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ORIGINAL ARTICLE

Prognostic factors for Taiwanese patients with cutaneous melanoma undergoing sentinel lymph node biopsy

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Background/purpose: Sentinel lymph node biopsy (SLNB) is a standard procedure in the management of clinically node-negative melanoma. However, few studies have been performed on SLNB in Asia, which is an acral melanoma-prevalent area. This study evaluated the clinicopathologic prognostic factors of disease-free survival (DFS) and overall survival (OS) in Taiwanese patients with cutaneous melanoma who received wide excision and SLNB. The prognosis of patients with false-negative (FN) SLNB was also evaluated.
Methods: Malignant melanoma cases were reviewed for 518 patients who were treated between January 2000 and December 2011. Of these patients, 127 patients with node-negative cutaneous melanoma who received successful SLNB were eligible for inclusion in the study.

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Results: The SLNB-positive rate was 34.6%. The median DFS was 51.5 months, and the median OS was 90.9 months at the median follow-up of 36.6 months. Multivariate analysis revealed that patients whose melanoma had a Breslow thickness greater than 2 mm had a significantly shorter DFS than patients whose melanoma had a Breslow thickness of 2 mm or less [hazard ratio (HR), 3.421; $p = 0.005$]. Independent prognostic factors of OS were a Breslow thickness greater than 2 mm (HR, 4.435; $p = 0.002$); nonacral melanoma (HR, 3.048; $p = 0.001$); and an age older than 65 years (HR, 2.819; $p = 0.036$). During the follow-up period, 13 of 83 SLN-negative patients developed a regional nodal recurrence. The SLNB failure rate was 15.7% and the FN rate was 22.8%. Compared to patients with a true-positive SLNB, patients with FN SLNB had a significantly shorter DFS ($p = 0.001$) but no significant difference in OS ($p = 0.262$).

Conclusion: Except for the pathologic subtypes, prognostic factors in Taiwan are similar to those used in other melanoma-prevalent countries. Identifying and closely monitoring patients at risk of nodal recurrence after a negative SLNB is important.

Introduction

In the United States, cutaneous melanoma, the most serious form of skin cancer, is the fifth most common cancer in men and the sixth most common cancer in women.[1] Sun exposure is a major risk factor for melanoma.[2] Superficial spreading melanoma (SSM) is the most common melanoma subtype in Caucasians. By contrast, cutaneous melanoma is relatively uncommon in Asians, for whom acral lentiginous melanoma (ALM) is the most common type of melanoma.[3–6] Acral lentiginous melanoma is deeper in thickness than other melanoma subtypes, and ALM with a thickness greater than 4 mm is more common in Asians and Pacific Islanders than in Caucasians and blacks.[7]

Sentinel lymph node biopsy (SLNB) was first described in 1992 and has become the standard of care in the treatment of clinically node-negative melanoma.[8,9] However, SLNB is associated with a risk of a false-negative (FN) SLNB, which is indicated by a tumor-negative sentinel lymph node (SLN) with the subsequent development of clinically positive nodes.[10,11] An FN SLNB can have a significant impact on a patient's disease-free survival (DFS) outcome.[10]

Few studies have been performed on SLN (especially FN SLNB) in Asia, which is an ALM-prevalent area. Because there are differences between Western and Asian countries in the prevalence of pathologic melanoma subtypes, we retrospectively analyzed the clinicopathological prognostic factors and the results of FN SLNB in Taiwanese patients with cutaneous melanoma.

Methods

Patients

From January 1, 2000 to December 31, 2011, 518 patients who had a discharge diagnostic code of melanoma (172.*, V10.82, M87203-87903)—based on the ninth revision of *The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*—were treated at the Chang Gung Memorial Hospital (CGMH) at Linkou in Taiwan. The records of these patients were reviewed. Patients who had melanoma *in situ*, metastatic melanoma, mucosal melanoma, and ocular melanoma were excluded from the study. A total of 209 patients had operable cutaneous melanoma. Of these patients, the records of 132 patients who had no clinical evidence of nodal or distant metastasis and who underwent SLNB were reviewed for clinicopathological features and outcomes. None of the patients received adjuvant high-dose interferon-α. Pathological diagnosis was reviewed by an experienced pathologist. Staging was determined in accordance with the American Joint Committee on Cancer (AJCC) staging system, which was published in 2010.[12,13] Patients diagnosed before 2010 were re-staged by using the *AJCC Cancer Staging Manual* (7th edition).[13] This study was approved by the institutional review board of the CGMH.

