Ann Surg Oncol (2015) 22:2972–2977
DOI 10.1245/s10434-015-4615-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – MELANOMAS

Detailed Pathological Examination of Completion Node Dissection Specimens and Outcome in Melanoma Patients with Minimal (<0.1 mm) Sentinel Lymph Node Metastases

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ABSTRACT

Background. Nonsentinel lymph nodes (NSLNs) are rarely involved in patients with minimal volume melanoma metastases in sentinel lymph nodes (SLNs). Therefore, it has been suggested that completion lymph node dissection (CLND) is not required. However, the lack of routine immunohistochemical staining and multiple sectioning may have led to failure to identify additional positive nodes. The present study sought to more reliably determine the tumor status of NSLNs in patients with minimally involved SLNs and their clinical outcome.

Methods. A total of 21 tumor-negative CLND specimens from 20 patients with SLN metastases of <0.1 mm in diameter treated between 1991 and 2013 were examined with a more detailed pathologic protocol (five new sections stained with/for H&E, S-100, HMB45, Melan-A, and H&E). Clinical follow-up data were also obtained.

Results. Of the 343 examined NSLNs, 1 was found to harbor a 0.18-mm subcapsular sinus metastasis. No metastases were identified in the other NSLNs. Median follow-up was 48 months (range 17–130 months). Six patients (30 %) developed a recurrence. At the end of follow-up, 15 patients (75 %) were alive without sign of melanoma recurrence and 5 patients (25 %) had died of melanoma. Estimated 5-year melanoma-specific survival was 64 %. The patient with the additional positive NSLN remains without recurrence after 130 months follow-up.

Conclusions. Although the risk of additional nodal involvement is low, detailed pathologic examination may identify NSLN metastases not identified using routine protocols. Therefore, nodal clearance appears to be the safest option for these patients, pending the results of prospective trials.

Sentinel lymph node (SLN) biopsy provides accurate staging of melanoma patients and important prognostic information. It has also been shown that regional disease control is improved in SLN-positive patients who undergo a completion lymph node dissection (CLND).[1] Furthermore, evidence of improved melanoma-specific survival in these patients has been reported.[1] Additional involved nodes are found in only 7–33 % of CLND specimens, raising the possibility that the majority of the patients do not have additional nodal metastases and could potentially be safely spared a node dissection and its associated morbidity.[1] Multiple studies have found that SLN tumor burden is a strong predictor of both non-SLN (NSLN) positivity and patient outcome in SLN-positive melanoma patients.[2] One study of 15 patients reported no additional metastases in CLND specimens and a 5-year overall survival rate of 100 % in patients with a SLN metastasis less than 0.1 mm.[3] Based on this study and 3 subsequent multicenter studies—two reporting 91 % and the other 83 % 5-year overall survival rates for such patients—the investigators concluded that these minimal metastases in SLNs are biologically different from larger metastases in that

First Received: 7 December 2014;
Published Online: 20 May 2015

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they do not progress, and thus these patients can be safely spared a CLND.[3–6] The appropriateness of this conclusion has been challenged because of the limited clinical follow-up in these studies, some overlapping cases, and possible lead-time bias. Additional limitations of these studies include the relatively small numbers of nodes that were examined per dissection specimen and the failure to examine multiple sections or immunohistochemistry (IHC) for pathologic examination of NSLNs in CLND specimens. As a consequence, the number of involved nodes may have been underestimated in these studies, which would undermine the basis for the authors' recommendations.

The aims of the present study were to firstly establish the frequency of NSLN involvement in patients with minimal SLN metastasis through detailed pathologic analysis, including using IHC, of all nodes in CLND specimens previously pathologically reported as negative, and secondly, to determine their clinical outcome.

PATIENTS, MATERIALS, AND METHODS

Patient Selection

This study was conducted with institutional Human Ethics Review Committee approval. A total of 20 patients with SLN metastases with a maximum diameter of less than 0.1 mm and reported to be without positive lymph nodes in the CLND specimen managed between January 1991 and December 2013 were identified from the Melanoma Institute Australia research database. One patient had two eligible nodal fields. Patient and tumor characteristics are summarized in Table 1. Of the 20 patients, 8 were male (40 %) and 12 female (60 %). The median age was 55 years (range 25–78 years). The median Breslow thickness of the primary tumors was 1.58 mm (range 0.40–6.00 mm), 7 (35 %) were ulcerated, and the median mitotic rate was 3/mm^2 (range 0–21/mm^2). SLN biopsy was performed in the neck in 2 patients, the axilla in 6 patients, and the groin in 12 patients (with 1 patient having bilateral groin dissections). The median number of excised SLNs was 2 (range 1–5), and the median maximum diameter of the largest tumor deposit in the SLN was 0.07 mm (range 0.02–0.09 mm). The median number of nodes per CLND was 12 (range 6–69).

