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ORIGINAL ARTICLE – MELANOMA

Sentinel Node Biopsy for Melanoma Patients with a Local Recurrence or In-Transit Metastasis

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ABSTRACT

Background. Sentinel node (SN) biopsy (SNB) is not routinely performed for melanoma patients with local recurrence (LR) or in-transit metastasis (ITM). This study aimed to describe the technique, findings, and prognostic value of this procedure, and the outcome for such patients at our institution.

Methods. Prospectively collected data were obtained from the Melanoma Institute Australia database. Patients who had SNB for LR or ITM between 1992 and 2015 were included in the study. Patient and primary tumor characteristics, lymphoscintigrams, SNB results, and follow-up data were analyzed.

Results. Overall, 7999 patients underwent SNB, 128 (1.6%) of whom met the selection criteria. The SNB procedure was performed for 85 of 1516 patients with LR (6%), 17 of 1671 patients with ITM from a known primary tumor (1%), and 26 of 170 patients who presented with ITM from an unknown primary site (15%). The SN identification rate was 100%. Metastatic melanoma was identified in an SN from 16 of the 128 patients (13%). Follow-up data were available for 114 patients. The false-negative rate was 27%. The SN-positive patients had significantly worse overall survival than the SN-negative patients, with respective 5-year survival rates of 54% and 81% ($P = 0.01$).

Conclusion. The SNB procedure was performed infrequently for LR or ITM. The SNs were positive for 13% of the patients with LR or ITM. Positive SNs were associated with worse overall survival. Despite the false-negative rate of 27%, the procedure yielded information that was relevant for staging and prognosis. The SNB procedure should be considered for patients with LR or ITM.

Sentinel node (SN) biopsy (SNB) is routinely performed for staging and to improve regional control for patients who have a clinically localized intermediate-thickness primary melanoma, with likely improvement in survival outcome for node-positive patients.[1] The tumor status of the SN is the strongest predictor of recurrence and overall survival.[1]

Information on the results of SNB for patients with local recurrence (LR) or in-transit metastasis (ITM) is sparse.[2–4] About 5% of melanoma patients experience LR and another 4% experience ITM.[5] These disease manifestations imply a poor prognosis, with a 5-year melanoma-specific survival of 61% for patients with ITM as a first site of recurrence.[5]

The SNB could be used to select patients most likely to benefit from adjuvant systemic therapy or particularly intensive follow-up care, and also to identify lower-risk patients for whom adjuvant systemic therapy might be avoided.[6] The few studies performed previously suggest that SNB may be of value for patients with LR or ITM.[2–4] However, the clinical benefit of the procedure is uncertain

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because up to 43% of the patients with ITM as a first-site recurrence will experience distant disease without regional node involvement.[5]

In this study the experience with SNB in patients with LR or ITM at Melanoma Institute Australia was analyzed. The study aimed to assess technical aspects of lymphatic mapping in these patients, the rates of SN identification and involvement, the false-negative rate, the influence of the SNB result on disease staging, and the survival outcomes.

PATIENTS AND METHODS

All the patients gave informed consent for entry of their data into the Melanoma Institute Australia research database, and approval for the study was given by the Royal Prince Alfred Hospital Research Ethics Committee (MIA 2015-154). Patients undergoing SNB for LR or ITM between 1992 and 2015 were identified from the prospectively collected database. Three groups were selected: patients with one or more LRs from a known primary tumor, patients who had recurrence with one or more ITMs from a known primary tumor, and patients presenting with their first ITM from an unknown primary.

Patients with an unknown primary melanoma who had undergone SNB for a recurrent ITM were excluded from the study, as were patients in whom the lesion could possibly have been a primary dermal melanoma and patients with distant metastases at the time of SNB. Patients who had undergone a simultaneous regional node dissection and patients with less than 6 months of follow-up assessment were included in the study but excluded from the follow-up analyses.

