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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is a widely accepted standard procedure for patients with clinically localized melanoma. Melanoma prevalence and Clark's subtype differ between Asians and Caucasians. Here we evaluated our experience on SLNB for cutaneous melanoma in a Japanese population.

Methods: SLNB was performed for patients with melanoma between July 2000 and June 2014. We retrospectively analyzed 102 patients regarding association of clinicopathological features with sentinel lymph node (SLN) status, melanoma-specific survival (MSS), and disease-free survival (DFS).

Results: A positive SLN was significantly associated with primary Breslow thickness. Compared with 43 patients with negative SLN, 59 patients with positive SLN had significantly shorter MSS (5-year survival rate, 94.3% vs. 63.2%, $p = 0.0002$) and DFS (5-year survival rate, 92.7% vs. 63.4%, $p = 0.0004$). According to our subgroup analyses, nine patients with positive non-SLN had significantly shorter MSS compared with 32 patients with negative non-SLN (5-year survival rate, 32.4% vs. 68.5%, $p = 0.0273$). The survival of 51 Japanese patients with acral lentiginous melanoma (ALM) was not inferior to the survival of patients with other Clark's subtype.

Conclusions: Breslow thickness is an important factor for both MSS and DFS, and the

status of SLN is the most predictive prognostic factor in Japanese patients with clinically localized melanomas, as in case of Caucasians. Features of ALM may be different between Asians and Caucasians.

Key words: sentinel lymph node biopsy, clinically localized melanoma, melanoma, disease-free survival, melanoma-specific survival

INTRODUCTION

Involvement of regional lymph nodes is the most important prognostic factor for survival and recurrence among individuals with cutaneous melanoma.[1-4] Since the first report by Morton et al.[1] in 1992, numerous studies have proven the prognostic value of sentinel lymph node biopsy (SLNB),[2,5-9] and the American Joint Committee on Cancer (AJCC) has recommended SLNB for patients with certain types of melanoma, such as thick (>1 mm) or ulcerated melanomas.[10] However, compared with the Western countries, in Asian countries, where melanoma is relatively uncommon, few studies on the use of SLNB[11-17] have been conducted. In addition to differences in prevalence, Asians and Caucasians differ in terms of Clark's subtype. Among Caucasians, superficial spreading melanoma (SSM) is the most common subtype and acral lentiginous melanoma (ALM) is the fourth common subtype.[18,19] In contrast, ALM is the most common subtype among Asians and it has a worse prognosis for Caucasians compared with other Clark's subtype.[18,20,21]

The objectives of the present study were to investigate the clinical usefulness of SLNB and to evaluate the outcomes based on the status of SLN among Japanese patients with clinically localized cutaneous melanoma.

METHODS

Patients

This was a retrospective study of 107 patients who underwent SLNB for cutaneous melanoma at Okayama University Hospital between July 2000 and June 2014. Patients with melanoma *in situ* (n = 5) and those with clinical or radiographic evidence of lymph node and visceral metastases were excluded.

SLNB has been performed for patients with cutaneous melanoma at Okayama University Hospital since 1999; however, these procedures were performed by dye method alone, which has a poor SLN detection rate. Since 2000, the method for SLNB included a combination of dye, radioisotope, and gamma probe; the study period included procedures that used this combination.

The clinicopathological features and outcomes of the study population were reviewed. Variables recorded were sex, age, location, Clark's subtype, Breslow thickness, Tumor (T) stage, presence of ulceration, Clark level, number of SLNs, relapse, and outcomes. Written informed consent for SLNB was obtained from all patients and this study was approved by the Institutional Ethics Committee of Okayama University.

SLNB procedure

Preoperative lymphoscintigraphy was performed in all patients by injecting Tc-99m-phytate intradermally around the primary site or surgical scar of excisional biopsy. Dynamic and static images were obtained beginning 15 min after injection and continuing every 5 min until an SLN was visualized. The position of SLN was marked with a pen after identification using handheld gamma probe. Since 2011, a combination of single-photon emission computed tomography and computed tomography (SPECT/CT) has been used at our institution for accurate visualization of SLNs.