SLN Biopsy and Completion Lymph Node Dissection

Dynamic and static lymphoscintigraphy using technetium-99m antimony trisulfide colloid was followed by SLN identification using blue dye and a hand-held gamma-ray detection probe. A SLN was defined as a lymph node receiving direct lymphatic drainage from the primary melanoma site. SLNs were cut into 3-mm thick slices and embedded in paraffin blocks. Four (five after 2008) consecutive sections were cut and stained with hematoxylin and eosin (H&E; first and last section) and IHC (S-100, HMB45, and after 2008 Melan-A). Lymph nodes from the CLND specimen had originally been sliced into 3-mm thick slices (or processed whole if 3 mm or less in thickness), embedded in paraffin, and stained with H&E only.

Pathological Assessment

Formalin-fixed, paraffin-embedded tissue samples of all CLND lymph nodes were retrieved from the archival files of the Department of Tissue Pathology and Diagnostic Oncology at the Royal Prince Alfred Hospital, Sydney, Australia. Five consecutive 4-μm thick sections were cut from the original paraffin block(s) of each node and stained according to the SLN protocol. The first and last sections were stained with H&E and analyzed in each case to confirm the presence of lymph node tissue. The second, third, and fourth sections were stained with IHC for S-100, HMB45, and Melan-A, respectively. IHC was performed on a Dako Autostainer Plus (Dako, Glostrup, Denmark) using the Ultravision Quanto AP Detection System (TL-060-QAL, Thermo Scientific, USA) and visualized using the Permanent Fast Red Quanto Substrate System (TA-060-QAL, Thermo Scientific, USA). Following deparaffinization of the tissue sections, heat-induced epitope retrieval was applied for 20 min using high-pH Dako Envision FLEX target retrieval solution (Dako, USA). The sections were incubated with monoclonal mouse anti-Human Melanosome Clone HMB45 (1:100 dilution; Dako), monoclonal mouse anti-Human Melan-A, Clone A103 (1:50 dilution; Dako), or polyclonal rabbit anti-Human S100 A and B (1:400 dilution; Novocastra, Leica Biosystems, Germany), respectively, for 30 min followed by incubation with hematoxylin (Dako) for 5 min.

Histological Assessment

Two investigators (L.H.J.H. and S.W.) independently evaluated all histology slides. Morphological and IHC characteristics were used to identify nodal melanoma metastases.[7] Cases were scored as positive based on IHC staining and cell morphology. Cases in which there was diagnostic uncertainty were reviewed by R.V. and R.A.S.

Statistical Analysis

The SPSS statistical package version 22 (SPSS Inc., Chicago, IL) was used for all statistical analyses. Disease-free survival and melanoma-specific survival were calculated from the time of SLN biopsy and were censored at the

