatic SLN and number of metastases in HE/CK staining.

Statistical analysis

The primary endpoint of this study was OS, defined as the interval between the date of SLNB and the date of death from any cause or last follow-up date. The secondary endpoint was DFS (defined as the interval between the date of SLNB and the date of diagnosis of recurrence). Patients who were not followed up were treated as censored. Kaplan–Meier product-limit method and univariate and multivariate Cox proportional hazards models were performed to evaluate the prognostic impact of the size and number of metastatic SLNs. The measure of association in this study was hazard ratio (HR) with a 95% confidence interval (CI). Confounding variables considered in multivariate analyses were age (≤ 63 vs. >63 years), sex (male vs. female), primary site (tongue vs. other), resection method (transoral vs. pull-through), and pathological T classification (CIS or 1 vs. 2 vs. 3 or 4a). All statistical analyses were performed using STATA version 16 (Stata Corp., College Station, TX, USA). All tests were two-sided, and values of $P < .05$ were considered statistically significant.

Study design and ethics

This study was a subgroup analysis of a multicenter, randomized controlled phase III trial [2] involving 16 institutions in Japan. This phase III trial was registered with the UMIN Clinical Trials Registry (UMIN000006510) in November 2011. The clinical trial was approved by the ethics committees in each institution and performed under the safety and efficacy evaluation committee's oversight. 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; 2) Fukushima Medical University Hospital; 3) Graduate School of Medical Science, Kanazawa University; 4) Saitama Medical University International Medical Center; 5) Gunma University Hospital; 6) National Defense Medical College; 7) National Cancer Center Hospital East; 8) International University of Health and Welfare Mita Hospital; 9) Juntendo University Hospital; 10) National Cancer Center Hospital; 11) Tokyo Medical University; 12) Kyorin University School of Medicine; 13) Aichi Cancer Center Hospital and Research Institute; 14) Osaka International Cancer Institute; 15) Faculty of Medicine, Kyoto University; 16) Faculty of Medicine, University of the Ryukyus. The protocol adhered to the principles of the Declaration of Helsinki and all the participants provided written informed consent.

Declarations

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Author Contributions

TK, KT, DK, and YH contributed to the study concept and design, quality control of data and algorithms, data analysis and interpretation, and manuscript preparation and editing. DK was responsible for statistical analysis. All authors contributed to data acquisition, manuscript review, and final approval of the manuscript and are accountable for all aspects of the work.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1

