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Prognostic factors in distinct melanoma types

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CHAPTER 3

Outcome of melanoma patients who did not proceed to sentinel node biopsy after preoperative lymphoscintigraphy

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ABSTRACT

Background. At our institution, a planned sentinel node biopsy (SNB) procedure is occasionally canceled after preoperative lymphoscintigraphy. This study reports the frequency of this, the reasons, and the management and outcomes of these patients.

Methods. All patients with clinically localized cutaneous melanoma treated at Melanoma Institute Australia between 2000 and 2009 whose planned SNB procedure was not undertaken after lymphoscintigraphy were included in this retrospective study.

Results. Of the 3148 patients in whom the procedure had been planned, 203 patients (6.4 %) did not have a SNB. The main reason for not proceeding with SNB (in 84 % of cases) was the lymphoscintigraphic demonstration of multiple drainage fields and/or multiple sentinel nodes (SNs). Patients who did not proceed to SNB were significantly older than those who did, more often had melanomas of the head or neck, and had more SNs and more nodal drainage fields. Of the 203 patients, 181 (89 %) were followed with high-resolution ultrasound of their SNs, which identified 33 % of the nodal recurrences before they were clinically apparent. Patients whose SNB was canceled had significantly worse recurrence-free survival and regional node disease-free survival, but melanoma-specific survival was similar. Compared to SN-positive patients, node-positive patients without SNB had significantly more involved nodes when a delayed lymphadenectomy was performed, but melanoma-specific survival was not significantly different after a median follow-up of 42 months.

Conclusions. Lymphoscintigraphy with ultrasound follow-up of previously identified SNs is an acceptable management strategy for patients in whom a SNB procedure is likely to be challenging.

INTRODUCTION

In patients with intermediate-thickness melanomas, sentinel node biopsy (SNB) has become a routine procedure that provides staging and prognostic information, reduces the risk of a nodal recurrence and results in improved melanoma-specific survival when combined with completion node dissection in those who are node positive.^{1,2} Preoperative lymphoscintigraphy is an essential element of the procedure.^{3,4} At Melanoma Institute Australia, a planned SNB is sometimes canceled after preoperative lymphoscintigraphy has been performed. The decision not to proceed with sentinel node biopsy is based on weighing the drawbacks against the benefits. The benefits are improved staging, improved regional control and early treatment of nodal involvement with an improved survival rate. The drawbacks concern the duration and extent of the operation, difficulty of the operation, the risk of morbidity, and the general health of the patient. These patients are then followed with ultrasound (US) of their nodal field. This practice is not known to occur elsewhere on a regular basis.

The purposes of this study were to gather information on these patients and to determine whether this is an acceptable management strategy. Specific aims were to determine the incidence of omitting the intended SNB and the reasons for it in order to document the characteristics of these patients, to investigate the methods of follow-up, to report the stage of the disease at time of regional nodal recurrence, and to describe the ways in which these metastases were detected and managed. Survival was compared to that of patients who did undergo SNB, and melanoma-specific survival of node-positive patients in both populations was also compared.

PATIENTS AND METHODS

Patients

MIA's prospectively collected database was queried to identify patients with clinically localized cutaneous melanoma in whom SNB was performed (SNB group) between November 2000 and December 2009 and for patients in whom the planned biopsy was canceled after lymphoscintigraphy had been performed (SNB-canceled group). Patients were excluded from the study if they had melanoma-in situ, multiple primary melanomas, (micro)satellites, or in-transit metastases; if preoperative US revealed nodal metastasis; if no sentinel node (SN) was identified intraoperatively; if wide local excision was performed before lymphoscintigraphy; or if SNB was performed elsewhere. The protocol of this retrospective cohort study was approved by MIA's research committee.

Methods

Sentinel node biopsy is routinely recommended in patients with a melanoma ≥ 1 mm Breslow thickness. It is discussed with patients with a melanoma between 0.75 and 1.00 mm Breslow thickness in the presence of adverse histologic features such as ulceration or an elevated tumor mitotic rate. The techniques of lymphoscintigraphy and SNB used at MIA have been described in detail previously.^{5,6} Briefly, 30 MBq (0.8 mCi) technetium-99m antimony trisulfide colloid is injected intradermally as close as possible to the melanoma site, followed by dynamic and static imaging. Since 2008, single photon emission computed tomography with integrated computerized tomography (SPECT/CT) has been routinely added. A SN is defined as any node on a direct lymphatic drainage pathway from the primary tumor.⁷ Patent blue dye and a handheld gamma ray detection probe are used to guide the intraoperative detection of the SNs.³ Multiple sections of each removed SN are examined histopathologically using hematoxylin and eosin and immunohistochemical stains (S100 and HMB-45).⁸ Completion lymph node dissection has typically been performed in patients with an involved SN, unless they participated in a study (MSLT-II) in which they were randomized to observation of the nodal region.⁹ Follow-up intervals are at the discretion of the surgeon.

