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Review

Sentinel Node Biopsy in Melanoma: A Short Update

Gerardo Ferrara[a] Antonietta Partenzi[b] Alessandra Filosa[a]

[a]Anatomic Pathology Unit, Macerata General Hospital, Macerata, Italy;
[b]Anatomic Pathology Unit, USL Umbria 2, Foligno Hospital, Foligno, Italy

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Abstract
Several controversies are still ongoing about sentinel node biopsy in melanoma. It is basically a staging procedure for melanoma >0.75 mm in thickness or for thinner melanoma in the presence of ulceration, high mitotic rate, and/or lymphovascular invasion. Complete lymph node dissection after a positive sentinel node can also allow a better locoregional disease control but seems not to prevent the development of distant metastases. The use of sentinel node biopsy in atypical Spitz tumors should be discouraged because of their peculiar biological properties.

Introduction

Twenty-five years after its introduction in clinical practice, several questions still remain to be answered about sentinel node biopsy (SNB) in melanoma. Its undisputable indication is disease staging, i.e., the recognition of "clinically occult" stage III (N+) disease. The National Comprehensive Cancer Network (NCCN) indication for SNB is Breslow thickness (BT) >0.75 mm but also, on an individual basis, for thinner melanoma is the presence of "conventional risk factors" (ulceration, high mitotic rate, lymphovascular invasion) [1]. Uncertainty persists for (i) patients older than 70 years: in these patients the lower incidence of nodal metastasis and the higher 5-year mortality rate discourage SNB [2]; (ii) BT >4 mm (pT4) and/or micromacrosatellitosis (pN2c): under these circumstances, the high disease stage makes SNB a means to simply achieve a palliative locoregional control of the disease; (iii) regression: this may underestimate BT but might be even a favorable prognostic factor; (iv) desmoplastic

Gerardo Ferrara, MD
Anatomic Pathology Unit, Macerata General Hospital
Via Santa Lucia, 2
IT–62100 Macerata (Italy)
E-Mail gerardo.ferrara@libero.it

Table 1. Comparison of the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) data from the 2006 third interim analysis and from the 2014 final report

	Third interim analysis, 2006 [4]		Final report, 2014 [5]			
Follow-up:	5 years		10 years			
Selection criteria:	Patients with intermediate thickness primary cutaneous melanoma		Patients with intermediate and/or thick primary cutaneous melanoma			
Thickness:	Breslow 1.20–3.50 mm		Breslow 1.20–3.50 mm		Breslow >3.50 mm	
Arms:	SNB	observation	SNB	observation	SNB	observation
Enrolled patients, *n*	814	533	814	533	186	128
Compliant patients, *n*	769	500	770	500	173	128
Melanoma-specific survival, %	*87.1±1.3*	*86.6±1.6*	*81.4±1.5*	*78.3±2.0*	*58.9±4.1*	*64.4±4.6*
Disease-free survival, %	*78.3±1.6*	*73.1±2.1*	*71.3±1.8*	*64.7±2.3*	*50.7±4*	*40.5±4.7*
Melanoma-specific survival if N+, %	*n.g.*	*n.g.*	*62.1±4.8*	*41.5±5.60*	*48.0±7.0*	*45.8±7.8*
Melanoma-specific deaths, n/total (%)	96/769 (12.5)	69/500 (13.8)	125/770 (16.2)	103/500 (20.6)	64/173 (36.7)	39/117 (34.1)
N+ melanoma-specific deaths, n/total deaths (%)	32/96 (33.3)	38/78 (48.7)	n.g.	n.g.	n.g.	n.g.
N– melanoma-specific deaths, *n*/total deaths (%)	64/96 (66.7)	40/78 (51.3)	n.g.	n.a.	n.g.	n.a.
Sentinel node positives, *n*/total (%)	122/764 (15.9)	n.a.	122/764 (15.9)	n.a.	57/173 (32.9)	n.a.
Disease-free survival if N+, %	53.4±4.9	n.a.	62.1±4.8	n.a.	48.0±7.0	n.a.
Nodal relapse, *n*/total, %	26/769 (3.4)	78/500 (15.6)	31/765 (4.0)	87/500 (17.4)	12/173 (6.9)	44/117 (37.6)
Overall incidence of nodal metastatic melanomas, *n*/total, %	122+26/769 (19.2)	78/500 (15.6)	122+31/769 (19.8)	87/500 (17.4)	64+12/173 (43.9)	44/117 (37.6)
Prognostic false negatives, *n*/total, %	26/642 (4.05)	n.a.	31/643 (4.8)	n.a.	12/116 (10.3)	n.a.
Melanoma-specific survival if N+, %	72.3±4.6	52.4±5.9	62.1±4.8	41.5±5.60	48.0±7.0	45.8±7.8
Prognostic false positives, %	19.2 – 15.6 = 3.6	n.a.	19.8 – 17.4 = 2.4	n.a.	43.9 – 37.6 = 6.3	n.a.
Melanoma-specific death after 5 years, *n*	n.a.	n.a.	125–96 = 29	103–69 = 34	n.a.	n.a.
Nodal relapse after 5 years, *n*	n.a.	n.a.	31 – 26 = 5	87 – 78 = 9	n.a.	n.a.

