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ORIGINAL ARTICLE

Role of sentinel lymph node biopsy in patients with Merkel cell carcinoma: statistical analysis of 403 reported cases

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Abstract
Background Merkel cell carcinoma (MCC) is a rare cutaneous malignancy with a high rate of nodal metastasis. Sentinel lymph node biopsy (SLNB) is used in MCC and other cancers to identify regional node micrometastases in patients with clinically negative nodes; however, whether SLN status is associated with recurrence or prognosis in MCC is unclear.
Methods A statistical analysis was performed of 397 published cases of MCC with SLNB results from 22 reports and 6 new cases, in order to elucidate any correlation between SLN status and recurrence, and to determine false-negative rates for SLNB.
Results Of these 403 cases, 128 (31.8 %) had positive SLNs; 16 of these 128 (12.5 %) developed recurrence (6 nodal, 10 distant). Of 275 patients with negative SLNs, 27 (9.8 %) developed recurrence (19 nodal, 8 distant). Patients with positive SLNs had a greater risk of distant metastasis (OR 2.82; $P = 0.037$; 95 % CI 1.089–7.347). The false-negative rate for SLNB in all 403 patients was 12.9 %. Use of the immunohistochemical approach to diagnosis of micrometastasis with anti-CK20 antibody did not affect the false-negative rate.
Conclusions Patients with positive SLNs had a greater risk of distant metastasis in MCC; positive SLN was an important prognostic factor in MCC. Further studies using standardized, more-sensitive techniques to examine entire SLNs may decrease the false-negative rate, and improve the significance of SLNB in MCC.

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Introduction

Merkel cell carcinoma (MCC) is a rare aggressive cutaneous malignancy with high rates of nodal and distant metastasis. Nodal metastasis is the more common, and clinical nodal metastasis is an unfavorable prognostic factor. However, in one report, more than 30 % of clinically negative regional lymph nodes were actually positive for microscopic metastasis [1]. Pathological assessments of regional lymph nodes in patients with MCC who have no clinically positive lymph node metastasis are therefore important.

Sentinel lymph node biopsy (SLNB) is a technique to find micrometastases in regional lymph nodes in patients with clinically negative nodes, used for various cancers such as malignant melanoma and breast cancer. Ideally, SLNB allows precise disease staging with minimal surgical intervention and helps to determine whether to perform complete lymph node dissection (CLND). Positive SLNs are a poor prognostic factor in cutaneous malignant melanoma [2]. In patients with MCC with clinically negative regional lymph nodes, SLNB is performed worldwide followed by wide local excision of primary tumors. Although several reports have investigated the correlation between SLN status and recurrence or prognosis in MCC, these studies were not large enough to draw definitive conclusions. With the addition of 6 new patients with MCC in our facility, we have summarized the available reported MCC cases with eligible SLNB results and statistically analyzed the detailed recurrence sites in patients with or without SLN metastases and determined the false-negative rate for SLNB in MCC.

Methods

From 2006 to 2011, six patients with clinically negative regional nodes in MCC each underwent SLNB at Fukuoka University Hospital, using a blue dye and radioisotope (RI) method. Tc^{99m} phytic acid was used as the radioisotope tracer; 2 % patent blue solution was used for blue dye. Examinations with H&E and immunohistochemistry with anti-CK20, anti-chromogranin and anti-synaptophysin antibodies were performed on all resected SLNs. Patients with positive SLNs underwent secondary CLND following radiation therapy (RT) to the region, whereas patients with negative SLN had no further regional treatment.

For the statistical analysis of reported cases, a literature search was performed in PubMed using the key terms "Merkel cell carcinoma" and "sentinel lymph node"; papers with definite methods and detailed recurrence data were included. Statistical analyses were performed with SPSS II for Windows. Fisher's exact test was used to determine statistical significance. $P < 0.05$ was defined as statistically significant.

Results

Patients in Fukuoka University Hospital

Of 6 patients, one (17 %) had positive SLN and five were negative (83 %). The patient who had positive SLN developed distant metastasis within 6 months, although he underwent CLND and RT. Two (40 %) of the five patients with negative SLN had recurrences. Of those two patients, one had nodal metastasis within 2 months (i.e., a false-negative case); the other had distant metastasis within a month. All 3 patients who developed recurrence died of the disease.

Statistical analysis of reported cases

A literature search yielded 23 reports published from 1997 to 2012. These reports described patients with clinically node-negative MCC who underwent SLNB using RI methods or combined blue dye and RI methods. A review by Gupta et al. [1], which consisted of their 30 patients and 92 other reported cases, was excluded as it did not state recurrence sites or recurrence rates in detail. A total of 403 cases from the remaining 22 reports, all of which included SLN status, recurrence, recurrence sites and methods of pathological examination, were used for the statistical analysis (Table 1) [3–24].