Statistical analysis

Clinicopathologic variables in relation to type of management (i.e. SNB versus SNB canceled) were analyzed and compared. The unpaired *t* test was used for hypothesis testing of normally distributed continuous variables, and the Mann-Whitney *U* test was used for continuous data that were not normally distributed. Calculation of P-values for categorical data was done with Pearson's χ^2 or Fisher's exact test, as appropriate. All test statistics were two tailed, and the significance level was set at $P < 0.05$. Survival rates were calculated by the Kaplan–Meier product-limit method. Covariates (management, gender, age, primary tumor site, Breslow thickness, tumor mitotic rate, ulceration, and tumor histology) were compared with the log-rank test. Patients with an unknown cause of death were excluded from the melanoma-specific survival analyses ($n = 102$). The mean and median follow-up duration in the group without SNB were both 42 months (interquartile range 18.5–65.5 months). Type of management was the variable of interest in this study. To adjust for potential confounders, known prognostic factors (gender, age, primary tumor site, Breslow thickness, tumor mitotic rate, ulceration, and tumor histology) were added to the multivariable Cox proportional hazards models.^{10–17} To increase the validity of the predictions outside the studied cohort, stepwise methods were not used and full models were built.¹⁸ The proportional hazards assumption was checked for all included variables. Stata 12 statistical software (StataCorp, College Station, TX) was

used for the assessment of the proportional hazards assumption. All other analyses were performed by SPSS 22.0 software for Mac (IBM SPSS, Chicago, IL).

RESULTS

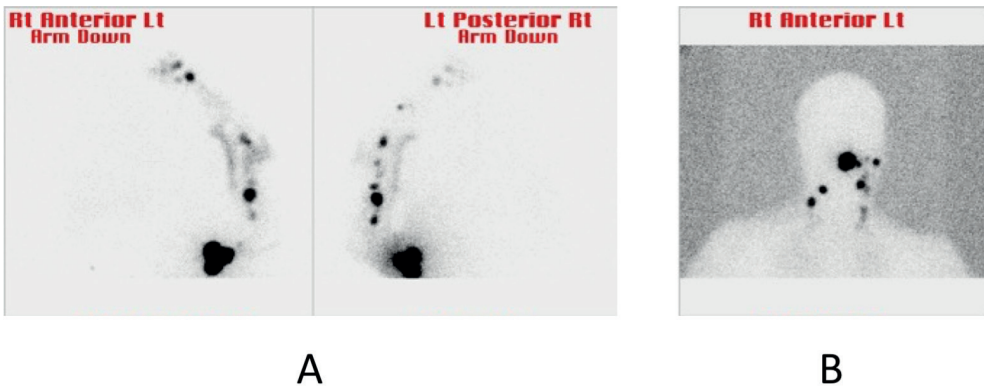
Frequency of omitting the intended SNB and reasons

A total of 3667 patients with a clinically localized cutaneous melanoma underwent lymphoscintigraphy before a planned SNB in the selected time period. After imaging, the scheduled SNB was canceled in 203 (6.4%) of the 3148 patients who fulfilled the study entry criteria and was performed in the remainder. The lymphoscintigraphic demonstration of multiple drainage fields and/or multiple SNs were the reasons for refraining from the initially intended SNB in 170 (84%) of these 203 patients. Figure 1 shows two examples of lymphoscintigrams of patients whose procedures were canceled. Other reasons for canceling the scheduled SNB were the lack of SN visualization on the lymphoscintigrams in seven patients (3%), an unusual drainage pattern (SNs close to the umbilicus and in both groins) in one patient (0.5%), and a lymphoscintigram considered not to accurately reflect drainage from the melanoma after reconstruction of the nose in one patient (0.5%). The reason for not performing the SNB could not be identified in the remaining 24 patients (12%).