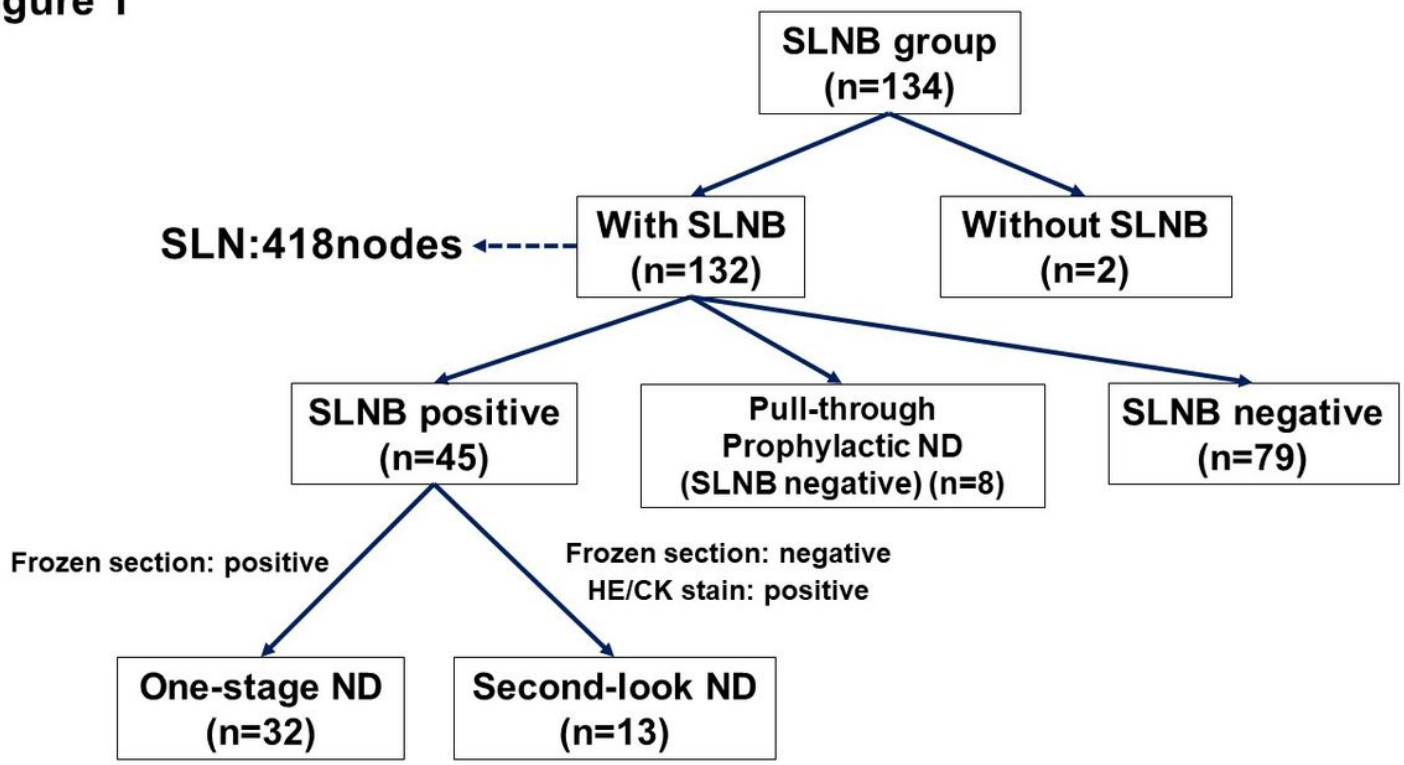

Figure 1

Flow diagram of the procedures in this study.

CK: Cytokeratin, HE: Hematoxylin-eosin, ND: Neck dissection, SLN: Sentinel lymph node, SLNB: Sentinel lymph node biopsy

Figure 2

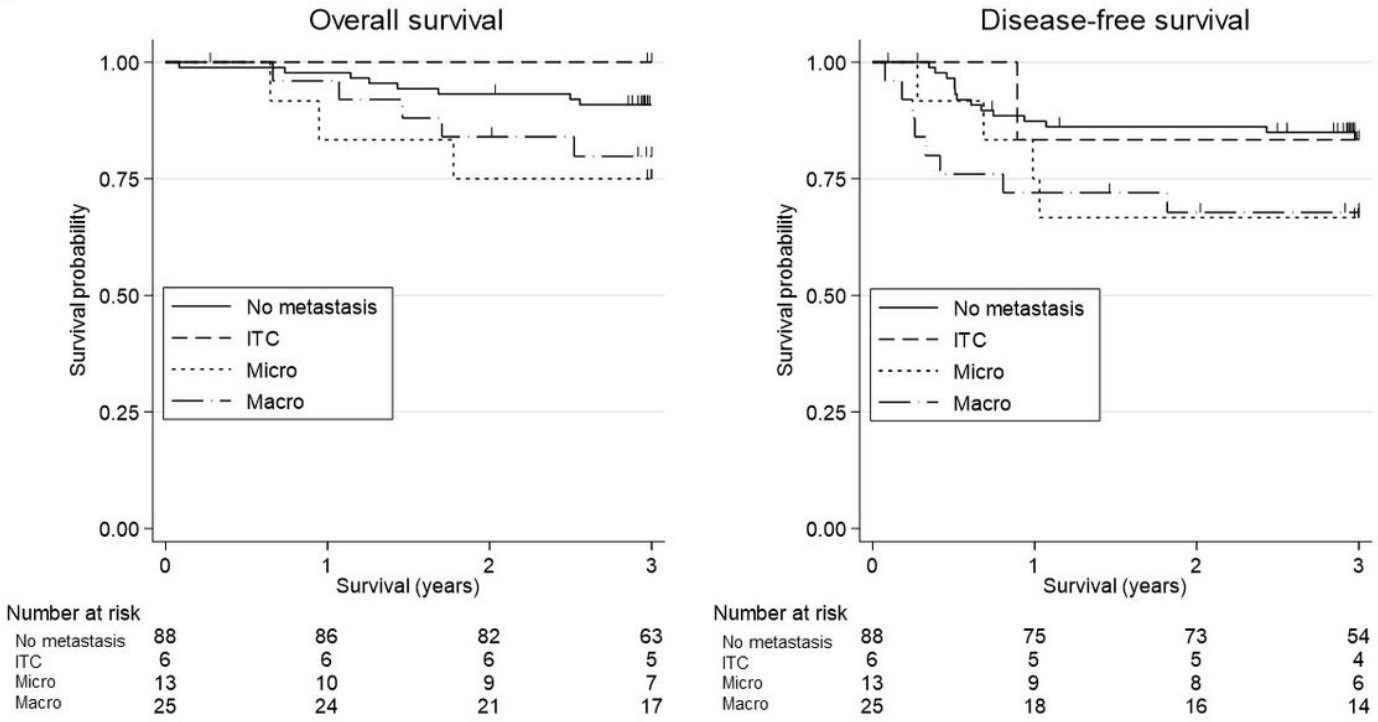

Figure 2

Kaplan–Meier curves of overall survival (OS) and disease-free survival (DFS) according to the size of the largest metastatic sentinel lymph node