SLNB

All patients underwent wide local excision (or amputation) of the primary melanoma and SLNB. An SLN lymphoscintigraphy was performed immediately after the subdermal injection of 1 mL of technetium-99 (1 mCi) sulfur colloid and vital blue dye. Surgical harvest of the SLN was performed 2–6 hours after lymphoscintigraphy.[14] All dissected SLNs were cut into serial sections and stained with hematoxylin and eosin (H&E). Further immunohistochemical staining with HMB-45 was performed if samples were negative on the H&E-stained sections. A positive SLN was defined as any sentinel node that exhibited evidence of metastatic melanoma cells either on H&E-stained sections or with HMB-45 staining. All patients who had a positive SLN underwent complete lymph node dissection (CLND).

A true-positive (TP) SLN was defined as a sentinel node biopsy that contained metastatic melanoma cells. An FN SLN was defined as an initially negative SLN but the patient subsequently develops clinically positive nodes within the mapped basin. A true-negative (TN) SLN was defined an initially negative SLN but the patient has no evidence of subsequent recurrence within the mapped basin.

The false-negative rate (FNR) was calculated by using the following formula:

$$[\mathrm{FNR} = \mathrm{FN}/(\mathrm{TP} + \mathrm{FN})]$$

in which the FNR is the number of patients with negative SLNB whose melanoma recurs divided by the sum of the number of patients with positive SLNB (with and without recurrence) and patients with negative SLNB whose melanoma recurs.[11] The SLNB failure rate was calculated as the percentage of patients with nodal recurrence in the same basin that had been negative at the initial pathologic evaluation.[15]

Statistical information

Continuous data are presented as the median with range, whereas categorical data are presented as the number and percentage. The overall survival (OS) time was defined as the period from the date of the tumor excision to the patient's death, the last follow-up assessment, or the data cut-off point. The DFS was defined as the period from the date of tumor excision to recurrence, the patient's death, the last follow-up assessment, or the data cut-off point. Survival was analyzed by using the Kaplan–Meier method. Univariate analysis was performed by using the Cox proportional hazard model to identify prognostic factors of survival. To avoid missing potential significant factors, variables with a p value < 0.10 in the univariate analysis were further analyzed by using multivariate analysis. A two-sided statistical test was used for analysis. Statistical analyses were performed by using SPSS software (version 17.0; SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

There were 132 consecutive patients with clinically node-negative cutaneous melanoma who underwent wide excision (or amputation) and SLNB. The SLN detection rate was 100% by lymphoscintigraphy. During surgery, 127 of 132 (96.2%) patients had a successful SLNB. There were 63 men and 64 women among the 127 patients who received successful SLNB. The median age of the patients was 63.7 years (range 6–87 years). A total of 90 (70.9%) patients had ALM and 100 (78.7%) patients had a primary site located on the lower extremities. Table 1 summarizes the patients' characteristics.

Table 1 The characteristics of the 127 patients.

Characteristic	No. of patients (%)
Sex	
Female	64 (50.4%)
Male	63 (49.6%)
Age, y [median (range)]	63.7 (6–87)
<55	29 (22.8%)
55–65	29 (22.8%)
>65	69 (54.4%)
Pathology	
ALM	90 (70.8%)
NM	19 (15.0%)
SSM	11 (8.7%)
Other	7 (5.5%)
Location	
Upper extremity	14 (11.0%)
Lower extremity	100 (78.8%)
Head and neck	4 (3.1%)
Trunk and back	9 (7.1%)
T stage (Breslow thickness)	
T1 (0–1 mm)	12 (9.4%)
T2 (1.01–2 mm)	33 (26.0%)
T3 (2.01–4 mm)	38 (30.0%)
T4 (>4 mm)	36 (28.3%)
Unknown	8 (6.3%)
Ulceration	
Yes	52 (41.0%)
No	67 (52.7%)
Unknown	8 (6.3%)
Clark level	
I–III	15 (11.8%)
IV–V	106 (83.5%)
Unknown	6 (4.7%)
SLNB	
Positive	44 (34.6%)
Negative	83 (65.4%)

ALM = acral lentiginous melanoma; NM = nodular melanoma; SLNB = sentinel lymph node biopsy; SSM = superficial spreading melanoma.

SLNB results

Forty-four patients had a positive SLNB; hence, the SLNB positive rate was 34.6%. The positive rate for stage T1 was 25.0% (3 of 12 patients); stage T2, 12.1% (4 of 33 patients); stage T3, 44.7% (17 of 38 patients); and stage T4, 50.0% (18 of 36 patients). The positive rate for additional metastatic lymph nodes by further CLND for stage T1 was 33.3% (1/3); stage T2, 25.0% (1/4); stage T3, 23.5% (4/17); and stage T4, 27.8% (5/18) (Fig. 1).