Figure 1. Examples of lymphoscintigrams that made surgeon decide to cancel the SNB.

A. Four SNs in left upper arm, two infraclavicular SNs, and two supraclavicular SNs.

B. SNs in left preauricular region, three SNs in left submandibular region, one SN in right submandibular, and one SN in right mid neck region.



Characteristics of patients, melanomas and lymphoscintigrams

Table 1 shows the clinical and pathologic characteristics of all patients who had or did not have a SNB procedure. Compared to patients who had a SNB, patients in the SNB-canceled group were more often male (69% versus 60%; $P = 0.01$), were older (mean 62 years versus 57; $P < 0.001$), more often had a primary melanoma in the head and neck region (38% versus 16%; $P < 0.001$), had a lower tumor mitotic rate (median of 2 and 3; $P = 0.01$) and had a different distribution of melanoma types ($P < 0.001$). SNB was significantly more often omitted in patients with a melanoma that was < 1 mm in Breslow thickness ($P = 0.03$). SNB-canceled patients more often had a superficial spreading melanoma and less frequently a nodular melanoma. Clark level and incidence of ulceration were similar in the two populations. Lymphoscintigraphy revealed drainage to significantly more nodal regions (mean 1.7 and 1.3) and to more SNs (mean 3.7 and 2.4) in SNB-canceled patients. Their SNs were most often located in the neck (47%), while the most frequent SN region in the others was the axilla (49%).

Table 1. Clinicopathologic characteristics of patients in whom the SNB was canceled and patients in whom SNB was performed.

Characteristic	SNB canceled (n=203)	SNB performed (n=2945)	P-value
Gender			0.01#
Male	139 (68.5)	1758 (59.7)	
Female	64 (31.5)	1187 (40.3)	
Age (years)			
Mean (SD)	62 (16.9)	57 (15.3)	<0.001§
Primary tumor site			<0.001#
Head and neck	77 (37.9)	465 (15.8)	
Upper limb	15 (7.4)	773 (26.2)	
Lower limb	45 (22.2)	740 (25.1)	
Trunk	66 (32.5)	967 (32.8)	
Breslow thickness			0.12#
0 – 1 mm	40 (19.7)	424 (14.4)	
1.01 – 2 mm	78 (38.4)	1283 (43.6)	
2.01 – 4 mm	60 (29.6)	836 (28.4)	
> 4 mm	22 (10.8)	394 (13.4)	
Missing	3 (1.5)	8 (0.3)	
Median (IQR)	1.65 (0.85-2.45)	1.80 (0.95-2.65)	0.10§
Tumor mitotic rate/mm²			0.002#
0	34 (16.7)	290 (9.8)	
≥1	156 (76.8)	2519 (85.5)	
Missing	13 (6.4)	136 (4.6)	
Median (IQR)	2 (0-4)	3 (1-5)	0.01§

Ulceration			0.49#
Absent	138 (68.0)	2047 (69.5)	
Present	43 (21.2)	730 (24.8)	
Missing	22 (10.8)	168 (5.7)	
Histology			<0.001#
Superficial spreading melanoma	96 (47.3)	1264 (42.9)	
Nodular melanoma	35 (17.2)	935 (31.8)	
Other	40 (19.7)	377 (12.8)	
Missing	32 (15.8)	368 (12.5)	
Clark level			0.06*
II	9 (4.4)	49 (1.7)	
III	48 (23.6)	784 (26.6)	
IV	125 (61.6)	1847 (62.7)	
V	16 (7.9)	223 (7.6)	
Missing	5 (2.5)	42 (1.4)	
No. of SNs identified on lymphoscintigram			<0.001*
0	7 (3.4)	1 (0)	
1	6 (3.0)	809 (27.5)	
2	31 (15.3)	984 (33.4)	
≥3	153 (75.4)	1131 (38.4)	
Missing	6 (3.0)	20 (0.7)	
Mean (SD)	3.7 (1.7)	2.4 (1.2)	<0.001§
Drainage site of identified SNs			<0.001*
Axilla	42 (20.7)	1453 (49.3)	
Groin	47 (23.2)	789 (26.8)	
Neck	95 (46.8)	618 (21.0)	
Popliteal	2 (1.0)	16 (0.5)	
Other	9 (4.4)	66 (2.2)	
Missing	8 (3.9)	3 (0.1)	
No. of drainage sites			<0.001*
0	7 (3.4)	0 (0.0)	
1	102 (50.2)	2281 (77.5)	
2	46 (22.7)	565 (19.2)	
3	36 (17.7)	82 (2.8)	
4	11 (5.4)	14 (0.5)	
Missing	1 (0.5)	3 (0.1)	
Mean (SD)	1.7 (1.1)	1.3 (0.6)	<0.001§