The results concerning the end points of the study are given in italics. Prognostic false negatives refer to SNB– cases in which nodal recurrence was found at follow-up. Prognostic false positives refer to the percent difference between the SNB+ cases and nodal recurrences in the observation group. SNB, sentinel node biopsy; n.g., not given; n.a., not applicable.

subtype: this has a 9% incidence of nodal metastases [3] (enough for SNB), but it is mainly diagnosed in the head-neck area (where the surgical failure rate is high) in elderly patients (see above), both features arguing against SNB.

Review/Discussion

Regarding the therapeutic implications of SNB, the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) compared the 5-year [4] and 10-year [5] outcome of patients with melanoma ≥1.20 mm thick who were randomly assigned to an SNB arm (complete lymph node dissection [CLND] if SNB+) or an observation arm (elective lymph node dissection if clinical nodal relapse) (see Table 1). After 10 years, the rate of nodal relapse after a negative

Table 2. Differential criteria between nodal nevus and nodal metastatic melanoma

Nodal nevus	Nodal metastatic melanoma
Capsular/trabecular location	Intraparenchymal location
Monomorphic cells	Pleomorphic cells
Cells with little cytoplasm	Cells with abundant cytoplasm
Reticulin around single cells	Reticulin around nests
HMB45 negative	HMB45 positive
MIB1/KI67 negative	MIB1/KI67 highly labeled
p16 positive	p16 negative
Soluble adenylyl cyclase: dot-like Golgi staining pattern	Soluble adenylyl cyclase: nuclear or diffuse cytoplasmic staining pattern
CD31/ERG/podoplanin: endothelial lining around melanocytes	CD31/ERG/podoplanin: curvilinear vessels around nests
Melanoma fluorescence in situ hybridization test negative	Melanoma fluorescence in situ hybridization test positive

SNB was much lower than the nodal relapse rate in the observation arm (4 vs. 17.4%), thus confirming that SNB is effective in selecting patients for CLND and locoregional disease control. More importantly, SNB+ patients had a better 10-year melanoma-specific survival compared with the relapsing patients of the observation group (62.1 ± 4.8 vs. 41.5 ± 5.60%). In our view, however, since no significant difference in the 10-year melanoma-specific survival was found between the two groups (81.4 ± 1.5% vs. 78.3 ± 2.0), SNB– patients paradoxically might have had a worse melanoma-specific survival than the nonrelapsing patients of the observation group (SNB prognostic false negatives; data not shown). In addition, a proportion of SNB+ cases might have been prognostic false positives, the latter corresponding to the difference between the rates of nodal involvement in the SNB arm (SNB+ plus SNB– with nodal recurrence) and of the nodal disease in the observation group [6]. Given an optimal randomization, such a difference should have been progressively set to zero. Instead, the difference, although decreasing from the third interim analysis (3.6%) [4] to the final report (2.4%) [5], was still sizable after 10 years. Pathology protocols must consider the occurrence of prognostic false positives: a complete step-sectioning of the SNB samples allows the detection of an additional 28% of metastases compared with the EANM-EORTC protocol [7], but many of the additional SNB+ will be prognostic false positives. Molecular hyperstaging with reverse transcriptase polymerase chain reaction has the same problem; moreover, it is hampered by the incidence of false positives due to nodal nevi. Thus, the implementation of more accurate pathology protocols for SNB examination is probably to be discouraged.

Current guidelines recommend that SNB+ cases must be managed with CLND [1]. However, provided that about 20% of intermediate thickness melanomas are SNB+, nonsentinel node involvement is expected to be found in 20% of this 20%, i.e., only in 4% of all intermediate thickness melanomas. Some models have been proposed to predict positivity of nonsentinel nodes in SNB+ cases. Irrespective of these, however, indication for CLND is now less stringent according to the results of the third analysis of the MSLT-2 trial, a randomized controlled trial comparing CLND versus ultrasound-based observation in 1,755 SN-positive melanoma patients [8]. In this trial, after 3 years, the CLND group showed a slightly higher disease-free survival than the observation group (68 ± 1.7 vs. 63 ± 1.7%), due to a higher rate of disease control in the regional nodes (92 ± 1.0 vs. 77 ± 1.5%); however, no statistically significant 3-year melanoma-specific survival between the two groups was detected (86 ± 1.3