TABLE 1 Patient and tumor characteristics

Case no.	Age	Sex	Primary melanoma					SLN biopsy site	No of SLNs positive/ removed	Maximum size SLN tumor deposit (mm)	No of nodes in CLND	Positive NSLNs on review/ presence of nevus	Recurrence	Status at last follow-up
			Anatomic site	Melanoma subtype	Breslow thickness (mm)	Mitotic rate (/mm^2)	Ulceration							
1	48	F	Trunk	SSM	1.05	2	No	Groin	1/1	0.06	22	0	No	Alive NSR
2	39	F	Trunk	NM	0.65	2	No	Axilla	1/1	0.05	7	0	No	Alive NSR
3	78	M	Trunk	NM	3.70	18	Yes	Axilla	1/2	0.06	20	0	Yes	Dead of melanoma
4	54	M	Trunk	NM	6.00	21	Yes	Axilla	1/5	0.07	27	0, nevus	Yes	Dead of melanoma
5	65	F	Lower limb	ALM	3.50	3	No	Groin	1/1	0.07	7	0	Yes	Dead of melanoma
6	72	M	Lower limb	ALM	3.10	0	No	Groin	1/2	0.09	7	0	Yes	Dead of melanoma
7	60	F	Upper limb	SSM	1.10	0	No	Axilla	1/4	0.09	20	0	No	Alive NSR
8	61	F	Lower limb	MBN	1.15	5	No	Groin	1/2	0.07	13	0	No	Alive NSR
9	34	F	Lower limb	Not known	1.10	3	Unknown	Groin	1/3	0.09	24	0	No	Alive NSR
10	34	F	Lower limb	SSM	0.95	2	No	Groin	1/3	0.05	11	1, nevus	No	Alive NSR
11	43	F	Lower limb	SSM	0.95	1	No	Groin	1/3	0.09	8	0	No	Alive NSR
12	49	F	Lower limb	NM	2.50	10	Yes	Groin	1/2	0.09	6	0	Yes	Dead of melanoma
13	66	F	Trunk	SSM	3.88	2	Yes	Axilla	1/2	0.05	16	0	No	Alive NSR
14	62	M	Lower limb	NM	0.40	0	Unknown	Groin	1/2	0.09	16	0	Yes	Alive NSR
15	45	M	Head and neck	NM	1.20	2	Unknown	Neck	1/3	0.05	69	0	No	Alive NSR
16	25	M	Trunk	SSM	1.00	2	No	Neck	1/4	0.05	17	0	No	Alive NSR
17	32	M	Lower limb	SSM	1.00	11	Yes	Groin	1/3	0.07	11	0	No	Alive NSR
18	76	F	Lower limb	NM	4.70	3	Unknown	Groin	1/3	0.02	8	0	No	Alive NSR
19	55	F	Trunk	SSM	2.20	15	Yes	Left groin	1/2	0.08	6	0	No	Alive NSR
								Right groin	1/2	0.07	6	0, Nevus		
20	57	M	Upper limb	Not known	3.30	6	Yes	Axilla	1/2	0.04	7	0	No	Alive NSR

SLN sentinel node, *NSLN* nonsentinel node, *CLND* completion lymph node dissection, *M* male, *F* female, *ALM* acral lentiginous melanoma, *MBN* malignant blue nevus, *NM* nodular melanoma, *SSM* superficial spreading melanoma, *Alive NSR* alive, no sign of recurrence

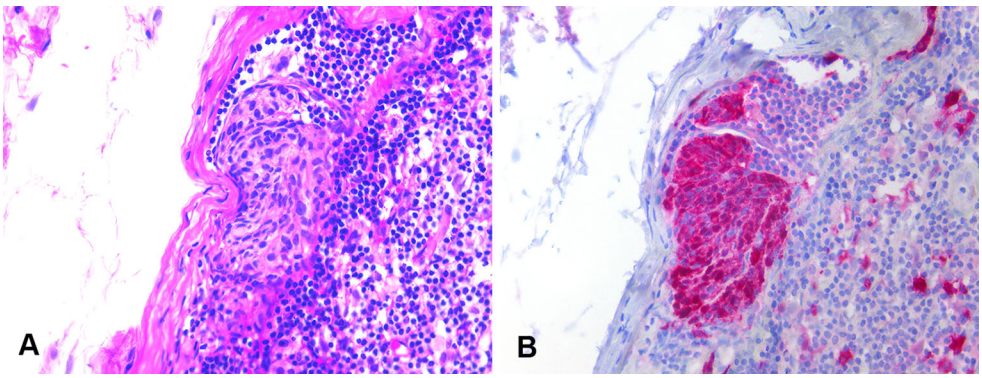

FIG. 1 Metastatic melanoma deposit in the subcapsular sinus of the positive lymph node from a CLND specimen. Original magnification ×400. **a** H&E stained section. **b** Section stained immunohistochemically for S-100 protein

last contact date if there were no events. Survival analysis was performed using the Kaplan–Meier method.

RESULTS

Detailed Pathologic Analysis of NSLN Nodes in CLND Specimens

Multiple H&E and IHC-stained sections of all 343 lymph nodes identified in the CLND specimens were histologically examined. In one patient a metastasis was identified in 1 of 11 lymph nodes (Fig. 1; Table 1). This subcapsular sinus deposit had a maximum diameter of 0.18 mm. No metastases were identified in the multiple tissue sections of the other 342 lymph nodes. In three patients a capsular nevus was identified.