Data are expressed as n (%) unless otherwise specified

Pearson's chi square

§ unpaired *t* test

§ Mann-Whitney *U* test

* Fisher's exact test

Recurrence and survival

Of the 203 SNB-canceled patients, 181 (89%) were followed with high-resolution US of their lymph node fields at each follow-up visit. The other patients were followed with physical examination of their node fields, while one patient was followed with CT scans. Regional lymph node recurrence was more common in the SNB-canceled group (12% versus 4% in the SNB group), whereas a distant metastasis was the more frequent first recurrence in the SNB group (6% versus 3% in SNB-canceled group; $P < 0.001$) (Table 2).

Table 2. Characteristics regarding treatment and recurrence of patients in whom the SNB was canceled and patients in whom SNB was performed.

Characteristic	SNB canceled (n=203)	SNB performed (n=2945)	P-value
Site of first recurrence			<0.001*
Local	17 (8.4)	103 (3.5)	
In-transit	3 (1.5)	94 (3.2)	
Regional nodal	25 (12.3)	131 (4.4)	
Distant	7 (3.4)	163 (5.5)	
Multiple sites	5 (2.5)	110 (3.7)	
SN status			
Negative	NA	2531 (85.9)	NA
Positive	NA	404 (13.7)	
Missing	NA	10 (0.3)	
CLND			
Performed	NA	316 (10.7)	NA
Not performed	NA	2629 (89.3)	
No. of metastatic nodes			
Mean (SD)	2.4 (2.2)	1.7 (1.7)	0.02§

Data are expressed as n (%) unless otherwise specified

NA not applicable, CLND completion lymph node dissection

§ unpaired *t*-test

* Fisher's exact test

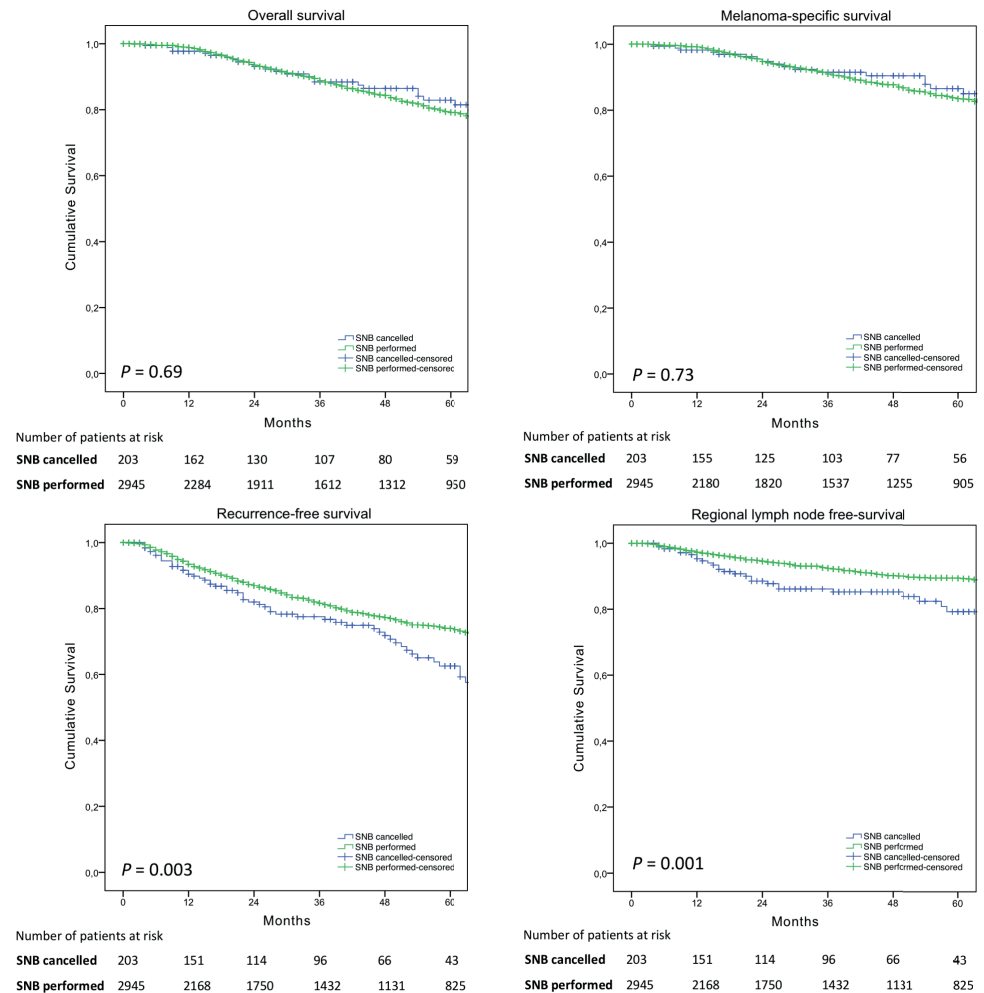
Univariable analysis showed that SNB patients had significantly improved recurrence-free and regional lymph node disease-free survival (Table 3). Melanoma-specific and overall survival were similar in the two groups (see also Figure 2). After adjusting for all major prognostic factors, the multivariable analyses showed the same associations as the univariable analyses with respect to melanoma-specific survival [hazard ratio (HR) SNB-canceled group = 0.88;