The procedure was as follows: After administering general or spinal anesthesia, a blue dye was injected intradermally around the primary tumor or scar of a previous excisional biopsy and then SLNs were identified with a handheld gamma probe. Lymph nodes that stained blue and showed more than one-tenth radioactivity compared with the most active lymph node were regarded as SLNs. After excising the SLNs, radioactive count was measured *ex vivo* using the handheld gamma probe. The radioactive count of the lymph node basin was also measured to confirm whether there were any other radioactive nodes in the area.

Histopathological evaluation

Each excised SLN was fixed in formalin, bisected along the major axis, and embedded

in paraffin. Next, 10–20 serial sections were obtained from each specimen and then stained with hematoxylin and eosin (HE) and processed for immunohistochemistry (IHC) using S-100, HMB45, tyrosinase, and MART-1 (the protein antigen). If the presence of tumor cells in SLNs was confirmed by HE or IHC, complete lymph node dissection (CLND) was recommended and performed in majority of patients. In almost all patients, surgery was performed the day after SLNB. We stratified patients with positive SLN who underwent subsequent CLND into two subgroups, depending on the presence of tumor cells in non-SLNs: negative non-SLN and positive non-SLN.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). Associations between SLN positivity and other clinicopathological parameters were assessed using a either Chi-square test or Fisher exact test for categorical variables and Student's t-test for continuous variables. Melanoma-specific survival (MSS) was calculated from the date of first histopathological examination to the date of death from melanoma or the date of last follow-up examination. Disease-free survival (DFS) was calculated from the date of first histopathological examination to the date of first disease relapse or the date of last

follow-up examination. Kaplan–Meier method was used to evaluate MSS and DFS and log-rank test was used to compare survival curves. Univariate analysis was performed using Cox proportional hazard model to identify prognostic factors for MSS and DFS. Factors with a *p*-value of <0.10 in the univariate analysis were further analyzed by multivariate analysis. All statistical tests were two-sided. Significance level was determined at $p < 0.05$.

RESULTS

Patient data

The characteristics of the 102 consecutive patients with clinically localized cutaneous melanomas are shown in Table 1. There were 43 male patients (42.2%) and 59 female patients (57.8%). Mean age at diagnosis was 62.5 years (range 21–94). In this patient series, Clark's subtype of all melanomas located on the hands and feet was ALM, which was also the most frequent subtype (n = 51, 50%). Mean Breslow thickness was 3.36 mm (range 0.31–13.0). T stage was pT1 in 16 patients (15.7%), pT2 in 20 patients (19.6%), pT3 in 37 patients (36.3%), and pT4 in 29 patients (28.4%). Ulceration was present in 57 patients (55.9%). Clark level was II in six patients (5.9%), III in 21 patients (20.6%), IV in 55 patients (53.9%), and V in 20 patients (19.6%). Mean number

of SLNs was 2.57 (range 1–7). Median follow-up duration was 54.5 months (range 6–160). During follow-up, relapses were observed in 20 patients (19.6%): three showed local, satellite, or in-transit metastases; one patient showed regional lymph node metastasis; and 16 patients developed distant metastases as the first site of relapse. Twenty-four patients (23.5%) died during follow-up, 18 of them due to secondary melanoma.

SLNB results and comparison of patients with positive and negative SLNs

Among 102 patients with invasive cutaneous melanomas, SLN detection rate was 100%. Forty-three patients (42.2%) showed presence of tumor cells in SLNs; of these, 41 (95.3%) underwent subsequent CLND, whereas the remaining two (4.7%) refused additional surgical intervention. None of these patients who refused surgery had relapses during follow-up. Of the 41 patients who underwent CLND, nine (22.0%) showed involvement of a non-SLN; of these positive non-SLN patients, five (55.6%) had relapses. During follow-up, none of the patients with negative SLN showed regional lymph node metastasis. Therefore, the rate of false-negative patients was 0%.

The characteristics of patients with positive and negative SLNs are shown in Table 2. Among the 16 pT1-stage patients, presence of tumor cells in SLNs was detected in

five (31.2%); these 5 patients had Breslow thicknesses of 0.70, 0.70, 0.75, 0.90, and 0.74 mm and three of them (60.0%) had no ulceration (i.e., pT1a disease). Among the 10 patients with Breslow thickness values <0.75 mm, three (30.0%) had positive SLN.