Of the 403 patients, 128 had positive SLN (31.8 %). Of these 128 patients, 16 had recurrences (12.5 %) of which 6 were nodal (4.7 %) and 10 were distant (7.8 %). In 275 patients who had negative SLN, however, 27 (9.8 %) developed recurrences, of which 19 (6.9 %) were nodal and 8 (2.9 %) were distant.

The status of SLN was neither associated with total recurrence (nodal + distant; OR 1.312; $P = 0.488$; 95 % CI 0.68–2.532) nor nodal recurrence (OR 0.633; $P = 0.508$; 95 % CI 0.258–1.701). Patients with positive SLN had a greater statistical risk of distant metastasis (OR 2.82; $P = 0.037$; 95 % CI 1.089–7.347; Table 2). Of 275 patients who had negative SLN, 19 developed nodal recurrence. The false-negative SLNBs were possibly caused by either incompletely removed SLN or false pathological diagnosis. The possible total false-negative rate [false-negative/(false-negative + true positive) = 19/(19 + 128)] was 12.9 %. Use of the immunohistochemical approach to diagnose micrometastasis with anti-CK20 antibody did not affect the false-negative rate. Of 19 false-negative cases, 18 were diagnosed using anti-CK20 antibody and 1 without anti-CK20 antibody, giving false-negative rates of 17.3 and 2.3 %, respectively. Diagnosis with ($n = 269$) or without ($n = 134$) anti-CK 20 antibody did not significantly change the positive SLN rate (31.9 vs. 31.3 %, respectively; Table 3).

Discussion

Compared with other skin malignancies, MCC has a high tendency to metastasize, especially in draining lymph nodes; 25 % of all MCC patients have clinical nodal metastasis. Clinical nodal metastasis is an unfavorable prognostic factor; the 5-year survival rate of patients with nodal metastasized MCC is <50 % [25]. Allen et al. [26] analyzed 251 MCC patients and found that patients with clinically negative nodes had a 5-year survival rate of 75 %, whereas patients with pathologically negative nodes had a 5-year survival rate of 97 % ($P = 0.009$). Gupta et al. [1] analyzed 122 patients with clinically negative nodes and found that 32 % had pathological metastatic nodal disease. In our statistical analysis of 403 cases, the SLN-positive rate was 31.8 %, similar to the results of Gupta et al. [1]. Therefore, it is clear that SLNB is useful at least for staging MCC. In malignant melanoma, SLN positivity has been shown to be a definite poor prognostic factor; furthermore, a randomized controlled study [29] has demonstrated that SLNB-positive patients with CLND afterwards showed a significantly better 5-year survival rate than those who did not undergo SLNB and CLND after clinical swelling of lymph nodes. From these studies, SLNB provides a better prognosis by finding micrometastases in draining lymph nodes at an earlier stage. On the other hand, it has not yet been clear whether SLN status is definitely associated with recurrence or prognosis in MCC.

Table 1 Summary of reported MCC cases with sentinel lymph node biopsies

n	SLN status	Number (%) of SLN+	CK20 to assess SLN	Recurrence	Recurrence site	False negative rate	Distant recurrence	Follow-up (median, months)
Messina et al. [3]								
12	SLN+	2 (16 %)	No	0				NS
	SLN−	10	No	0				10.5
Pfeifer et al. [4]								
1	SLN+	1 (100 %)	NS	0				NS
Ames et al. [5]								
7	SLN+	3 (43 %)	NS	1 (33 %)	Distant 1		1	
	SLN−	4	NS	0				11[a]
Hill et al. [6]								
18	SLN+	2 (11 %)	No	0				7
	SLN−	16	No	0				7
Sian et al. [7]								
2	SLN+	2 (100 %)	No	0				NS
Kurul et al. [8]								
1	SLN−	1	NS	0				6
Wasserberg et al. [9]								
3	SLN+	2 (67 %)	No	0				13
	SLN−	1	No	0				8
Zeitouni et al. [10]								
2	SLN+	1 (50 %)	NS	1 (100 %)	Nodal 1			16
	SLN−	1	Yes	0				16
Allen et al. [11]								
26	SLN+	5 (19 %)	Yes	0				14
	SLN−	21	Yes	0				19
Duker et al. [12]								
5	SLN+	4 (80 %)	Yes	0	NS 1			12
	SLN−	1	Yes	0				21
Rodrigues et al. [13]								
6	SLN+	3 (50 %)	No	1 (33 %)	Distant 1		1	
	SLN−	3	No	0	NS 1			20[a]
Mehrany et al. [14]								
60	SLN+	20 (33 %)	NS	2 (10 %)	Nodal 1, distant 1		1	12
	SLN−	40	NS	1 (3 %)	Distant		1	7.3
Su et al. [15]								
10	SLN+	4 (40 %)	Yes	0				19
	SLN−	6	Yes	0				19
Michl et al. [16]								
7	SLN+	4 (57 %)	NS	1 (25 %)	Distant 1		1	12
	SLN−	3	NS	0				12
Pan et al. [17]								
5	SLN−	5	NS	1 (20 %)	Nodal 1			14
Blom et al. [18]								
11	SLN+	2 (18 %)	NS	0				
	SLN−	9	NS	0				42[b]
Schmalbach et al. [19]								
10	SLN+	2	Yes	0				41
	SLN−	8	Yes	1 (13 %)	Nodal 1	33 %		30.5