Patient Follow-Up Data

Median follow-up after SLN biopsy was 48 months (range 17–130 months). The patient with the NSLN metastasis has had no disease recurrence after 130 months (Table 1). Of 20 patients, 6 (30 %) developed a recurrence. In three patients (14 %) the first presentation of recurrence was local/in transit. Of these three patients, 1 developed in transit metastases after 1 year, distant metastases 2 years later, and he died 7 months thereafter. The second patient developed in transit metastases 15 months after SLN biopsy, subsequent distant metastases within a month, and she died 2 months later. The third patient developed a local recurrence after 16 months, 4 months later in transit disease, 2 years later distant metastases, and he died the subsequent month. The fourth patient developed a recurrence in the contralateral node field after 17 months and an in transit metastasis after 23 months on the ipsilateral side. He has remained disease-free after excision. The fifth patient developed distant metastases after 26 months and died 20 months later. The sixth patient developed distant metastases after 17 months and died 2 months later. At the end of follow-up, 15 patients (75 %) were alive without sign of melanoma recurrence and 5 patients (25 %) had died of melanoma. Kaplan–Meier estimated 5-year melanoma-specific survival was 64 % (Fig. 2) and estimated 5-year recurrence-free survival was 68 %.

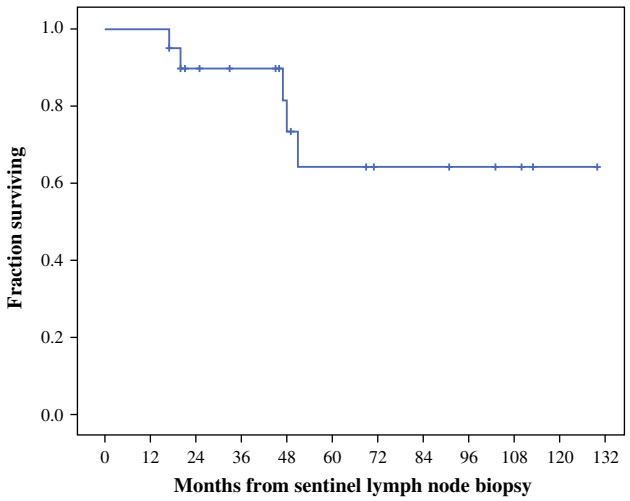

FIG. 2 Kaplan–Meier estimated melanoma-specific survival

DISCUSSION

Whether or not to perform a CLND in some SLN-positive melanoma patients is a subject of debate.[8–11] Most currently available data support the conclusion that all melanoma SLN metastases, however small, will ultimately progress to clinically relevant disease if the patient is followed for a sufficient period of time.[1] Ongoing clinical trials, such as the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) and a European Organisation for Research and Treatment of Cancer study, will ultimately determine whether CLND is necessary in all patients with a positive SLN.[12,13] Pending the outcome of these trials, many investigators have attempted to identify

predictors of both NSLN involvement in CLND specimens and patient outcome in SLN-positive patients. Following a review of the literature, we identified 31 predictive factors based on characteristics of the patient, the primary melanoma, or the SLN metastasis. The tumor burden in the SLN is clearly an important potential predictive factor, and multiple individual factors reflecting aspects of disease burden have been studied. While in large patient cohorts many of these factors have been predictive of both NSLN positivity and patient outcome, thus far none of these has proved to be accurate enough to predict CLND status in individual patients.[2] Concerning prediction of outcome, 1 study evaluated the natural course of the disease in 16 patients with a positive SLN with tumor penetrative depth $\leq$0.30 mm who were observed for more than 5 years and found no nodal recurrence.[11,14]