We observed significant differences in pathological features between patients with positive SLN and those with negative SLN for Breslow thickness (p = 0.0184) and T stage (p = 0.0188). Relapses were significantly more frequent in patients with positive SLN than those with negative SLN (34.9% vs. 8.5%, p = 0.0019). There were no significant differences between these two groups in terms of sex, age, location, Clark's subtype, presence of ulceration, Clark level, and the number of SLNs.

Survival analyses

Median follow-up duration for MSS was 54.5 months (range 6–166) and that for DFS was 54.5 months (range 3–166). Patients with positive SLN had significantly shorter 5-year survival rates for MSS (63.2% vs. 94.3%; p = 0.0002; Fig. 1) and DFS (63.4% vs. 92.7%; p = 0.0004; Fig. 2) compared with patients with negative SLN. Both MSS and DFS were better in patients with negative SLN than those with positive SLN.

Of the 43 patients with positive SLN, 41 (95.3%) underwent additional CLND, and only nine of the 41 patients (22.0%) showed involvement of a non-SLN. In the

subgroup analysis that compared negative non-SLN (n = 32) and positive non-SLN (n = 9), the 5-year MSS rate was significantly shorter for patients with positive non-SLN compared with those with negative non-SLN (32.4% vs. 68.5%; p = 0.0273; Fig. 3); the difference in 5-year DFS rate between these subgroups did not reach statistical significance (40.0% vs. 67.9%; p = 0.0765; Fig. 4).

Univariate and multivariate analyses

The factors associated with MSS and DFS are shown in Tables 3 and 4, respectively. In the univariate analysis for MSS, significant prognostic factors were Breslow thickness (p < 0.0001), presence of ulceration (p = 0.0268), number of SLNs (p = 0.0103), and positive SLN (p = 0.0017). These four factors and Clark level (p < 0.10) were also included in the subsequent multivariate analysis (Table 3), which revealed that the independent prognostic factors associated with MSS were Breslow thickness [hazard ratio (HR) 1.37, 95% confidence interval (CI) 1.14–1.65, p = 0.0007] and positive SLN (HR 8.88, 95% CI 2.22–35.57, p = 0.0020). In the univariate analysis for DFS, the significant prognostic factors were Breslow thickness (p < 0.0001), presence of ulceration (p = 0.017), Clark level (p = 0.0346), number of SLNs (p = 0.0318), and positive SLN (p = 0.0014). These five factors were included in the subsequent

multivariate analysis (Table 4), which showed that the important prognostic factors associated with DFS were Breslow thickness (HR 1.28, 95% CI 1.09–1.50, $p = 0.0029$) and positive SLN (HR 5.13, 95% CI 1.77–14.91, $p = 0.0026$).

DISCUSSION

Involvement of regional lymph nodes is the most important prognostic factor for patients with cutaneous melanoma.[1-4] Therefore, SLNB, which can potentially identify patients with occult nodal involvement, has been a standard procedure for patients with clinically localized melanomas. Because SLNB is accounted for in the final version of melanoma staging and classification[10], it plays an important role in not only prognostication but also staging. In this study, both MSS and DFS were better in the patients with negative SLN than those with positive SLN (Figs. 1 and 2).

These results suggest that the status of an SLN is a strong predictor of survival in Japanese patients with clinically localized melanomas. Although occult tumor cell involvement of regional lymph nodes exists, these metastases are too small to detect at this stage by imaging methods such as ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography. Therefore, at our institute, we have been performing SLNB for all patients with clinically localized melanomas, except

patients clinically considered to have melanoma *in situ*, although SLNB is generally performed for patients with 1.0–4.0-mm-thick primary melanoma.

According to consensus in the National Comprehensive Cancer Network Guidelines,[22] SLNB should be discussed and offered to patients with primary melanomas >1.0 mm thick. In general, SLNB is not recommended for melanomas that are ≤0.75 mm in Breslow thickness. For melanomas that are 0.76–1.0 mm thick, SLNB should be discussed and considered, although the yield is low and clinical significance is modest for a positive SLN.