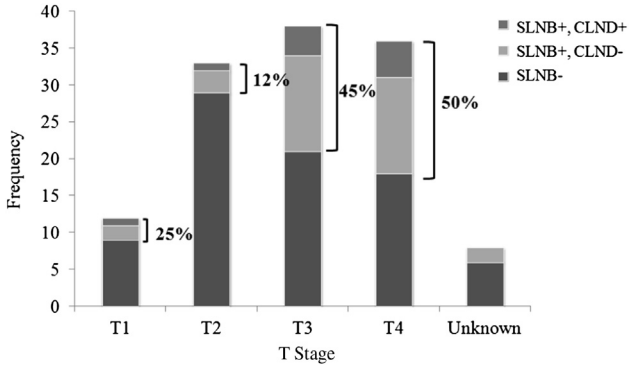

Figure 1 Results of sentinel lymph node biopsy (SLNB) and complete lymph node dissection (CLND) for SLNB-positive patients. Patients with stage T3 or T4 melanoma have a higher rate of SLNB positivity, compared to patients with stages T1 or T2. The CLND results reveal additional positive lymph nodes for all T stages.

Clinicopathological prognostic factors of DFS

The median length of DFS was 51.5 months and the estimated 5-year DFS rate was 44.5% in 127 patients with node-

negative cutaneous melanoma who had a successful SLNB. Univariate analysis revealed that male sex, a Breslow thickness greater than 2 mm, ulceration, Clark's level IV/V, and positive lymph nodes were associated with a poorer DFS prognosis (Table 2). A Breslow thickness greater than 2 mm was the only significant independent prognostic factor of DFS, as determined by multivariate analysis [hazard ratio (HR), 3.421; $p = 0.005$]. The Clark's level and ulceration were confounded by the Breslow thickness and were not significant prognostic factors, as determined by multivariate analysis.

Clinicopathologic prognostic factors of OS

The median length of OS was 90.9 months and the estimated 5-year OS rate was 59.8% in the 127 patients with node-negative cutaneous melanoma who received a successful SLNB. Univariate analysis revealed that an age greater than 65 years, male sex, nonacral melanoma, a Breslow thickness greater than 2 mm, and ulceration were associated with a poorer OS prognosis (Table 3). A Breslow thickness greater than 2 mm (HR, 4.435; $p = 0.002$), nonacral melanoma (HR, 3.048; $p = 0.001$), and an age greater than 65 years (HR, 2.819; $p = 0.036$) were independent prognostic factors of OS, as determined by multivariate analysis. Ulceration tended to be a prognostic factor of OS (HR, 1.920; $p = 0.067$), whereas male sex was not a significant prognostic factor, as determined by multivariate analysis.

False-negative sentinel lymph nodes

During a median follow-up of 36.6 months (mean, 44.8 months; range, 1.0–136.4 months), 13 of 83 patients with negative SLN had clinically positive nodes within the mapped basin. The overall SLNB failure rate and FNR were 15.7% and 22.8%, respectively. The SLNB failure rate for stage T1 was 0% (0 of 12 patients); stage T2, 6.1% (2 of 33 patients); stage T3, 7.9% (3 of 38 patients); and stage T4, 22.2% (8 of 36 patients). The SLNB failure rate increased as the T stage increased and was significantly higher at stage T4 than at stages T1–T3 (OR, 8.640; $p = 0.001$). Compared to patients with TP SLN, patients with FN SLN had a significantly poorer DFS ($p = 0.001$); however, there was no difference between the groups in OS ($p = 0.262$) (Figs. 2 and 3). The difference in DFS was maintained after adjusting for the Breslow thickness (adjusted HR, 3.167; $p = 0.001$).

Discussion

In this retrospective study, the SLNB positive rate was 34.6% in 127 Taiwanese patients who received SLNB. Acral lentiginous melanoma was furthermore the most common

Table 2 Univariate and multivariate analyses of clinicopathological factors associated with disease-free survival (DFS) in 127 patients.