The study defined LR as a recurrence within 5 cm of the original melanoma site. For patients with a known primary tumor, ITM was defined as a cutaneous or subcutaneous recurrence located more than 5 cm from the primary site, between that site and the draining nodal region. These definitions were used because in the Institute's database, ITMs are defined as lesions located more than 5 cm from the primary melanoma scar. In the absence of a known primary tumor, subcutaneous melanoma deposits were considered to be ITMs. For cutaneous lesions, classification as an ITM was based on the opinion of the pathologist, who was made aware that the data showed no evidence or history of a primary melanoma.

The technique of lymphoscintigraphy and SNB for primary melanoma at Melanoma Institute Australia has been published previously.[7,8] For the LRs and ITMs in our cohort, similar methods for SN retrieval were used. The radiopharmaceutical and blue dye usually were injected at the site of the ITM or local recurrence. For the patients with ITMs, the injections were at the primary tumor site in one patient and at both the primary tumor and the ITM in two patients. In one patient with multiple ITMs, the one closest to the node field was used. The injection generally was intradermal. For one patient, the injection was intradermal and subcutaneous, and for another patient, it was deep to the ITM.

The study defined SN as any lymph node receiving direct lymphatic drainage from the lesion.[9] An SN procedure was classified as false-negative if nodal recurrence was experienced in the region from which a tumor-negative SN was procured. Staging was performed according to the 8th-edition American Joint Committee on Cancer (AJCC)–Union for International Cancer Control (UICC) melanoma staging system.[10]

Data on patient and primary tumor characteristics, lymphoscintigraphy and SNB outcomes, subsequent therapy, and follow-up assessment were collected from the database and patient files. Normality of distribution was assessed with the Kolmogorov–Smirnov test. Numbers with percentiles, means with standard deviations, or medians with interquartile ranges (IQR) were reported. The false-negative rate was calculated by dividing the number of false-negative procedures by the sum of the false-negative and true-positive procedures. Fisher's exact test was used to evaluate recurrence rates.

The overall survival curves of patients with positive and negative SNs were compared using the Kaplan–Meier method, and the survival distribution was tested using the log-rank test (Mantel–Cox). A multivariate Cox regression was performed to assess overall survival difference between SNB results when potential confounders were taken into account. Due to the sample size limitation, only two variables (age and primary site) could be included in the analysis. Other parameters including Breslow thickness and ulceration were excluded from the multivariate analysis due to the high proportion of missing values. Data analysis was performed using IBM SPSS Statistics 24 and R software.[11,12]

RESULTS

Of the 7999 patients who underwent SNB between 1992 and 2015, 128 (1.6%) met the study criteria. The median follow-up duration from SNB to last visit was 4 years (Table 1). An SNB was performed for 85 of 1516 patients who had LR from a known primary tumor (6%), 17 of 1671 patients with ITM from a known primary tumor (1%), and 26 of 170 patients with ITM from an unknown primary tumor (15%).

Of the 102 patients with a known primary tumor (10%), 13 had undergone a previous SNB for their original melanoma. In 2 of these 13 patients (15%), a positive SN had

TABLE 1 Patient characteristics

Characteristics	Outcome *n* (%)
No. of patients included	128
Local recurrence with known primary tumor	85
ITM with known primary tumor	17
ITM with unknown primary tumor	26
Mean age (years)	61 ± 11
Male/female	64 (50)/64 (50)
Primary tumor[a]	
Breslow thickness: mm (IQR)	1.2 (0.9–2.0)
Ulceration present	19 (26)
Mitotic rate per mm^2 (IQR)	2 (1–5)
Location of the primary melanoma	
Head and neck	19 (15)
Trunk	18 (14)
Upper extremity	30 (23)
Lower extremity	35 (27)
Occult	26 (20)
AJCC–UICC stage primary tumor (8th ed)	
0 (in situ)	6 (5)
1	53 (41)
1/2	9 (7)
2	25 (20)
3	30 (23)
Unknown[b]	5 (4)
Prior SNB for primary tumor	13 (10)
SN tumor positive	2
Completion lymph node dissection	2
Additional non-SNs positive	0
Time from diagnosis of primary to recurrence for which SNB was performed: months (IQR)[c]	40 (17–78)
Overall follow-up (primary melanoma to last follow-up visit): months (IQR)	92 (42–155)
Time from SNB to last follow-up visis: months (IQ$)	52 (22–95)