Han et al.[23] observed that among 1,250 patients with melanomas <1.0 mm in Breslow thickness, 65 (5.2%) had positive SLN; in this report, SLNB can be avoided in patients with melanomas <0.75 mm in Breslow thickness and was recommended when the primary tumor is ≥0.75 mm in Breslow thickness, particularly if with ulceration. For melanomas >4.0 mm in Breslow thickness, it is generally accepted that SLNB is not always considered because of high risk for distant metastasis.

The status of SLN was shown to be an important prognostic factor in pT4 patients, as well as in patients with melanomas between 1.0 and 4.0 mm in Breslow thickness.[9,24] In this study, five of 16 (31.2%) patients with Breslow thickness values <1.0 mm had positive SLN; three of 10 (30.0%) patients with Breslow thickness values

< 0.75 mm had positive SLN. These results suggest a higher rate of SLN positivity in this cohort of Asian patients with Breslow thickness values <1.0 mm compared with Caucasians. Although the number of patients in this study was small, the adaptive criteria for SLNB in Japanese populations, which differ from those for Caucasians, may be established by future large-scale studies.

The incidence of melanoma in Asian countries is lower than that in Western countries. There are fewer studies on SLNB from Asian countries[11-17] compared with Western countries. The studies performed in Asian countries have revealed rates of SLN positivity ranging 15.5%–41.8%.[11-17] The rate of SLN positivity in this study was 42.2%, which is relatively high compared with previously obtained values. This result may be attributable to the exclusion of patients with melanoma *in situ* who underwent SLNB; if these patients (n = 5) were included in our analyses, SLN positivity rate would have decreased to 40.2%, which is consistent with previous studies, but is still higher than the rates shown in Caucasian studies.[25] The result may be associated with increased Breslow thickness values, which correlates with SLN positivity, observed in the present study population compared with those of patients in most Caucasian studies.[22]

In a US-based study, Bradford et al.[18] demonstrated that ALM had greater Breslow thickness values than other Clark's subtype. Among patients with ALM in Western

countries, majority of whom are Caucasians, the rates of SLN positivity ranged 24%–40%.[21,26,27] Furthermore, prognosis of ALM in Caucasians was considered worse compared with other subtypes.[18,20,21] In Asian countries, where ALM is the most common subtype, ALM is not always considered to have a worse prognosis compared with others. Among patients with clinically localized melanomas, survival of patients with ALM who underwent SLNB was not inferior compared with that of patients with others (Tables 3 and 4). Uhara et al.[13] reported that the prognosis in Japanese patients with melanoma was similar to that in Caucasians, although majority of their patients had ALM. In addition, studies in Taiwan[14, 28] found that ALM is an independent prognostic factor for better overall survival in multivariate analysis. These results suggest that features of ALM, including prognosis, are different between Asians and Caucasians.

Our present findings revealed that Breslow thickness was an important factor for both MSS and DFS and that SLN positivity was the most predictive prognostic factor in patients with clinically localized melanomas. Despite the small number of patients, these results are consistent with those of previous studies on Caucasians.[2-4,20,29] In general, patients with negative SLN are spared of further surgery and patients with positive SLN undergo additional CLND of the regional basin. In the present study, only

9 of 41 (22.0%) patients who underwent additional CLND showed involvement of a non-SLN. That is, the remaining 32 (78.0%) patients did not have involvement of a non-SLN and additional CLND could be avoided.

According to a meta-analysis in 2013, the rate of non-SLN positivity ranged 7.8–38.3%.[30] Therefore, although additional CLND is recommended for patients with positive SLN, the therapeutic effect remains unclear. The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I)[2] was initiated in 1994 to assess therapeutic benefit of SLNB and subsequent CLND for patients with a positive SLN. Patients with melanomas of at least 1-mm Breslow thickness or Clark level IV were randomized either to SLNB with subsequent CLND, if SLN metastasis was found, or to observation with CLND when regional lymph node metastasis was revealed later. The final report of the MSLT-I[4] showed that in patients with intermediate-thickness melanomas, defined as 1.20–3.50 mm, and those with thick melanomas, defined as >3.5 mm, performing SLNB significantly improved 10-year DFS rates compared with nodal observation. However, the performance of SLNB showed no improvement in 10-year MSS rates for both intermediate-thickness and thick melanomas.