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age				
<55	0.801 (0.369–1.738)	0.575		
55–65	1			
>65	1.383 (0.743–2.576)	0.307		
Sex				
Female	1		1	
Male	1.954 (1.173–3.254)	0.010	1.397 (0.792–2.466)	0.249
Type				
ALM	1		1	
Other	1.664 (0.985–2.811)	0.057	1.562 (0.882–2.766)	0.126
Location				
Extremities	1			
Other	1.397 (0.664–2.941)	0.379		
Breslow thickness				
≤2 mm	1		1	
>2 mm	5.422 (2.622–11.211)	<0.001	3.421 (1.459–8.024)	0.005
Ulceration				
Yes	2.992 (1.742–5.138)	<0.001	1.625 (0.871–3.030)	0.127
No	1		1	
Clark's level				
I/II/III	1		1	
IV/V	3.647 (1.133–11.744)	0.030	1.677 (0.483–5.821)	0.415
LN status				
Negative LN	1		1	
Positive LN	1.610 (0.971–2.668)	0.065	0.951 (0.540–1.676)	0.863

ALM = acral lentiginous melanoma; CI = confidence interval; HR = hazard ratio; LN = lymph node.

Table 3 Univariate and multivariate analyses of clinicopathological factors associated with overall survival (OS) in 127 patients.

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, y				
<55	2.031 (0.705–5.847)	0.189	1.299 (0.414–4.075)	0.654
55–65	1			
>65	3.333 (1.286–8.636)	0.013	2.819 (1.072–7.416)	0.036
Sex				
Women	1		1	
Men	2.160 (1.172–3.980)	0.014	1.539 (0.784–3.020)	0.210
Type				
ALM	1		1	
Other	2.289 (1.271–4.122)	0.006	3.048 (1.551–5.990)	0.001
Location				
Extremities	1			
Other	1.515 (0.705–3.255)	0.287		
Breslow thickness				
≤2 mm	1			
>2 mm	5.684 (2.479–13.036)	<0.001	4.345 (1.841–10.255)	0.002
Ulceration				
Yes	3.314 (1.768–6.211)	<0.001	1.920 (0.956–3.854)	0.067
No	1		1	
Clark's level				
I/II/III	1			
IV/V	2.067 (0.638–6.700)	0.226		
LN status				
Negative LN	1			
Positive LN	1.463 (0.814–2.629)	0.204		

ALM = acral lentiginous melanoma; CI = confidence interval; HR = hazard ratio; LN = lymph node.

type of melanoma with more than one-half of all patients having a Breslow thickness greater than 2 mm. During the follow-up period, 13 of 83 patients with a negative SLN developed regional nodal recurrence. The resultant SLNB failure rate was 15.7% and the FNR was 22.8%. Compared to patients with TP SLN, patients with FN SLN had a significantly unfavorable DFS, but there was no difference between the two groups in the OS. To the best of our knowledge, this is the first report concerning FN SLN in Asia.

The standard of care for the treatment of clinically node-negative melanoma has been SLNB. However, few

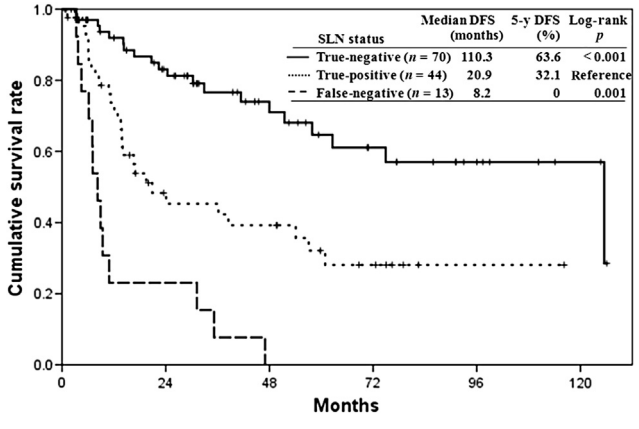

Figure 2 Comparison of disease-free survival (DFS) in the true-negative (TN) group, the true-positive (TP) group, and the false-negative (FN) group. The DFS is significantly shorter in the FN group than in the TP group ($p = 0.001$). SLN = sentinel lymph node.