Studies assessing predictors of NSLN metastasis are frequently hampered by limitations in the pathologic assessment of CLND specimens including small numbers of examined NSLNs, minimal sampling of each NSLN, not using sensitive IHC pathological staining techniques, and lack of interobserver reproducibility for certain scoring systems. Despite the limited pathological assessment, the survival reported in these studies was between 80 and 100 % for patients with minimal SLN tumor burden.[3–6] However, median follow-up was only 30–37 months, and much longer follow-up would be required to conclude that it is safe to omit CLND in these patients. The present study is the first to provide a thorough validation of the tumor status of NSLNs in patients with a minimally involved SLN. Using more detailed sampling and pathologic examination of all NSLNs from CLND specimens previously reported as negative, we found 1 NSLN metastasis in 1 of 20 patients. This highlights the fact that a metastasis in a NSLN may be missed because of a sampling error. Therefore, previous studies concluding patients with minimally involved SLNs do not require CLND as such specimens were reported pathologically as metastasis-free should be interpreted with caution, because these studies were relying on minimal pathologic examination of NSLNs in CLND specimens. The fact that more recent studies have demonstrated that with longer follow-up some patients with minimal SLN metastases will die of melanoma (including 25 % of patients in this study), suggests that even these patients have a significant risk of disease progression.[15,16] This said, it is also known that even 10–15 % of SLN negative patients will die of melanoma within 5–10 years.[1] CLND can prevent further dissemination from involved lymph nodes but cannot change the clinical outcome of patients who already have distant metastases.

A possible limitation of our study is the extent of pathological assessment. Using our standard SLN pathologic examination protocol, only five extra sections were cut. For logistic reasons, we were unable to examine the SLN tissue in its entirety (which would require examination of up to 600 sections per tissue block). As our protocol already resulted in more than a thousand slides to assess, an even more extensive evaluation was beyond the capability of resources available to us.

Our study reveals that the prognosis of patients with a minimal SLN metastasis is not as good as is often assumed. Of twenty patients with a SLN metastasis with a diameter less than 0.1 mm and a negative CLND specimen, 6 patients (30 %) developed a recurrence, although none of them recurred in the surgically treated nodal field. Our cohort had an estimated 5-year melanoma-specific survival of 64 %, whereas Van Akkooi et al. and Van der Ploeg et al. reported 5-year survival rates between 83 % and 100 % in overlapping patient cohorts.[3–6] An explanation for this discrepancy may be the length of follow-up or the sample size. The Van Akkooi and Van der Ploeg studies had median follow-up of 30–37 months, whereas in our study the median follow-up was 48 months. The excellent survival rates of Van Akkooi et al. and Van der Ploeg et al. might have been influenced by lead-time bias, which is a known confounder in the interpretation of survival data in clinical studies assessing minimally involved SLNs. Lead-time bias refers to the observation that the smaller the metastasis, the longer it is likely to take for the disease recurrence to be detected, as described by Scolyer et al.[9] It is known that in some patients melanoma metastases may be clinically undetected for more than 10 years after initial treatment.[1] Therefore, in patients with minimal volume SLN metastases, very long clinical follow-up is required to accurately evaluate survival data. This said, our study has a small sample size and a random effect cannot be excluded. The results of MSLT-II may shed further light on the clinical benefit of CLND in patients with minimally involved SLNs.[12]

A general argument often raised when considering the topic of whether or not a CLND should be performed is its complication rate. Several studies have reported complication rates of between 23 and 66 % after CLND compared with rates between 5 and 14 % after SLN biopsy alone.[16–20] Nevertheless, compared with patients with palpable nodal disease, a node dissection for a positive SLN often requires a less extensive operation and has been clearly shown to be associated with less morbidity, and a better quality of life, with no requirement for postoperative radiation therapy.[21,22,23]

In conclusion, melanoma patients with minimal-volume SLN metastases have a low risk of additional NSLN metastases in CLND specimens, but in this study they had a 64 % 5-year melanoma-specific survival. Despite the small size of the SLN metastasis, these patients may harbor NSLN involvement not identified utilizing routine

pathologic examination protocols. At Melanoma Institute Australia, CLND remains the standard treatment of patients with an involved sentinel node.

ACKNOWLEDGMENT This project received a Grant from the Friends of the Mater Foundation, North Sydney NSW. LHJH received a research grant from the Groningen Melanoma and Sarcoma Foundation and was funded by het Vreedefonds and Melanoma Institute Australia. The authors gratefully acknowledge the support and assistance of colleagues at the Department of Tissue Oncology and Diagnostic Pathology, Royal Prince Alfred Hospital and Melanoma Institute Australia. Funding support from the National Health and Medical Research Council, Cancer Institute New South Wales, Melanoma Institute Australia, and The Melanoma Foundation of the University of Sydney is also gratefully acknowledged. R.A.S. is a National Health and Medical Research Council Practitioner Fellow, and R.V. is supported by a Cameron Fellowship through Melanoma Institute Australia. J.F.T. is supported by the Melanoma Foundation of the University of Sydney.

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