Table 1 continued

n	SLN status	Number (%) of SLN+	CK20 to assess SLN	Recurrence	Recurrence site	False negative rate	Distant recurrence	Follow-up (median, months)
Maza et al. [20]								
23	SLN+	11 (49 %)	Yes	2 (18 %)	Nodal 1 distant 1		1	50
	SLN−	12	Yes	2 (33 %)	Nodal 2 in-transit 2	15 %		36
Ortin-Perez et al. [21]								
8	SLN+	3 (37 %)	Yes	0				60
	SLN−	5	Yes	0				48
Warner et al. [22]								
11	SLN+	3 (27 %)	Yes	2 (66 %)	Nodal 2			
	SLN−	8	Yes	3 (63 %)	Nodal 3 in-transit 2	50 %		16[a]
Fields et al. [23]								
153	SLN+	45 (29 %)	Yes	4 (9 %)	Nodal 1 distant 3		3	
	SLN−	108	Yes	15 (14 %)	Nodal 9 distant 6	17 %	6	41[b]
Howle et al. [24]								
16	SLN+	8 (50 %)	Yes	1 (12.5 %)	In-transit 1 intra+distant 1		1	12.5
	SLN−	8	Yes	2 (25 %)	Nodal 2	20 %		22
Shibayama et al. (this study)								
6	SLN+	1 (16.6 %)	Yes	1 (100 %)	Distant 1		1	6
	SLN−	5	Yes	2 (40 %)	Nodal 1 distant 1	50 %	1	12.8
Total								
403	SLN+	128 (31.8 %)		16/128 (12.5 %)			10 (7.8 %)	
	SLN−	275		27/275 (9.8 %)		12.9 %	8 (2.9 %)	

SLN sentinel lymph node, *CK20* cytokeratin20, *NS* not stated

[a] Median follow up period of all patients undergoing SLNB

[b] Maximum follow up period of all patients undergoing SLNB

Because patients with clinically negative regional nodes have a poorer prognosis than those who are pathologically negative, the most current AJCC staging system separates stages I and II into (A) and (B) subgroups, where (A) denotes a negative pathological node evaluation, and (B) a negative clinical node evaluation [25]. As this new staging was based on a report that did not describe recurrences or causes of death with detail [27], considering that when MCC occurs in elderly patients (who often die from other causes), assessing the direct impact of SLN status on prognosis in MCC patients can be difficult. Several reports have discussed the correlation between SLN status and recurrence or prognosis, but their conclusions offer little consensus. Two reports showed SLN status to be associated with recurrence or prognosis in MCC [1, 14]; whereas two other reports showed the opposite results [20, 23]. This is the first study to statistically analyze detailed recurrence sites in patients with SLN-positive or -negative MCC, and we showed that positive SLNs have a greater risk of distant metastasis (OR 2.82; $P = 0.037$; 95 % CI 1.089–7.347) suggesting that positive SLN is an unfavorable prognostic factor in MCC. Also, our analysis included cases who underwent additional treatment (CLND and/or RT) to a regional node after the results of positive SLN. Patients with a positive SLN tended to undergo additional treatment, while patients with a negative SLN generally did not. Therefore, our results may emphasize that when SLN are positive, the prognosis is worse even with additional treatment. Multivariate analysis could not be performed because there were not enough data available from published cases.