In a subgroup analysis of MSLT-I of patients with positive SLN from intermediate-thickness melanomas, the 10-year MSS rates significantly improved for

patients who had undergone subsequent CLND compared with those with delayed CLND (62.1% vs. 41.5%, respectively, $p = 0.006$).[4] Other studies demonstrated that in patients with positive SLN, there was no significant difference in MSS between those who underwent immediate CLND and those who underwent nodal observation only.[31-33] In addition, among patients with positive SLN, systemic recurrence occurred in 8% of nodal observation patients compared with 27% of those who underwent immediate CLND ($p < 0.001$).[31] Complications occurred more frequently in patients subjected to CLND after SLNB than those who had SLNB alone.[34,35] Therefore, although SLNB plays an important role in prognostication of patients with clinically localized melanomas, the therapeutic effect of additional CLND after SLNB has not been demonstrated. These results suggest that patients who have low risk for non-SLN positivity could be spared from CLND, even if they are SLN positive.

It was demonstrated that involvement of a non-SLN was the most important predictor of poor survival in patients with positive SLN who proceeded to have CLND.[36, 37] In the present study, the 5-year MSS was significantly shorter for patients with positive non-SLN compared with patients with negative non-SLN. Therefore, several attempts have been made to predict involvement of non-SLN based on clinicopathological factors of patients who underwent CLND after SLNB. According to

the 2013 meta-analysis, factors that were found to be significantly associated with non-SLN positivity were presence of ulceration, satellitosis, neurotropism, >1 positive SLN, angiolymphatic invasion, extensive location, macrometastases >2 mm, extranodal extension, and capsular involvement. Based on the results of 450 Japanese patients who underwent SLNB, Namikawa et al.[12] demonstrated that a <1.0-mm maximum diameter of melanoma with SLN was a predictor of the absence of non-SLN positivity. It may be possible to omit CLND for patients at low risk for non-SLN positivity. However, there is no precise evidence with regard to omitting CLND for patients with positive SLN. Therefore, at our institute majority of such patients undergo CLND after SLNB.

A current prospective study the Multicenter Selective Lymphadenectomy Trial II (MSLT-II)[38] is comparing CLND with close follow-up by ultrasound, in patients with positive SLN. The results of these trials may provide valuable information regarding patients who could be spared of CLND.

Systemic therapy had not been shown to improve survival in patients with metastatic melanomas until 2011. Dacarbazine alone had been the international standard cytotoxic chemotherapy, despite its low response rate. Currently, there are some novel agents that improve survival in patients with inoperable regional and visceral metastases: MAP kinase pathway inhibitors, such as vemurafenib, dabrafenib and

trametinib, and immunotherapy with ipilimumab and nivolumab. In the near future, the value of these new agents for adjuvant therapy may be demonstrated in patients with earlier melanomas (i.e., operable regional metastases). Then, SLNB will play important roles in not only prognostication but also selection of patients who will benefit from these agents. When adequate systemic therapy becomes available, the importance of SLNB is likely to increase.

In conclusion, we observed that Breslow thickness is an important factor for both MSS and DFS, and the status of SLN is the most predictive prognostic factor in Japanese patients with clinically localized melanomas who undergo SLNB. These results are consistent with those in Caucasians, although the features of ALM are different between Asians and Caucasians. However, the benefit of additional CLND for patients with positive SLN remains unclear. Depending on the result of the MSLT-II trial, additional CLND could be spared in some patients, even if SLNs are positive.

ACKNOWLEDGMENTS

We are very grateful to the members of our laboratory for preparing the pathological specimens. No funding was received.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Kaplan–Meier curve for melanoma-specific survival (MSS) according to sentinel lymph node status (positive, *n* = 43; negative, *n* = 59).

Figure 2. Kaplan–Meier curve for disease-free survival according to sentinel lymph node status (positive, *n* = 43; negative, *n* = 59).

Figure 3. Kaplan–Meier curve for melanoma-specific survival according to non-sentinel lymph node status (positive non-SLN, *n* = 9; negative non-SLN, *n* = 32).