ITM in-transit metastasis, *IQR* interquartile range, *AJCC* American Joint Committee on Cancer, *UICC* Union for International Cancer Control

[a]Occult primary tumor with ITM and melanoma in situ at initial presentation was excluded from this analysis. Characteristics of the remaining 95 patients are presented. Details are missing for Breslow thickness in 5 patients, ulceration status in 23 patients, and mitotic rate in 15 patients

[b]Patients with a Breslow thickness of 1–2 mm in whom ulceration status was unknown and sentinel lymph node biopsy was not performed

[c]Occult primary tumors are excluded

been found at that time, which was followed by a completion lymph node dissection. The current SN was in the same nodal region in all but 1 of these 13 patients. Another recurrence had developed in 10 patients (8%) before the recurrence for which the SNB was performed.

An SN was successfully retrieved from all 128 patients. The SN was tumor-positive in 16 patients (13%) (Table 2). The highest positivity rate (41%) was found in the subgroup of 17 patients who had experienced an ITM from a known primary tumor. A positive SN was found in 3 of the 11 patients with a negative SNB for the primary lesion (27%). Of the 16 patients with a positive SN, 12 underwent completion lymph node dissection. In four of these patients (33%) additional non-SNs were positive.

Seven patients received adjuvant radiotherapy, and two patients received adjuvant immunotherapy in the Cancer-Vax trial.[13] Adjuvant therapy usually was started for patients with multiple recurrences that developed fast. The SNB outcome never resulted in treatment with isolated limb infusion or perfusion, adjuvant radiotherapy, or systemic therapy.

TABLE 2 Results of sentinel node (SN) biopsy and outcome

	Local recurrence with known primary site (n = 85) n (%)	ITM with known primary site (n = 17) n (%)	ITM with occult primary site (n = 26) n (%)	Total (n = 128) n (%)
Preoperative lymphoscintigraphy	81 (98)	13 (76)	22 (85)	116 (91)
Median SNs harvested: n (IQR)	2 (1–4)	2 (2–4)	2 (1–3)	2 (1–4)
Patients with positive SN	7 (8)	7 (41)	2 (8)	16 (13)
Median positive SNs: n (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Patients available for follow-up analyses	73	17	24	114
Follow-up duration: months (IQR) (29–97)	58 (28–96)	44 (21–100)	45 (21–100)	56
Status at last follow-up				
Alive without disease	44 (60)	5 (29)	16 (67)	65 (57)
Alive with disease	3 (4)	4 (24)	–	7 (6)
Alive, status unknown	8 (11)	–	2 (8)	10 (9)
Deceased from melanoma	11 (15)	6 (35)	4 (17)	21 (18)
Deceased from unrelated cause	2 (3)	1 (6)	–	3 (3)
Deceased, cause unknown	5 (7)	1 (6)	2 (8)	8 (7)

IQR interquartile range

Follow-up information was available for 114 patients. Recurrence developed in 11 (69%) of the 16 SN-positive patients and 21 (23%) of the 98 SN-negative patients (Table 3; $P = 0.0003$, Fisher's exact test). A nodal recurrence was experienced by 8 (8%) of the 98 patients with a negative SN, with 6 of these developing in the SNB region (Table 3). As a result, the false-negative rate was 27%. None of these patients had a prior SNB. One patient who underwent completion lymph node dissection for a positive SN experienced a nodal recurrence in the same region. Distant metastases developed in 18 patients (16%) after a median of 76 months (interquartile range [IQR], 12–126 months). Six patients with a negative SN (6%) and seven patients with a positive SN (44%) experienced their first subsequent metastasis at a distant site ($P = 0.00001$, Fisher's exact test). For the patients with a negative SN, most of the recurrences were ITMs. These occurred primarily in patients with an unknown primary tumor who had ITM (Table 3).