95% confidence interval (CI) 0.5 - 1.5] and overall survival (SNB-canceled group HR = 0.84; 95% CI 0.6 - 1.3).

Table 3. Results of univariable survival analyses of categorical variables.

	5-year recurrence-free survival	5-year regional lymph node-free survival	5-year melanoma-specific survival	5-year overall survival
Management				
SNB canceled	63%	79%	87%	83%
SNB performed	74%	90%	84%	79%
P-value	0.003	0.001	0.73	0.69

Figure 2. Melanoma-specific, overall, recurrence-free and regional lymph node-free survival according to type of management.



Concordant with univariable analysis, recurrence-free survival (HR = 1.59; 95% CI 1.2 - 2.2) and regional lymph node-free survival (HR = 2.24; 95% CI 1.4 - 3.5) were significantly worse without SNB in multivariable analyses. Two of the 21 patients who were followed with clinical examination of their nodal regions developed a recurrence. One patient was found to have in-transit metastases after 4 months and died of melanoma 16 months after the primary melanoma was diagnosed. Another patient developed liver and spleen metastases and died 9 months after the primary melanoma was diagnosed. None of these 21 patients developed a nodal recurrence.

Immediate lymphadenectomy versus delayed lymphadenectomy

In the SNB-canceled group, 27 patients (13%) developed a recurrence in the identified regional node field, and all but one received a delayed regional node dissection. The regional node recurrence was found at physical examination by a doctor in 10 patients (37%) and by US in nine (33%); the other eight patients (30%) noticed the recurrence themselves. The mean number of metastatic nodes in these patients was higher than in the patients who underwent a completion node dissection because of an involved SN (2.4 versus 1.7; $P = 0.02$). Five patients in the former group had distant metastases when regional nodal recurrence was diagnosed (18.5%). Melanoma-specific survival was similar in the two groups in the univariable and multivariable analysis (SNB-canceled group HR = 0.49; 95% CI 0.2 - 1.2; $P = 0.13$).

DISCUSSION

SNB remains the standard, but the new approach of follow-up with focused US after lymphoscintigraphy identifies metastases early and avoids complex surgery when the surgeon thinks that the risks exceed the potential benefits. In addition to the complex or unusual lymph drainage pattern, lack of SN visualization on the lymphoscintigrams, and an unreliable lymphoscintigram, there may have been other factors that led to the decision to omit SNB. These patients tended to be male and somewhat older, and their melanomas were more often in the head and neck region. Their lesions were generally thinner and had a lower tumor mitotic rate compared to patients in whom the surgeon proceeded with the planned SNB. Lymphoscintigraphy identified more SNs and drainage fields in patients in whom SNB was canceled than those in whom the procedure was carried out.