Figure 4. Kaplan–Meier curve for disease-free survival according to non-sentinel lymph node status (positive non-SLN, *n* = 9; negative non-SLN, *n* = 32).

TABLES

Table 1. Clinicopathological features of 102 patients with invasive cutaneous melanoma who underwent sentinel lymph node biopsy

Parameters	No. of patients (%)
Gender	
Male	43 (42.2%)
Female	59 (57.8%)
Mean age (range)	62.5 (21-94)
Primary site	
Head and neck	14 (13.7%)
Trunk and extremities	37 (36.3%)
Hand and foot	51 (50.0%)
Histopathological subtype	
SSM	38 (37.2%)
NM	6 (5.9%)
ALM	51 (50.0%)
Other	7 (6.9%)
Mean Breslow thickness (range)	3.36 (0.31-13.0)
T stage	
T1	16 (15.7%)
T2	20 (19.6%)
T3	37 (36.3%)
T4	29 (28.4%)
Ulceration	
Present	57 (55.9%)
Absent	45 (44.1%)
Clark level	
Ⅱ	6 (5.9%)
Ⅲ	21 (20.6%)
Ⅳ	55 (53.9%)
Ⅴ	20 (19.6%)
Mean number of SLNs (range)	2.57 (1-7)
Relapse	
Yes	20 (19.6%)
No	82 (80.4%)
Site of first relapse	
Local/Satellite/in-transit metastases	3 (15.0%)
Regional lymph nodemetastases	1 (5.0%)
Distant metastases	16 (80.0%)
Death	
Yes	24 (23.5%)
No	78 (76.5%)
Cause of death	
due to melanoama	18 (75.0%)
other cause	6 (25.0%)

SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma.

Table 2. Clinicopathological features associated with status of sentinel lymph nodes in patients with cutaneous melanoma (*n* = 102)

	patients with a positive SLN (n = 43, 42.2%)	patients with a negative SLN (n = 59, 57.8%)	
Parameters	No. of patients (%)	No. of patients (%)	p value
Gender			0.8394
Male	19(44.2%)	24(40.7%)	
Female	24(55.8%)	35(59.3%)	
Mean age (range)	64.5(30-91)	61.0(21-94)	0.2965
Primary site			0.7918
Head and neck	6(13.9%)	8(13.6%)	
Trunk and extremities	14(32.6%)	23(39.0%)	
Hand and foot	23(53.5%)	28(47.4%)	
Histopathological subtype			0.4524
SSM	14(32.6%)	24(40.7%)	
NM	4(9.3%)	2(3.4%)	
ALM	23(53.5%)	28(47.4%)	
Other	2(4.6%)	5(8.5%)	
Mean Breslow thickness (range)	4.09(0.70-13.0)	2.83(0.31-13.0)	0.0184
T stage			0.0188
T1	5(11.6%)	11(18.6%)	
T2	5(11.6%)	15(25.4%)	
T3	14(32.6%)	23(39.0%)	
T4	19(44.2%)	10(17.0%)	
Ulceration			0.0686
Present	29(67.4%)	28(47.5%)	
Absent	14(32.6%)	31(52.5%)	
Clark level			0.1881
Ⅱ	1(2.3%)	5(8.5%)	
Ⅲ	6(14.0%)	15(25.4%)	
Ⅳ	25(58.1%)	30(50.8%)	
Ⅴ	11(25.6%)	9(15.3%)	
Mean number of SLNs(range)	2.86(1-7)	2.36(1-7)	0.1152
Relapse			0.0019
Yes	15(34.9%)	5(8.5%)	
No	28(65.1%)	54(91.5%)	
Site of first relapse			0.8007
Local/Satellite/in-transit metastases	2(13.3%)	1(20.0%)	
Regional lymph node metastases	1(6.7%)	0(0.0%)	
Distant metastases	12(80.0%)	4(80.0%)	
Patients with a positive non-SLN	9 (22.0%)	NA	

SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; SLN, sentinel lymph node; NA, not applicable.

Table 3. Univariate and multivariate analyses of factors associated with melanoma-specific survival in patients with cutaneous melanoma who underwent sentinel lymph node biopsy (*n* = 102)

	Univariate		Multivariate	
Factor	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.02 (0.99–1.05)	0.2911		
Gender (male vs female)	1.52 (0.59–3.94)	0.3893		
Primary site (hand and foot vs the others)	0.92 (0.35–2.39)	0.8641		
Histopathological subtype (ALM vs the others)	0.92 (0.35–2.39)	0.8641		
Breslow thickness (㎜)	1.32 (1.17–1.49)	< 0.0001	1.37 (1.14–1.65)	0.0007
Ulceration (present vs absent)	4.09 (1.18–14.25)	0.0268	1.13 (0.28–4.59)	0.8556
Clark level (Ⅳ or Ⅴ vs Ⅱ or Ⅲ)	6.98 (0.92–52.66)	0.0597	2.27 (0.25–20.47)	0.4636
Number of SLNs	1.38 (1.08–1.75)	0.0103	1.21 (0.92–1.60)	0.1659
Status of SLNs (positive vs negative)	7.37 (2.12–25.65)	0.0017	8.88 (2.22–35.57)	0.0020

HR, Hazard ratio; CI, Confidence interval; ALM, acral lentiginous melanoma; SLN, sentinel lymph node.

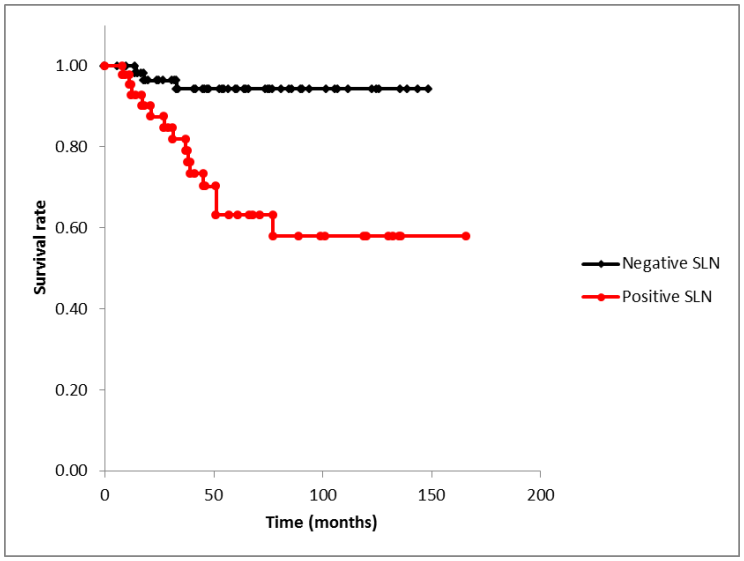
Table 4 Univariate and multivariate analyses of factors associated with disease-free survival in patients with cutaneous melanoma who underwent sentinel lymph node biopsy (*n* = 102)

	Univariate		Multivariate	
Factor	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.03 (0.99–1.06)	0.1106		
Gender (male vs female)	1.05 (0.44–2.48)	0.9185		
Primary site (hand and foot vs the others)	0.60 (0.25–1.46)	0.2627		
Histopathological subtype (ALM vs the others)	0.60 (0.25–1.46)	0.2627		
Breslow thickness (㎜)	1.29 (1.15–1.44)	< 0.0001	1.28 (1.09–1.50)	0.0029
Ulceration (present vs absent)	3.77 (1.27–11.20)	0.017	1.31 (0.40–4.25)	0.6573
Clark level (Ⅳ or Ⅴ vs Ⅱ or Ⅲ)	8.73 (1.17–65.10)	0.0346	3.33 (0.40–27.75)	0.2657
Number of SLNs	1.29 (1.02–1.62)	0.0318	1.14 (0.88–1.47)	0.3169
Status of SLNs (positive vs negative)	5.18 (1.89–14.18)	0.0014	5.13 (1.77–14.91)	0.0026

HR, Hazard ratio; CI, Confidence interval; ALM, acral lentiginous melanoma; SLN, sentinel lymph node.

FIGURES

Figure 1



$p = 0.0002$

Figure 2

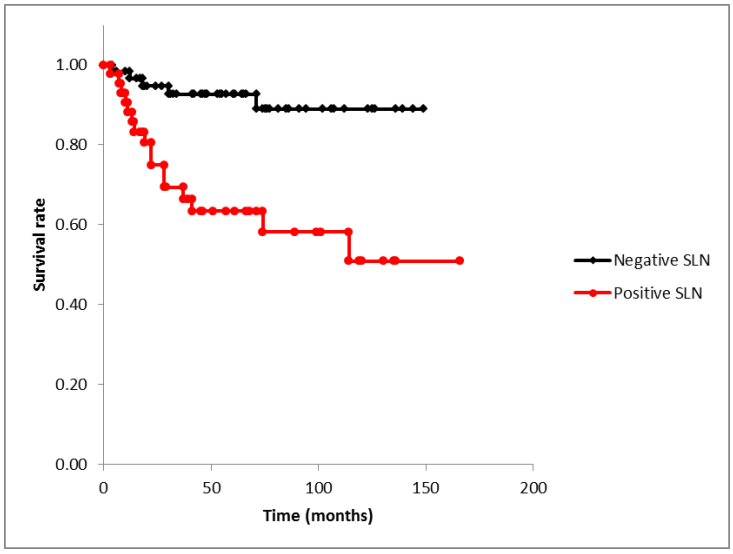


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Figure 3

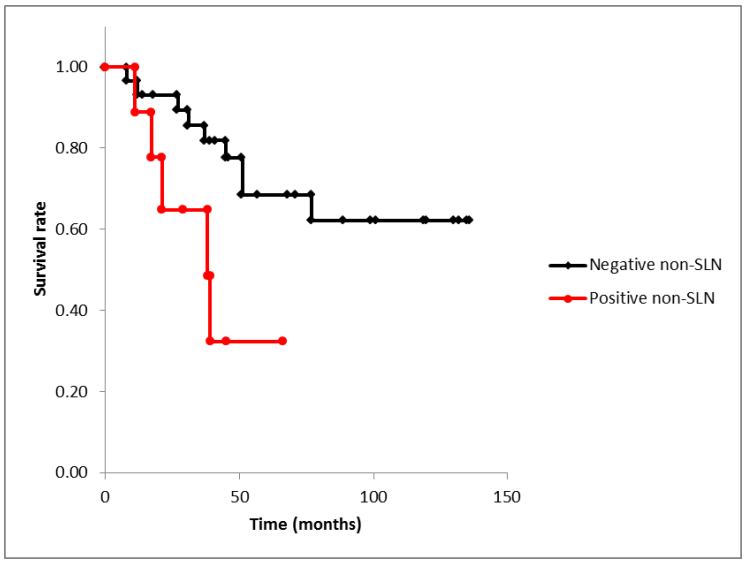

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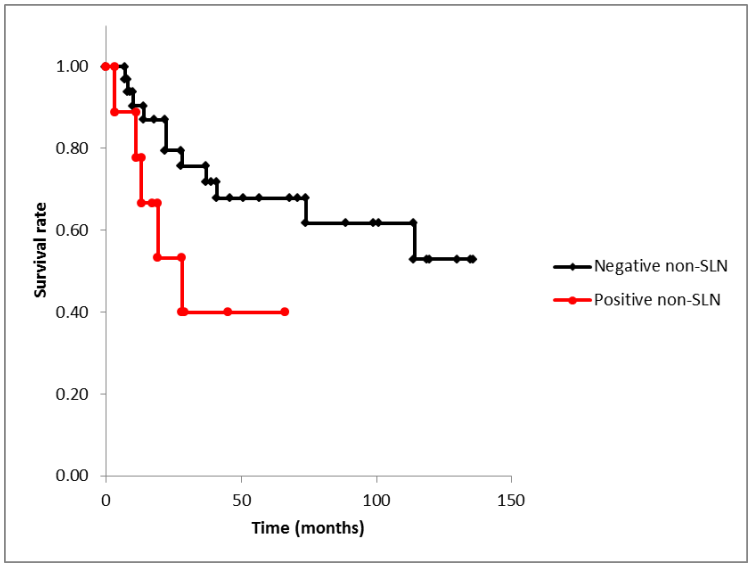
Figure 4



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