The SN-positive patients had a significantly worse overall survival than those with a negative SN (Fig. 1). The median survival was not reached for the SN-negative patients and was 5 years for the SN-positive patients. The 5-year cumulative overall survival rates were respectively 81% and 54% ($P = 0.01$). The multivariate analysis result confirmed the survival difference between the SN-negative patients and the SN-positive patients (Table 4). Thus, the tumor status of the SN appeared to be an independent predictor for overall survival.

DISCUSSION

The SNB procedure is infrequently performed for melanoma patients with LR or ITM. At our institution, only 1.6% of all SNBs have been performed for these indications. The SN identification rate was 100%. This is similar to the results obtained when the procedure is performed for a primary melanoma, with reported identification rates of 95–100%.[14,15]

In previous studies of SNB for patients with LR or ITM, the site and injection depth of the tracer fluids and blue dye with ITM were points of contention. In our population, injections typically were given intradermally around the site of the melanoma recurrence. This seems to be an appropriate approach from a physiologic point of view, and the success rate is high, although there is no evidence that one technique is better than another.

In the one patient with multiple ITMs, the lesion closest to the draining lymph node region was selected. Beasley et al.[16] used the same approach for patients with more than one ITM. Gipponi et al.[4] divided the total dose of radiotracer equally over the lesions. Most studies used intradermal injections, although intra- and peritumoral injections also have been described.[2,4,16,17]

TABLE 3 Recurrences after sentinal node biopsy (SNB)

	Total (n = 114) n (%)	SN-positive patients (n = 16)				SN-negative patients (n = 98)			
		Local recurrence (n = 7) n (%)	ITM with known primary site (n = 7) n (%)	ITM with occult primary tumor (n = 2) n (%)	Total for SN-positive patients n (%)	Local recurrence (n = 66) n (%)	ITM with known primary site (n = 11) n (%)	ITM with occult primary tumor (n = 24) n (%)	Total for SN-negative patients n (%)
Recurrences	32 (28)	3 (43)	6 (86)	2 (100)	11 (69)	9 (14)	4 (36)	8 (33)	21 (23)
Local only	1 (1)[a]					1 (2)			1 (1)[a]
ITM only	9 (8)		1 (14)		1 (6)	2 (3)		6 (25)	8 (8)
Nodal only	2 (2)[a]					1 (2)	1 (9)		2 (2)[a]
Local + ITM	1 (1)		1 (14)		1 (6)				
ITM + nodal	1 (1)					1 (2)			1 (1)
ITM + distant	1 (1)	1 (14)			1 (6)				
Nodal + distant	1 (1)					1 (2)			1 (1)
ITM + nodal + distant	5 (4)	1 (14)			1 (6)	1 (2)	2 (18)	1 (4)	4 (4)
Distant only	11 (10)[b]	1 (14)	4 (57)	2 (100)	7 (44)[b]	2 (3)	1 (9)	1 (4)	4 (4)[b]
No recurrence	82 (72)[c]	4 (57)	1 (14)	0	5 (31)	57 (86)	7 (64)	16 (67)	77 (77)

SN sentinel node, *ITM* in-transit metastasis

[a]One patient had a previous local recurrence before the SNB

[b]One SN positive patient had previous local, in-transit, and nodal recurrences; one SN-negative patient had a local recurrence before the SNB

[c]Six patients had a previous local recurrence before the SNB; one patient was SN-positive, and five patients were SN-negative