SNB for trunk, head, and neck melanomas was most frequently canceled, as lymphatic drainage of these primary lesions is less predictable than for melanomas on limbs, and drainage

is often to multiple sites.¹⁹⁻²¹ There is conflicting evidence on whether drainage to multiple nodal regions is an independent prognostic factor for SN metastasis.²²⁻²⁴ In truncal melanoma patients, multiple nodal region drainage was independently related to an increased risk of nodal metastases in one study, while another found no association between the number of drainage regions and disease progression.^{22,23} Drainage to a single nodal region was associated with a greater risk of locoregional recurrence in the Sunbelt Melanoma Trial.²⁴ In 35% of the patients with a melanoma in the head and neck region, a SN is located in the parotid gland.⁴ Identifying and removing such a SN can be challenging, particularly for surgeons who do not regularly undertake head and neck surgery, and there is always a risk of facial nerve injury.

There may also be a temptation to omit the procedure in patients who have a melanoma with a Breslow thickness outside the intermediate thickness range for which a survival benefit has been shown in case of metastasis.² SNB was significantly more often omitted in patients with a melanoma that had a Breslow thickness of <1 mm. Patients with thick primary tumors often have distant disease to begin with, and their prognosis is poor whether or not a node dissection is performed. However, our data do not suggest a reluctance to perform SNB in these patients, probably because of its value to improve regional control. This is relevant because operations for a palpable nodal recurrence are often more extensive; require a longer hospital admission; are associated with more morbidity, higher costs, and reduced quality of life; and may be followed by radiotherapy.²⁵ In addition to differences in lymphoscintigraphy findings and primary tumor factors, the population in whom the SNB was canceled was significantly older than the other group. Although increasing age is known to be associated with a reduced risk of nodal metastases, the patients' charts did not mention age as a reason to refrain from SNB.^{26,27}

The majority (89 %) of the patients without SNB were followed with high-resolution US of their lymph node regions at each follow-up visit. Guided by lymphoscintigrams including SPECT/CT since 2008, the nuclear medicine physicians at our institution mark the location of the SN or SNs with a small tattoo on the skin. This facilitates the relocalization of these SNs so that the nodes directly at risk of containing metastasis can be scrutinized using focused US. The minimum size for a lymph node metastasis to be detectable with US is commonly reported to be around 3 mm in the neck, 4 mm in the groin, and 5 mm in the axilla, whereas physical examination picks up a metastatic node only when it is at least 1 cm in size under favorable conditions.^{28,29}

There is evidence that routine US improves detection of nodal recurrence in patients who have not had a SNB.³⁰ The sensitivity of US ranges from 92 to 99% with a specificity of 98%,

while the sensitivity of physical examination is between 25 and 51% with a specificity of 91-98%.³¹⁻³⁹ A meta-analysis confirmed that US of lymph nodes for the detection of metastases is superior to physical examination.⁴⁰ In the present study, a third of the nodal recurrences were detected by focused US, confirming the usefulness of this technique in the follow-up of these patients.

Patients without SNB understandably had worse regional lymph node-free survival and a worse recurrence-free survival compared to patients who did undergo the procedure. If recurrence occurs in SNB-positive patients who have had a completion lymph node dissection, it will most likely be distant nodal or visceral metastasis. When regional node dissection was performed because of nodal recurrence, significantly more nodes were found to be involved compared to SN-positive patients who had an immediate lymphadenectomy. Although the number of metastatic nodes is known to be inversely correlated with survival, melanoma-specific survival was found to be similar in the two groups when multivariable analysis was performed.⁴¹ One may contemplate that the number of patients in the study may have been too small to establish an existing survival difference.

A number of studies have compared SNB with nodal observation, but none of these mentioned patients in whom SNB was canceled after lymphoscintigraphy and in whom the nodes were followed with focused US.^{2,42-48} To our knowledge, ours is the first such study. Refraining from SNB is not only the subject of this study but also might introduce ascertainment bias when comparing outcomes to those of patients who did undergo the procedure. The short follow-up for some patients and the incomplete pathology data (mainly on tumor mitotic rate and ulceration) are other limitations of the present study.

CONCLUSION

Omission of SNB after lymphoscintigraphy occurred in 6.4 % of the patients and was mainly due to the presence of multiple SNs and/or drainage sites. These patients are generally older and tend to have a melanoma in the head and neck region or on the trunk. Although associated with a worse regional lymph node-free survival and more involved nodes when a regional nodal metastasis occurs, overall and melanoma-specific survival are not impeded. As a result, US follow-up of SNs identified on lymphoscintigraphy is an acceptable management strategy when facing a challenging SNB.

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