In addition, adjuvant chemotherapy may prevent distant metastasis in SLNB-positive patients since MCC is very sensitive to chemotherapy. Surprisingly, the nodal recurrence rate of SLN-negative patients was higher (6.9 %) than that of positive ones (4.7 %), although it was not statistically significant. Cases with nodal recurrence despite negative SLN (6.9 %) were presumably due to the remaining SLNs, which had not been removed for false pathologic diagnosis, and were therefore regarded as false negatives. False-negative rates of several original reports varied widely (15–50 %). The final false-negative rate was 12.9 % in our study and might reflect current status properly. The false-negative rate in our study was similar to that reported for malignant melanoma (5–20 %) [28–31]. However, the true false-negative rate in MCC may be

Table 2 Sentinel lymph node status and recurrence site

Status	*n*	Recurrence (%)	Statistics[a]	Nodal (%)	Statistics[a]	Distant (%)	Statistics[a]
SLN+	128	16 (12.5 %)	OR 1.312	6 (4.7 %)	OR 0.633	10 (7.8 %)	OR 2.82
SLN−	275	27 (9.8 %)	$P = 0.488$	19 (6.9 %)	$P = 0.508$	8 (2.9 %)	$P = 0.037$[b]
			95 % CI 0.68–2.532		95 % CI 0.258–1.701		95 % CI 1.089–7.347

[a] Fisher's exact test, [b] Statistically significant ($P < 0.05$)

Table 3 Sentinel lymph node status and false-negative rate, tested with and without CK20, immunohistochemically

Status	*n*	With CK20 (%)	Without CK20 (%)
SLN+	128	86 (31.9 %)	42 (31.3 %)
SLN−	275	183	92
False-negative number	19	18	1
False-negative rate		17.3 %	2.3 %

SLN sentinel lymph node, *n* number, *CK20* cytokeratin20

higher than our result (12.9 %) because of the limited observation periods in some of the papers used for this study.

In malignant melanoma, the false-negative SLNB group (a negative SLNB result with nodal recurrence afterward) has been reported to have the lowest 2-year survival rate compared with the SLNB-negative group or the positive SLNB results followed by CLND. These facts imply that incorrect SLNB results can actually harm patients. Although no such research has been performed for MCC, reducing the false-negative rate may improve the prognosis by selecting appropriate patients for observation or suitable adjuvant therapy. Also, the high false-negative rate in MCC found in this study might justify adjuvant irradiation even with negative SLNs, when considering high radiosensitivity of this tumor and of the reduced rate of complications compared with CLND. A randomized clinical trial should be performed to confirm this issue.

One cause of the relatively high false-negative rate in MCC is that MCC often occurs in the head and neck area (24 % in this study), where lymphatic routes are complicated and SLNs are often hard to detect using radioactive tracers because SLNs are physically close to the primary tumor ("shine through" phenomenon). Regrettably, we could not perform statistical analysis on the relationship between primary site and false-negative rate, because some reports did not mention which primary sites resulted in a false negative. Considering that the highest recurrence rate (42 %) of the SLN-negative group in cutaneous melanoma was in the head and neck area [32], which is the commonest site of MCC, the high false-negative rate in MCC is also assumed to be due to this reason. A second possible cause is that lymph routes might change after primary resections are performed prior to an established clinical diagnosis of MCC. Lastly, difficulty in histopathological diagnosis of detected SLNs might affect the false-negative results even when the entire SLNs are removed operatively.

Immunohistochemical analysis of SLN with CK20 antibody appears to increase sensitivity for lymph node metastasis in MCC. Su et al. [15] reported 23 SLNs from 10 patients with MCC that appeared negative in routine H&E examination, but 5 (22 %) of these 23 SLNs were found to be positive when immunohistochemical markers were used. CK20 antibody was shown to have 100 % sensitivity. We therefore compared the rate of nodal recurrence with or without CK20 antibody as a diagnostic marker, but we found no statistical significance between their recurrence rates (Table 3). Thus, the major cause of false-negative results in MCC appears to come from insufficient detection of SLNB itself. However, this result may itself be biased; several reports that assessed SLNB without CK20 antibody were followed-up for less than a year and the sectioning protocols of the pathological examination of SLN varied among institutions. Some recent reports found an improved detection rate for SLNs using a combination of blue dye with radioactive and fluorescent tracers [33]. Although this new method of SLNB for MCC may reduce false-negative results, close follow-up is still needed, even in patients with negative SLNs.

In conclusion, patients with positive SLNs had a significantly greater risk of distant metastasis; a prognostic factor in MCC. We have shown a relatively accurate false-negative rate for SLNB in MCC, possibly due to uncertain surgical methodology rather than histopathological insensitivity. Further studies using a sensitive and standardized technique to examine entire SLNs may decrease the false-negative rate, and improve the significance of SLNB in MCC.

Conflict of interest The authors declare that they have no conflict of interest.

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