Title: Sentinel Node Biopsy for High-Risk Cutaneous Squamous Cell Carcinoma

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Abstract

Aim: The use of sentinel node biopsy (SNB) has not been established for cutaneous squamous cell carcinoma (SCC), and its clinical significance has not been clarified. We investigated the usefulness of and indication criteria for SNB for cutaneous SCC.

Materials and Methods: Twenty-six patients with high-risk cutaneous SCC that had undergone SNB were retrospectively reviewed. SNB was performed with either the dye method or a combined dye and radioisotope method.

Results: Of the 26 patients, recurrence or metastasis was observed in 5 cases (19.2%). Six cases (23.1%) were sentinel node (SN) metastasis-positive. All cases that were SN metastasis-negative survived, and 4 of 6 SN metastasis-positive (66.7%) cases died of the original disease. The 3-year survival rates of all cases, SN metastasis-negative cases, and SN metastasis-positive cases were 82.2%, 100%, and 20.8%, respectively. Tumour thickness was a significant risk factor for SN metastasis ($p = 0.049$). Recurrence occurred in 4 of 7 cases involving external genitalia, 3 of which died. The 3-year survival rates of external genitalia and nongenital cases were 47.6% and 94.1%, respectively ($p = 0.016$).

Conclusions: SNB aided the early discovery and treatment of latent lymph node metastasis and helped predict whether SN metastasis had occurred, and therefore helped predict patient prognosis. These results suggest that thickness of the primary lesion is an indication criterion for the use of SNB in cases of cutaneous SCC. SNB should be considered in cases where tumour thickness is ≥2 mm and actively performed in cases ≥ 5 mm.

Keywords: Squamous cell carcinoma, high-Risk SCC, sentinel node biopsy, regional lymph node metastasis

Introduction

Squamous cell carcinoma (SCC) is the second-most common skin cancer in the world, and the incidence of occurrence is rising [1–3]. The 5-year survival rates of SCC patients in the United States and Europe are 90% or higher, and metastasis occurs after treatment of the primary lesion in only 1–5% of cases [4–6]. Therefore, SCC is commonly considered a malignant tumour with a relatively good prognosis. However, patient and tumour risk factors that lead to multiple recurrences or metastases have been identified in a subset of patients, and the metastasis rate in this subgroup of high-risk SCC patients is remarkably high [6–10]. Most SCC metastases are lymphogenous, and regional lymph node metastasis occurs before distal metastasis in 80–85% of cases [1, 11–13]. As the 5-year survival rate of this high-risk SCC group is 26–34%, establishing appropriate detection and treatment strategies for SCC patients with lymph node metastasis is urgently needed to improve treatment results [6, 14]. The use of sentinel node biopsy (SNB) in cutaneous SCC should be considered and the indications for its use determined.

At present, the use of SNB has been established for melanoma and breast cancer. In melanoma, the presence of sentinel node (SN) metastasis is an important prognostic factor, and performing immediate regional lymph node dissection (RLND) based on the results of SNB is linked to improved prognosis [15]. Although small feasibility studies have been performed on the use of SNB in SCC in the West, the validity and significance of SNB for SCC are still in dispute [14, 16–18]. Past reports have not determined whether the use of SNB increases survival rates in patients with SCC, and there are currently no uniform guidelines for the usage of SNB.

The objective of this study was to investigate the usefulness of and determine the indication criteria for SNB in cases of cutaneous SCC, with the goal of establishing SNB as a useful technique for proper treatment of cutaneous SCC.

Materials and Methods

Patients

The records of 26 patients, who were diagnosed with high-risk cutaneous SCC and underwent SNB at our

hospital from July 2005 to April 2012, were retrospectively analysed. Inclusion criteria for the high-risk cutaneous SCC group included invasive carcinoma and at least 1 risk factor for recurrence (size greater ≥ 20 mm on the trunk or extremities; size ≥ 10 mm on the head; size ≥ 6 mm on the face, genitalia, hands, or feet; poorly defined borders; recurrent lesion; immunosuppression; site of prior radiotherapy or chronic inflammatory process; rapidly growing; or neurologic symptoms) as established in the clinical findings of the National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2012. Cases diagnosed as SCC in situ clinically or in preoperative biopsy, cases with clear regional lymph node metastasis found in careful preoperative exams, and cases with distal metastasis were excluded. All patients were fully informed regarding the use of SNB, and the procedure was performed only after obtaining their consent.