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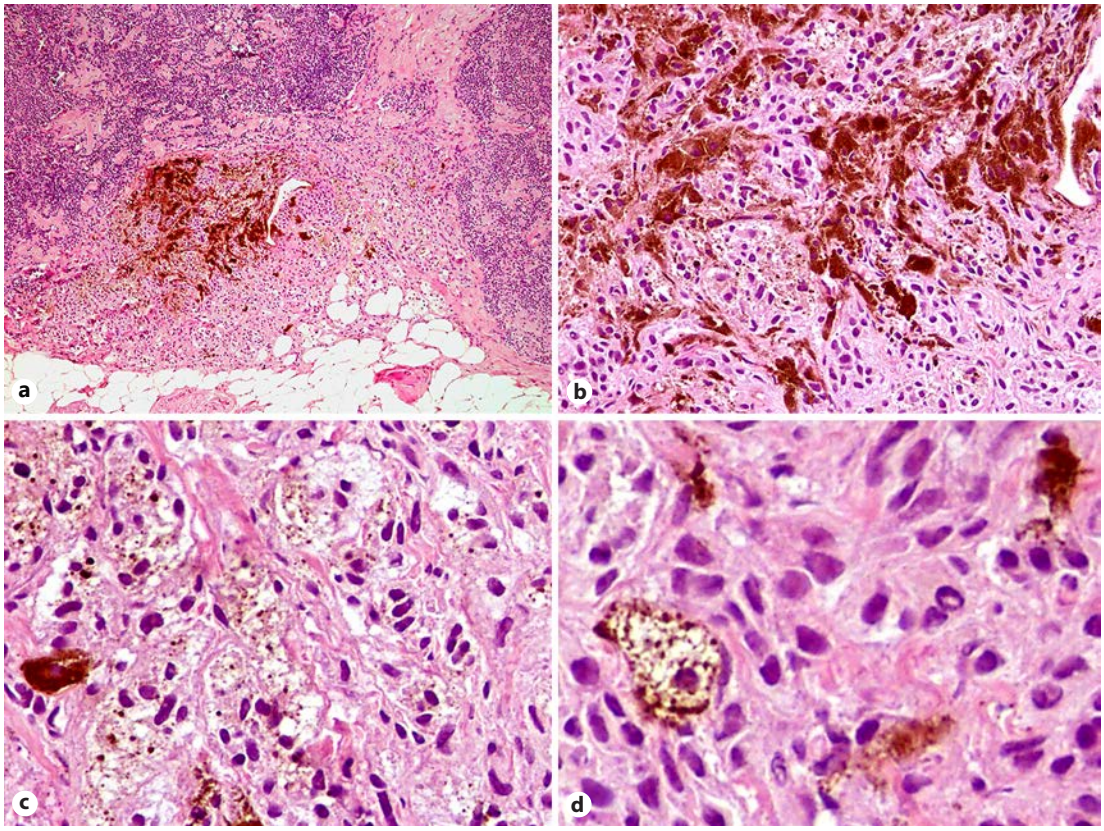

Fig. 1. Nodal deep penetrating nevus: the lesion is intracapsular (**a**) with a checkerboard pattern of melanin distribution (**b**), melanocytes with sebocyte-like features (**c**), and random cytological atypia (**d**).

and 86 ± 1.3%, respectively). Mainly based on these data, the NCCN guidelines now consider the "active nodal basin surveillance" as an alternative to CLND in sentinel node-positive melanoma patients [1].

Based on the assumption that a nodal disease means "metastasis" and, in fact, "malignancy" SNB was proposed for diagnostic purposes in difficult-to-diagnose melanocytic skin lesions [9]. The differential diagnosis between nodal nevus and metastatic melanoma is based on similar criteria as for cutaneous lesions (Table 2). Therefore, performing an SNB in morphologically equivocal primaries can be simply a "deferred diagnostic decision." Figure 1 shows an extraordinary case of deep penetrating nevus of the nodal capsule in a patient undergoing SNB for breast cancer. This case is an example of the scenarios which can complicate the microscopic evaluation of SNB. In addition, a recent meta-analysis showed that 98–99% of patients with atypical Spitz tumors had no evidence of disease after a median follow-up of 59 months, in spite of a 39% rate of SNB+ [10]. In order to avoid overtreatment of these patients, our strategy for morphologically ambiguous melanocytic tumors is to individuate the sentinel node with lymphoscintigraphy and then monitor it with echotomography.

In conclusion, SNB in melanoma is a staging procedure; it can help in selecting patients for a better locoregional disease control with CLND. Both SNB and CLND should ideally be discussed case by case, also because their role in preventing metastatic disease is disputable. SNB for difficult-to-diagnose melanocytic tumors should be discouraged.

Statement of Ethics

The present work complies with the guidelines for human studies and animal welfare regulations. Since it is a review, it required no patient consent, no study protocol approval, and no animal experiments.

Disclosure Statement

The authors have no conflicts of interest to disclose. There was no funding source for this work.

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