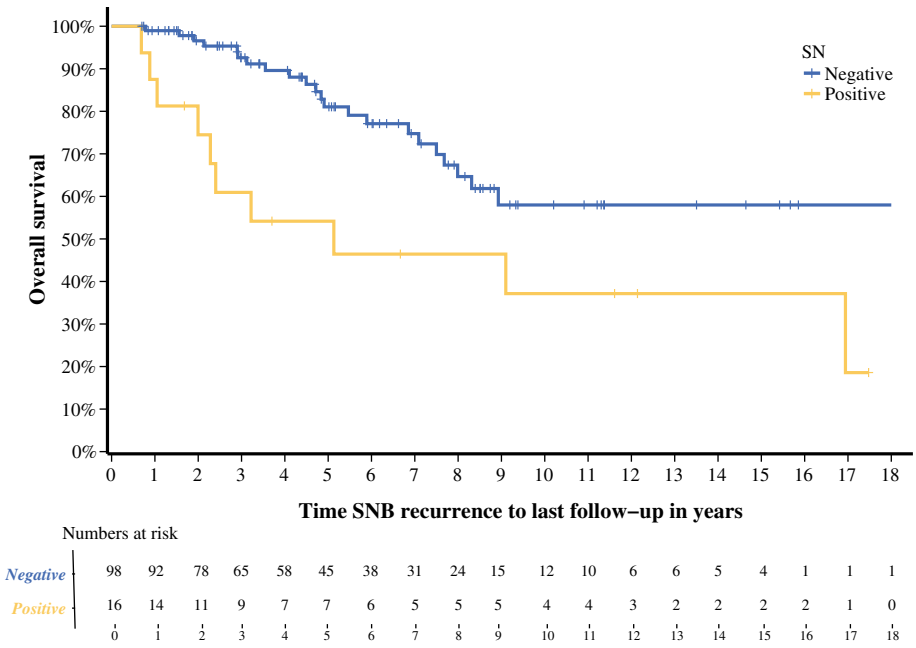

FIG. 1 Kaplan–Meier survival curve-positive and curve-negative sentinel node patient

The SN-positivity rate of 13% in the current study is at the low end of the 12–25% range reported when the procedure is performed for a primary melanoma.[1,18,19] Earlier studies have reported substantially higher positivity rates for patients with LR or ITM.[2,3,16,17,20,21] In the most recent (2017) and largest previous publication, Beasley et al.[3] described 59 patients with LR and 48 patients with ITM. For four patients (4%), SNB failed, and SNs were positive

TABLE 4 Uni- and multivariable overall survival regression

Variable	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Positive SNB				
No	1		1	
Yes	2.62 (1.21–5.64)	0.0141	3.64 (1.43–9.26)	0.0067
Age (years)	1.04 (1.01–1.08)	0.0110	1.05 (1.02–1.09)	0.0046
Breslow thickness (mm)[a]	1.03 (0.75–1.40)	0.8666		
Ulceration[a]				
No	1			
Yes	1.38 (0.52–3.65)	0.5125		
Primary site				
Head and neck	1		1	
Trunk	0.95 (0.20–4.47)	0.9615	0.68 (0.13–3.46)	0.9613
Upper extremity	1.02 (0.26–4.02)		0.98 (0.24–4.02)	
Lower extremity	1.35 (0.37–4.90)		0.95 (0.25–3.60)	
Occult	1.08 (0.27–4.36)		0.69 (0.13–3.79)	

HR hazard ratio, *CI* confidence interval, *SNB* sentinel node biopsy

[a]Variables are not included in the multivariable model due to the high proportion of missing data

in 41 cases (40%). Their patient population may have had more advanced disease than ours, but this could not be assessed because details of the primary tumors were not provided. Their SN-positivity rates for patients with LR were similar to those for patients with ITM. In our study, 41% of the patients with ITM from a known primary tumor had an involved SN, which was higher than the 8% for both the patients with LR and those with ITM from an occult primary.