Patients with no metastasis and isolated tumor cells (ITC) had better OS and DFS compared to those with micro- or macro metastasis [3-year OS: 90.9% (95% CI, 82.6–95.3) for no metastasis vs 100% for ITC vs 75.0% (95% CI, 40.8–91.2) for micro metastasis vs 79.8% (95% CI, 58.1–91.1) for macro metastasis, p= 0.166; 3-year DFS: 83.5% (95% CI, 73.7–89.9) for no metastasis vs 83.3% (95% CI, 27.3–97.5) for ITC vs 66.7% (95% CI, 33.7–86.0) for micro metastasis vs 67.8% (95% CI, 45.7–82.4) for macro metastasis, p= 0.174].

ITC: isolated tumor cell, Macro: macrometastasis, Micro: micrometastasis

Figure 3

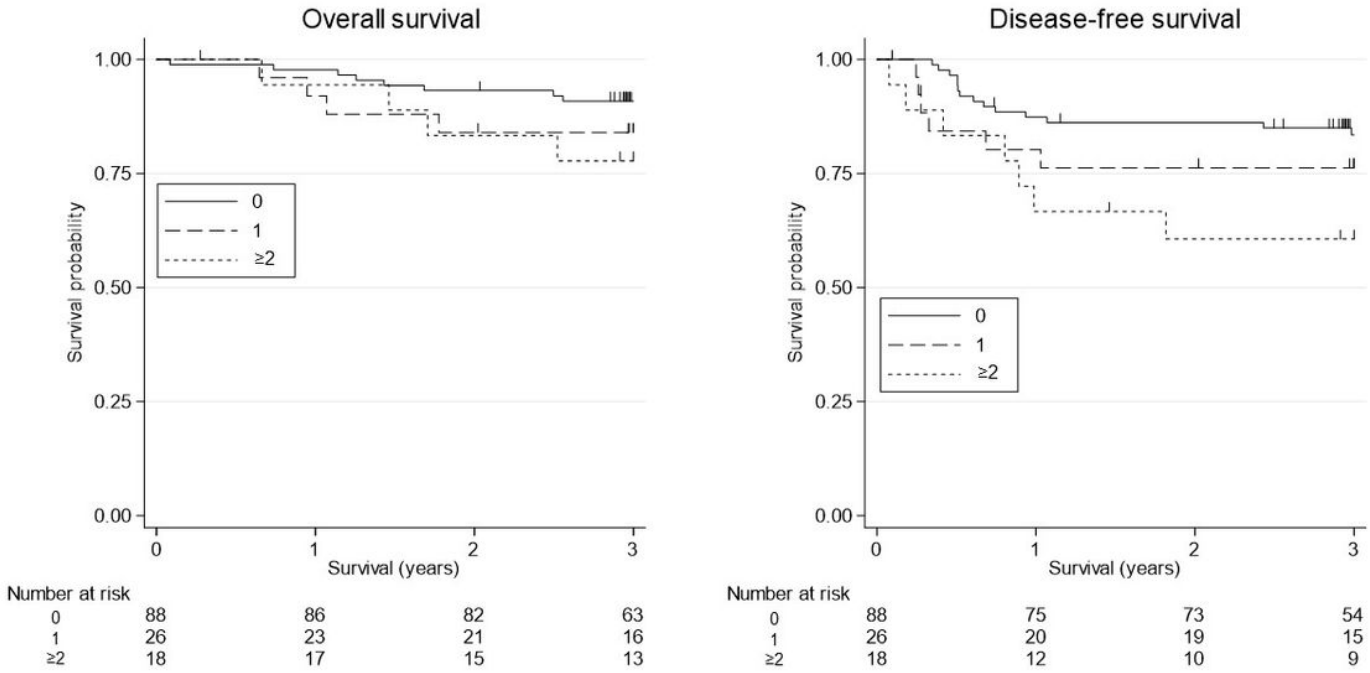

Figure 3

Kaplan–Meier curves of overall survival (OS) and disease-free survival (DFS) according to the number of metastatic sentinel lymph node

Patients with no metastasis had better OS and DFS compared to those with 1 or more than 2 metastases [3-year OS: 90.9% (95% CI, 82.6–95.3) for no metastasis vs 84.0% (95% CI, 62.8–93.7) for 1 metastasis vs 77.8% (95% CI, 51.1–91.0) for more than 2 metastases, p= 0.246; 3-year DFS: 83.5% (95% CI, 73.7–89.9). For no metastasis vs 76.3% (95% CI, 54.6–88.6) for 1 metastasis vs 60.6% (95% CI, 34.6–79.0) for more than 2 metastases, p= 0.068].

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx