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Can sentinel node biopsy be safely omitted in thin melanoma? Risk factor analysis of 1272 multicenter prospective cases

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ABSTRACT

Background: The indication to sentinel node biopsy (SNB) for thin melanomas (Breslow <1 mm) is still subject to controversies**.** The aim of this paper is to review all SNB performed for thin melanoma and to analyze factors related to lymphatic metastasis. Moreover, the diagnostic performance of the 5th, 6th, 7th and 8th AJCC classifications for cutaneous melanoma were investigated.
Methods: All sentinel node biopsies performed for thin melanomas were selected from a multicentre prospectively-collected database. For each patient the following was collected: age, sex, date of treatment, site of primary melanoma, histopathologic features (Breslow, Clark, number of mitoses/mm^2, presence of ulceration) and the results of the sentinel node biopsy.
Results: From 1998 to 2017 were performed a total of 1272 SNB for thin melanoma. Mean age was 51years with 48.7% of male patients. Overall, 5.6% positive SNB were found. At univariate and multivariate analyses, Breslow thickness and ulceration were related to the presence of lymphatic metastasis. We compared the four versions of the AJCC classification: among pT1a patients there were respectively 5.32%, 5.63%, 3.72% and 3.49% of positive SNB.
Conclusions: in thin melanoma Breslow thickness and ulceration were the only factors related to a positive SNB. Although convincing improvements resulted from the implementation of AJCC classifications with a reduction of positive biopsies among pT1a, a 10.71% rate among all positive nodes remains in the low-risk group. No recommendations can be drawn from this research and adjunctive evidences are needed to better identify patients at risk of nodal metastasis.

Introduction

Cutaneous melanoma represents the skin cancer which has the worst prognostic features. Up to 70% of patients with a newly diagnosed melanoma have a Breslow thickness <1.0 mm, i.e. “thin melanomas”. Despite the low melanoma-specific mortality for said tumors (4–7%), approximately 23% of deaths due to melanoma occur in patients with such lesions [1].

Since its introduction in 1992 by Morton [2], the Sentinel Node Biopsy (SNB) has been proved to be a powerful diagnostic tool for patients with cutaneous melanoma, allowing the detection of preclinical lymph node metastases. If its impact on overall survival has been questioned by the MSLT1 study [3,4], the prognostic importance of SNB in the identification of patients at high risk of relapse remains a cornerstone in the management of these patients, in particular in light of the evolution of medical therapy and the likely introduction of adjuvant therapies.

A general agreement on indications to SNB for melanomas with intermediate thickness has been reached; however, thin melanomas are still subject to controversies. Several factors have been

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considered as risk factors for nodal involvement (N+) in patients with thin melanoma: Breslow thickness > 0.75 mm, presence of mitoses, presence of ulceration, lympho-vascular invasion and presence of microsatellites [5–8]. Other authors postulated that high-risk features include Clark level IV or V, regression, and younger age (<40 years) [9–11].

Efforts to identify thin melanomas at risk of adverse clinical behaviour led to the release of three subsequent AJCC staging modifications from 2002 to 2017. Each of these classifications defined subgroups T1a and T1b using remarkably different criteria [12–14] (Tab 1). The distinction between T1a and T1b melanomas by the four classifications has been used to assess the nodal status [15,16], leading to significant changes in the management of patients within each historic period.

The aim of this paper was to review all SNB performed for thin melanoma and to analyze factors related to lymphatic involvement (N+). Moreover, the performance of the 5th, 6th, 7th and 8th AJCC classifications of cutaneous melanoma in the assessment of the lymphatic status was also evaluated.

Materials and methods

The current study is a retrospective analysis of prospectively collected data regarding SNB performed from 1998 to 2017 at four high-volume referral centres. All node biopsies performed for cutaneous melanoma with a thickness <1 mm were included in the analysis. The study protocol was reviewed and approved by the ethical committee of the coordinating centre. For each patient age, sex, site of primary melanoma, level of invasion according to Clark, thickness according to Breslow, ulceration and the number of mitosis/mm^2 were collected.

The Data was divided into three periods and classified according to the corresponding edition of the AJCC classification. In particular, patients operated before 2001 were classified with the 5th edition as pT1 (Breslow thickness < 0.75 mm or Clark II) or pT2 (Breslow thickness>0.75 mm or Clark III). Patients operated from 2002 to 2010 were classified according to the 6th edition as pT1a (Breslow thickness <1.0 mm and Clark level II or III without ulceration) or pT1b (Breslow thickness <1.0 mm and Clark level IV or V or present ulceration). Patients treated between 2011 and 2017 were classified according to the 7th edition as pT1a (Breslow thickness < 1.0 mm without ulceration and mitosis <1/mm$^{2)}$ or pT1b (Breslow thickness < 1.0 mm with ulceration or mitoses ≥ 1/mm^2) (see Table 1).

In order to compare the diagnostic performance of the AJCC classifications in predicting SNB positivity all patients were subsequently classified according to the 5th, 6th, 7th and 8th (pT1a: Breslow thickness <0.8 mm without ulceration; pT1b: Breslow thickness >0.8 mm but <1.0 mm or Breslow thickness <0.8 mm with ulceration, with Breslow thicknesses rounded to the nearest tenth) editions of the AJCC classification. Patients with incomplete data, such as mitoses count, were excluded from the present analysis.

Continuous variables were described as a mean and standard deviation, categorical variables as proportion with percentage. Association with positive biopsy was tested with the Mann-Whitney *U* test for continuous variables and with the Pearson's Chi-square test for categorical variables as appropriate; odds ratio with 95% confidence interval were also calculated. Variables found to be significantly associated with a positive biopsy were included in the multivariable analysis performed with logistic regression methods. Analyses were performed with the use of SPSS Software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Between 1998 and 2017, a total of1272 SNB for cutaneous melanoma with Breslow <1.0 mm were performed. The mean age was 51,01(±14.53) years and 48.7% of the patients were male. The primary sites of melanoma were as follows: head and neck in 4.1% of cases, trunk in 52.1%, upper extremities in 11.8% and lower extremities 32.1%. Sentinel Node Biopsy was positive in 76 patients (5.9%). Table 2 shows characteristics of patients according to the indication of sentinel node biopsy.

As shown in Table 3, the univariate and multivariate analyses of factors associated with positive sentinel node biopsy were: Breslow thickness, both as continuous variable and categorical with the cut-off >0.75 mm, and ulceration.

Table 4 shows the results divided into the three study periods according to the respective AJCC classification's edition.

A total of 855 patients had complete data allowing classification according to the four editions of the AJCC classification, which were compared (data about mitoses was missing for the remaining patients). Overall, SNB was positive in 56 patients (6.5%). As shown in Table 5 and Fig. 1, results for the 5th,6th, 7th and 8th edition of the AJCC classification were as follows: in pT1a patients (pT1 according to the fifth edition), a positive SNB was evident in 5.32%, 5.63%, 3.72% and 3.49%,respectively. Among the positive node biopsies, the pT1b class of each of the four editions detected the 82%, 35%, 82% and 89% respectively of positive nodes.

Discussion

A correct staging plays a key role in the management of patients with cutaneous melanoma. While clear consensus on the indication of SNB in intermediate-thickness melanoma exists, several studies investigated this issue in thin melanomas and no clear agreement has been reached.

For several decades, the AJCC staging system has been widely used for staging, prognostic assessment and clinical decision. Significant changes have been implemented in the staging of melanomas with Breslow thickness below 1 mm. In particular, the 6th edition identified the difference between T1a and T1b on the Clark's invasion level. On the other hand, the 7th edition shifted from Clark's level to the presence or absence of mitoses. Finally, in the 8th edition, mitotic rate was removed as a staging criterion for T1 tumors, as substratification of T1 tumors using a 0.8 mm cut-off (0,76 mm *de facto*, approximated to the first decimal place) showed stronger association with outcomes, if compared to the presence or absence of mitoses.