Dye method

Two percent Patent blue V dye was intradermally injected at a total volume of 1–2 mL at approximately 10 sites around the primary tumour site. After approximately 15 minutes, the skin was incised, and the lymphatic vessels in the regional lymphatic basin that had stained blue were traced. Lymph nodes that had stained blue were identified as SNs and removed.

Dye and radioisotope method

^{99m}Tc-phytate was intradermally injected at a total volume of 0.4 mL (100 MBq) at 4 sites around the primary tumour 1 day before surgery. Lymphoscintigraphy was performed both immediately and 3 hours after injection. The skin was marked with a pen using a gamma probe directly above the SN, and the dye was injected around the primary lesion 15 min before biopsy. The skin was incised directly over the SN, and using a gamma probe to trace the stained lymphatic vessels, blue-stained SNs were confirmed and removed. When radioactivity was identified as coming from multiple lymph nodes, all lymph nodes showing a count number of at least 10% of the hottest node were considered SNs. Dye-stained nodes or radioactive-positive nodes were considered as SNs and removed.

SNB

In cases 1–6 and 10, only the dye method was used. In cases 7–9, the dye and radioisotope method was used. All SNB procedures were conducted by A. Takahashi.

Pathological evaluation

In cases 1–9, 14, and 16, metastasis in the identified SN was first confirmed through a rapid, perioperative pathological exam, after which the diagnosis of metastasis was confirmed by a permanent tissue preparation using HE stain. In all other cases, the presence of metastasis was confirmed by a permanent preparation using HE stain alone.

Statistical processing

PASW Statistics 18 was used for statistical processing. Survival curves were analysed with the log-rank test using the Kaplan-Meier method. Risk factors for SN metastasis were examined using logistic regression analysis and the chi-squared test. A p-value of < 0.05 was considered as statistically significant.

Results

Detailed summaries of the tumour and patient characteristics are given in Table 1. The mean age of the patients (11 men, 15 women) receiving SNB was 70.5 years (range: 47–88 years). Primary lesions were located on the head and neck in 5 cases, on an upper extremity in 5 cases, on a lower extremity in 7 cases, on the trunk in 2 cases, and on the external genitalia in 7 cases. The mean tumour size was 4.1 cm (range: 1.5–10 cm), and the mean tumour thickness was 6.7 mm (median: 4.7 mm, range: 0.9–24.8 mm). Nineteen cases were considered well-differentiated, 5 cases were moderately-differentiated, and 2 cases were poorly-differentiated. SN were identified in all cases (average per case: 2.6): 5 in the cervical area (1 case also included a SN in the parotid area), 6 in the axilla, and 15 in the inguinal area (5 cases were bilateral, 1 case also included a SN in the popliteal area). Overall, 6 patients were SN-metastasis positive (23.1%), of which the primary lesion was on the external genitalia in 3 cases (No. 3, 8, 14), on an upper extremity in 2 cases (No. 5, 25), and on a lower extremity in 1 case (No. 10). RLND was performed in 6 cases in total. Of the 6, 5 were SN positive, and 1 was negative (case

4). One patient with positive SN (case 8) decided not to undergo lymph node dissection. The SN-negative patient (case 4) opted for RLND.

The mean follow-up period was 35.5 months (range: 10–91 months). During this observational period, 5 of the 26 cases (19.2%) experienced recurrence or metastasis. Among the cases without SN metastasis, all patients survived throughout the observational period, with only 1 patient (case 23) experiencing local recurrence and no cases experiencing regional lymph node metastasis or distal metastasis. Of the 6 cases in which SN metastasis was observed, 4 cases (66.7%) died due to distal metastasis. The overall mortality rate was 15.4% (4/26). The overall 3-year survival rate was 82.2% (Fig. 1). The 3-year survival rates of the SN metastasis-negative and positive cases were 100% and 20.8%, respectively (Fig. 2).

We investigated 5 potential risk factors for SN metastasis by logistic regression analysis: age, primary tumour site (external genitalia or nongenital), degree of differentiation, tumour size, and tumour thickness. The average ages of the SN-negative and SN-positive cases were 69.5 and 74.0 years, respectively. Three of the 7 external genitalia cases (42.9%) and 3 of the 19 nongenital cases (15.8%) were SN-positive. Three of the 19 well-differentiated cases (15.8%) and 3 of the 7 moderately and poorly differentiated cases (42.9%) were SN-metastasis positive. The average tumour size in the SN-negative and SN-positive cases was 3.9 and 4.8 cm, respectively. The average tumour thickness in the SN-negative and SN-positive cases was 5.5 and 10.8 cm, respectively. Of the 5 potential risk factors for SN metastasis investigated, a significant difference ($p = 0.049$) was only observed for tumour thickness. Metastasis did not occur in the 3 cases with tumour thickness < 2 mm, occurred in 1 of the 12 cases (8.3%) with tumour thickness 2–5 mm, and occurred in 5 of the 11 cases (45.5%) with tumour thickness ≥ 5 mm (Table 2). Further, the risk of SN metastasis was significantly higher when tumour thickness was ≥ 5 mm, compared to when it was 2–5 mm ($p = 0.043$).

Of the 7 external genital cases, recurrence occurred in 4 cases (57.1%), and 3 cases died (42.9%). In contrast, recurrence occurred in 1 of the 19 nongenital cases (5.3%) and 1 case died (5.3%). The 3-year survival rates for external genital and nongenital cases was 47.6% and 94.1% ($p = 0.016$), respectively (Fig. 3).

Discussion

Metastasis has been reported to occur in 11.0–47.3% of high-risk SCC patients [14]. In most of these cases, regional lymph node metastasis occurs before distal metastasis. Early discovery of latent lymph node metastasis by SNB followed by appropriate treatment is considered necessary to increase the 5-year survival rate of SCC patients with lymph node metastasis, which is currently 26–34% [6, 14]. However, SNB has not been established for use in the treatment of cutaneous SCC, and its clinical significance remains unclear. The purpose of our study was to examine the usefulness of and determine the indication criteria for SNB in cases of cutaneous SCC.

The current SN-metastasis positive rate in high-risk SCC patients has been reported to be 4.5–28.0% [19–21], with a false-negative rate of 0.0–15.4% [22, 23]. Our study found 6 of 26 cases (23.1%) to be SN-metastasis positive, which is within the range of past reports. No instances of regional lymph node metastasis occurred in the cases deemed SN-metastasis negative during the observational period in our study. This 0% false-negative rate shows that SNB for cutaneous SCC is highly reliable.

Demri et al. examined 19 cases of cutaneous SCC that were SN-metastasis negative [22]. Excluding 5 cases that died of other diseases during the observational period, the remaining 14 cases survived and did not experience regional lymph node or distal metastasis. Further, Reschly et al. reported that 5 cases of SN-metastasis negative cutaneous SCC survived without recurrence or metastasis and that 2 of 4 SN-metastasis positive cases (50%) died of the disease [14]. In our study, all cases that were SN-metastasis negative survived and had a 3-year survival rate of 100%. However, of the 6 cases that were SN-metastasis positive, 4 (66.7%) died of the disease, and this group had a 3-year survival rate of 20.8%. This clear difference in prognosis due to SN metastasis suggested that SNB could help predict patient prognosis.

Our examination of risk factor criteria to warrant the use of SNB suggested that tumour thickness was a risk factor for SN metastasis. Brantsch et al. analysed 615 cases of operable cutaneous SCC and found 0 cases of lymph node metastasis when the tumour thickness was $\leq$ 2.0 mm, a 4% metastasis rate (12/318) when the tumour thickness was 2.1–6.0 mm, and a 16% (14/90) metastasis rate when the tumour thickness was $\geq$ 6.0 mm [24]. Our study also examined the relationship between tumour thickness and SN metastasis. Metastasis did not

occur in cases where tumour thickness was < 2 mm (0/3 cases), occurred in 8.3% (2/13) of cases where tumour thickness was 2–5 mm, and occurred in 45.5% (5/11) of cases where tumour thickness was ≥ 5 mm. This suggests that a tumour thickness of ≥ 2 mm is risk factor for metastasis of cutaneous SCC, and high risk of SN-positive metastasis occurs when the tumour thickness is ≥ 5 mm. From this data, we consider SNB to be unnecessary when the tumour thickness is < 2 mm, but suggest that SNB be considered when the tumour thickness is ≥ 2 mm and actively performed when the tumour thickness ≥ 5 mm.

Although tumour thickness was the only risk factor to show a statistically significant difference between groups, 3 of the 7 cases that were moderately or poorly differentiated (42.9%) and 3 of the 7 cases involving the external genitalia (42.9%) experienced SN metastasis, which are relatively high rates. Also, the prognoses in cases involving the external genitalia were significantly poorer when compared to nongenital cases. The validity of SNB in vulvar cancer has been investigated in gynaecology. In an examination of methods used to diagnose lymph node metastasis that compared SNB using 99Tc with positron emission tomography, magnetic resonance imaging, ultrasonography, and blind needle biopsy, SNB was found to have the highest sensitivity [25, 26]. One study on the use of SNB for vulvar SCC reported that at T1/2, 127 of 403 cases (31.5%), with a tumour diameter ≤ 4 cm, were positive for metastasis and that 3.0% of the metastasis-negative cases experienced recurrence in the inguinal region [27]. Another report determined that, of 418 cases of vulvar SCC where the tumour diameter was 2–6 cm and had infiltration of 1 mm or more, 132 cases (31.6%) were SN metastasis-positive, with a 3.8% false-negative rate in metastasis-negative cases [28].

It has been reported that vulvar SCC has a high rate of SN metastasis, a low false-negative rate, and that SNB can alleviate complications, such as postoperative oedema [27–29], showing that SNB has reached a stage of clinical application for this disease. In this study, while consideration must be given to the fact that all 3 cases involving the external genitalia that were positive for SN metastasis had a tumour thickness of at least 10 mm, involvement of the external genitalia itself should be considered as a possible indication criterion for SNB.

Large-scale studies on the usefulness of and indication criteria for SNB in cutaneous SCC, similar to those that have been performed for melanoma, are needed to establish guidelines for using SNB in cutaneous SCC. In this study, we determined that tumour thickness was a risk factor that called for the use of SNB. Our study data

suggests that a positive SNB can be prognostic of lymph node metastasis. On the contrary, a negative SNB indicates that RLND can be delayed or avoided, and our data may suggest that a negative SNB indicates that the patient is disease-free. On the other hand, it is not yet known whether the survival rate of RLND after positive SNB is superior to that of RLND after clinical LN metastasis. This needs to be clarified by large randomized trial. Although a limitation of this study was the small sample size, we believe the results to be significant in the effort to establish SNB as a method of care for cutaneous SCC.

In conclusion, SNB aided the early discovery and treatment of latent lymph node metastasis and was helpful to predict whether SN metastasis had occurred and therefore helped predict patient prognosis. Although the scale of this study was small, our results suggest that tumour thickness of the primary lesion should be a selection criterion for using SNB in cases of cutaneous SCC. Currently, SNB is not part of the standard therapy for cutaneous SCC, and the clinical significance of this method remains unclear. Thus, the accumulation of cases and performance of precise scientific evaluations are needed to establish SNB as a standard treatment of care for cutaneous SCC. SNB should be considered in cases where tumour thickness is $\geq$ 2 mm and actively performed in cases where tumour thickness is $\geq$ 5 mm.

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Figure legends

Fig. 1 Overall survival of all patients.

Fig. 2 Overall survival according to nodal status (SN-metastasis positive or SN-metastasis negative)

Fig. 3 Overall survival according to primary site (external genital or nongenital)

Table 1. Patient characteristics

Patient No.	Age (years)	Sex	Size (cm)	Tumour Thickness (mm)	Degree of differentiation	Primary site	High Risk factors*	Basin	SNB finding	LND finding	Recurrence	Follow-up period (months)	Prognosis
1	69	F	3	4.2	WD	External genital	a	Inguinal	0/2			91	Alive
2	79	M	2.5	2.2	WD	Lower extremity	a	Inguinal	0/2			87	Alive
3	62	M	4	10.6	WD	External genital	a, b, e, f, g	Both Inguinal	3/3	1/9	DM	34	Dead
4	54	F	2	11.9	MD	Upper extremity	a, e, f	Axilla	0/2	0/24		75	Alive
5	76	F	2.3	5.5	MD	Upper extremity	a, g	Axilla	1/2	0/15	DM	18	Dead
6	59	F	4	5.2	WD	Lower extremity	a, b, e	Inguinal	0/1			69	Alive
7	53	M	3	9	WD	Upper extremity	a, d, f	Axilla	0/2			64	Alive
8	87	F	10	10.8	WD	External genital	a, b, f	Both Inguinal	2/3	NA	RM, DM	14	Dead
9	72	F	7	1.4	WD	Lower extremity	a, e	Inguinal/Popliteal	0/3			56	Alive
10	71	M	6.5	18.8	MD	Lower extremity	a, b, c, f	Inguinal	1/2	0/6		56	Alive
11	79	M	3.7	1.6	WD	Trunk	a	Axilla	0/2			54	Alive
12	77	F	4	2.1	WD	Upper extremity	a, b, e	Axilla	0/2			50	Alive
13	77	F	5	2.3	WD	Head and neck	a, b, e	Cervical/Parotid	0/4			47	Alive
14	77	F	1.5	17	WD	External genital	a, e	Both Inguinal	2/2	1/24	DM	15	Dead
15	47	M	3	4.5	WD	Head and neck	a, e, f	Cervical	0/6			45	Alive
16	72	F	2.5	0.9	PD	External genital	a	Both Inguinal	0/2			39	Alive
17	63	M	2.4	2.3	WD	Head and neck	a, f	Cervical	0/3			37	Alive
18	75	M	4	11.5	WD	Head and neck	a, f	Cervical	0/4			34	Alive
19	76	M	6	6.5	WD	Lower extremity	a, e	Inguinal	0/3			34	Alive
20	63	F	3	4.3	MD	External genital	a, b, e	Inguinal	0/2			32	Alive
21	60	F	5.6	24.8	WD	Trunk	a, f	Inguinal	0/3			22	Alive
22	76	M	2.2	4.8	WD	Lower extremity	a	Inguinal	0/2			19	Alive
23	79	F	6	3.2	MD	External genital	a, b	Both Inguinal	0/6		Local	20	Alive
24	72	F	1.8	2	WD	Head and neck	a	Cervical	0/2			31	Alive
25	71	M	4.5	2.2	PD	Upper extremity	a	Axilla	2/2	0/19		14	Alive
26	88	F	8	4.8	WD	Lower extremity	a, b, g	Inguinal	0/1			10	Alive

*a, size ≥ 20 mm (trunk/extremities), size ≥ 10 mm (head), size ≥ 6 mm (face, genitalia, hand/feet); b, poorly defined borders; d, immunosuppression; e, site of prior RT or chronic inflammatory process; f, rapidly growing; g, neurologic symptoms. WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; NA: not available; DM, distant metastasis; RM: regional lymph node metastasis; SNB, sentinel node biopsy; LND, lymph node dissection

Table 2.

Factors		SN-negative patients	SN-positive patients	P-value
Mean age (years)		69.5	74	0.174
Primary site	External genital	4 (57.1%)	3 (42.9%)	0.372
	Nongenital	16 (84.2%)	3 (15.8%)	
Degree of differentiation	WD	16 (84.2%)	3 (15.8%)	0.117
	MD or PD	4 (57.1%)	3 (42.9%)	
Size (mean)		3.9 cm	4.8 cm	0.784
Tumour thickness (mean)		5.5 mm	10.8 mm	0.049
	＜2 mm		0/3 (0%)	
	2–5 mm		1/12 (8.3%)	
	≥5 mm		5/11 (45.5%)	

SN, sentinel node; WD: well differentiated; MD, moderately differentiated; PD, poorly differentiated