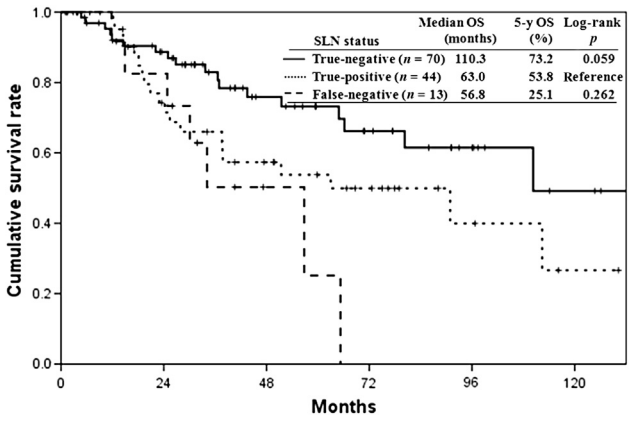

Figure 3 The comparison of the overall survival (OS) in the true-negative (TN) group, the true-positive (TP) group, and the false-negative (FN) group. There is no significant difference between the FN and TP groups in OS ($p = 0.262$).

studies have examined SLNB in non-Caucasian populations. Studies performed in Japan have demonstrated SLNB-positive rates ranging from 21.2% to 41.8%.[16–19] Hence, the overall SLNB positive rate of 34.6% in our study is consistent with the findings from studies performed in Japan, but it is higher than rates reported in studies involving Caucasian populations.[10,11] This is because patients in our study had thicker tumors. Tumor thickness is a significant independent predictor of SLN metastasis.[20] In Asia, ALM is the most common type of melanoma. It accounted for approximately 70% of all tumors in our study. Bradford et al[7] performed a study of ALM in the United States and found that ALM was associated with the highest tumor thickness, compared to all other cutaneous melanomas. In a comparison of ALM among different races, Asians were found to have a higher ALM thickness, compared to other racial groups.[7] Therefore, pathologic subtype and ethnicity seem to play an important role in cutaneous melanoma.

In the present study, we found that prognostic factors for OS were tumor thickness, an age greater than 65 years, nonacral melanoma, and possibly ulceration. Melanoma thickness and ulceration are the most important predictors of survival in the AJCC melanoma staging database of localized melanoma.[21,22] It is unclear why ALM is associated with a better prognosis in our patients since this type of melanoma is associated with a poorer prognosis, relative to other melanoma subtypes.[7] However, a previous study in Taiwan also reports that ALM is an independent prognostic factor for better OS, as determined by multivariate analysis.[23] One possible explanation is that the most common subtype of nonacral melanoma in our study and in a previous study[23] was nodular melanoma (NM). In Taiwan, SSM (which is associated with a better prognosis than either ALM or NM) accounts for only a small proportion of nonacral melanoma cases.

The overall FNR and SLNB failure rate in our study was 22.8% and 15.7%, respectively. A meta-analysis of 71 published studies—which included 25,240 patients with melanoma who underwent SLNB—reports an average FNR of 12.5% and a SLNB failure rate of 3.4%.[11] The higher FNR and SLNB failure rate in our study may be explained by the greater Breslow thickness of the melanoma and by the fact that none of the patients received high-dose adjuvant interferon-α. Valsecchi et al[11] previously reported that the SLNB failure rate increased as the Breslow thickness increased. This probably is related to the more aggressive tumor behavior of a thicker melanoma. High-dose adjuvant interferon-α can prolong DFS and may decrease regional recurrence.[24] In addition, Scoggins et al[10] report that patients with FN SLN have a statistically poorer DFS (but not OS) than patients with TP SLN. We similarly found that patients with FN SLN had a significantly unfavorable DFS (but no difference in OS), compared to patients with TP SLN. Further investigation that includes clinical features[10] and genetic alternations[25] is warranted to understand the tumor biology of cutaneous melanoma in patients with FN SLN.

The current study has several limitations. First, because of its retrospective single-institution nature, some bias may have been introduced because of incomplete data records. Second, none of our patients received high-dose adjuvant interferon-α, which has been shown to significantly improve the DFS of patients with high-risk melanoma. However, the results of interferon-α concerning OS have been less conclusive.[26,27] Third, the status of SLNBs was determined by using H&E staining and/or HMB-45 staining, rather than by the more sensitive reverse transcriptase polymerase chain reaction (RT-PCR) assay. The RT-PCR assay is more sensitive for detecting occult metastases, compared to routine histology.[28] However, the prognostic significance of a positive RT-PCR test remains uncertain.[29,30] Fourth, the mitotic rate was not routinely assessed in our patients. Therefore, we were unable analyze the prognostic significance of the mitotic rate, which is a prognostic factor specified in the AJCC staging criteria.[12]

In conclusion, the Breslow thickness is the most important prognostic factor for DFS and OS in Taiwanese patients with clinically node-negative cutaneous melanoma who receive primary surgery and SLNB. These prognostic factors are similar to those used in melanoma-prevalent countries. The FN SLNB affected the patients' DFS, but not their OS outcome. Therefore, it is important to identify and closely monitor patients at risk for nodal recurrence after a negative SLNB.

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