In five smaller studies of 12–38 patients with LR or ITM, SNs were positive in 27–53% of the cases.[2,4,16,17,20] Two of these studies included patients with more advanced primary tumors and more patients with multiple ITMs.[4,16] In the other three publications, these primary lesion characteristics were not reported in detail.[2,17,20]

The high false-negative rate in the current cohort must have been at least partly responsible for the low SN-positivity rate. If these missed metastases had been found during SNB, the positivity rate would have been 17% (22 of 128 positive SNs). Only two other studies, with respectively 16 and 7 SN-negative patients, looked for false-negative procedures, but none were found during 23 and 20 months of follow-up evaluation, respectively.[2,17]

The SN-positive patients had a greater chance of recurrence development than the SN-negative patients, particularly the development of distant metastases. Although the subgroups were small, analysis of the recurrence type in the different groups showed that the patients with ITM (from either a known or unknown primary tumor), who had a positive SN, had the greatest chance of experiencing distant metastases.

For the SN-negative patients, recurrences were most often ITMs. These recurrences were mainly in the group of patients who presented with ITM from an unknown primary tumor. For unknown reasons, some melanomas predominantly metastasize through lymphatics.[22] Read et al.[5] reported that disease was limited to ITMs without distant metastases in 36% of the 190 patients with ITM as the first site of recurrence.

A meaningful finding of the current study was the correlation between SN tumor status and prognosis in the study population. The 5-year overall survival rate was 81% for the patients with tumor-free SNs and 54% if an SN was involved ($P = 0.01$). Several other papers describe a (nonsignificant) trend toward improved survival for patients with a negative SN.[2–4]

The additional information on staging and prognosis is valuable considering the results of studies analyzing adjuvant targeted therapy and immunotherapy for high-risk stage 3 patients. In three recent studies, adjuvant nivolumab for resected stages 3b, 3c, and 4 disease, adjuvant pembrolizumab for the stage 3 patients, and adjuvant targeted therapy with dabrafenib plus trametinib for resected stage 3 melanoma were found to improve recurrence-free survival significantly.[23–25] For patients with LR or ITM, SNB could be used to select higher-risk patients who may have a greater chance to benefit from these adjuvant regimens.

The finding of a positive SN changed management for 9% of our patients because they had a completion lymph node dissection. The patients undergoing SNB for a primary melanoma showed a paradigm shift away from

completion node dissection. Both the second Multicenter Selective Lymphadenectomy Trial and the DeCOG trial demonstrated that the survival of SN-positive patients is equally good with observation and ultrasound follow-up assessment.[18,26] Whether the implications for management can be extrapolated to patients with LR or ITM is unclear, although this seems plausible.

The false-negative rate after a median follow-up period of 4 years was 27% because six SN-negative patients experienced a nodal recurrence in the biopsied region. The false-negative rates of SNB for patients with primary melanoma range between 6 and 38%.[27,28] At our institution, the false-negative rate of SNB for primary melanoma is 13%.[29] One explanation for the high rate found in the current study may be that an occult LR or ITM disperses melanoma cells to an additional lymph node. Also, nodal involvement can originate from the previously removed primary tumor. Because both sources do not necessarily drain to the same lymph node, this may suggest that the tracers should also be injected at the primary lesion site if SNB had not been performed previously.

A limitation of our study was its retrospective design. The subgroups were small because SNB is not performed regularly for patients with LR or ITM, which prohibited detailed analyses. Also, the definition of ITM differed from the definition in the 8th edition of the AJCC–UICC staging manual. In our database, ITM is defined as a lesion occurring more than 5 cm from the primary lesion instead of the 2 cm used in the staging manual.[22]

In conclusion, this study showed that SNB can be performed for patients experiencing LR or ITM with a high identification rate, although the false-negative rate was considerable (27%). A tumor-positive SN was found in 13% of the patients and was associated with more recurrences and a worse overall survival rate. For patients with LR or ITM, SNB improves staging and provides prognostic information. The presence or absence of SN involvement may play a useful role in the process of deciding whether to give or refrain from giving adjuvant systemic therapy and may influence decisions on the appropriate surveillance strategy.

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