These significant changes in the substaging and in the attribution to the T1a or T1b group have brought different diagnostic and therapeutic indications; several national guidelines do not recommend SNB for pT1a patients and suggest its use only for pT1b patients. The decision not to perform the SNB could potentially expose to the risk of understaging a relevant proportion of patients.

In a retrospective study from the Tuscan Cancer Registry (Italy), cases of T1 melanomas were selected and the histological reports reviewed. All pT1 melanomas were reclassified according to both the 6th and the 7th editions of the AJCC staging system. When using the 7th edition, 20% of all pT1a melanomas shifted to pT1b, and 32% of all pT1b melanomas shifted to pT1a [17].

In a Dutch study with a similar design, staging of 28% (57/207) of pT1a melanomas classified according to the 6th edition shifted to pT1b, when classified with the 7thedition, because of the presence of mitoses, whereas some 32% (17/53) of all pT1b melanomas shifted to pT1a. The percentage of pT1b melanomas relative to all pT1 melanomas rose from 20% to 36% [18].

Chu et al., in a retrospective study comparing the 6th and the 7th

Table 1
Last editions of AJCC classification of thin melanoma.

	6th edition 2002	7th edition 2010	8th edition 2017
T1a	Clark < IV AND no ulceration	mitosis = 0 AND no ulceration	BT < 0,80 mm AND no ulceration
T1b	Clark IV-V OR ulceration	mitosis >0 OR ulceration	BT ≥ 0,80 mm OR ulceration

5th edition 1997: T1 if BT < 0,75 mm AND Clark ≤ II, T2 if BT 0,75–1,5 mm OR Clark ≥ III.

Table 2
Patients characteristics according to indication of sentinel node biopsy (indacted by guidelines or personalized).

		Sentinel Node Biopsy Indication								p value
		SNB indicated				Personalized Indication				
		N	%	Mean	SD	N	%	Mean	SD	
Patients		948	74,10%			331	25,90%			
Period	<2001	69	8,4%			54	18,0%			<0,001
	2001–2010	319	38,7%			194	64,7%			
	2011–2017	437	53,0%			52	17,3%			
Centre	Bergamo	162	17,1%			27	8,2%			<0,001
	Padova	422	44,5%			210	63,4%			
	Palermo	112	11,8%			22	6,6%			
	Torino	252	26,6%			72	21,8%			
Sex	F	494	52,1%			161	48,6%			0,277
	M	454	47,9%			170	51,4%			
Age				51,04	14,48			50,90	14,72	0,876
Primary Melanoma site	Lower Limb	319	33,6%			91	27,5%			0,034
	Upper Limb	119	12,6%			32	9,7%			
	Head and Neck	39	4,1%			13	3,9%			
	Trunk	471	49,7%			195	58,9%			
Breslow				0,77	0,18			0,46	0,15	<0,001
Breslow	<0.75 mm	402	42,4%			331	100,0%			<0,001
	>0.75 mm	546	57,6%			0	0,0%			
Ulceration	No	897	94,6%			331	100,0%			<0,001
	Yes	51	5,4%			0	0,0%			
Mytosis	Absent	153	21,2%			129	100,0%			<0,001
	Present	568	78,8%			0	0,0%			
Sentinel Node Biosy	Negative	875	92,8%			321	97,6%			0,002
	Positive	68	7,2%			8	2,4%			

Table 3
Univariate and multivariate analysis of factors associated and related with positive sentinel node biopsy in thin melanomas.

		Negative SNB	Positive SNB	univariate analysis		multivariate analysis	
				OR	p	OR	p
Age		50,92(14,46)	52,43(16,16)	1007(0,991–1024)	0,386		
Sex							
	Female	618(51,7%)	32(43,4%)	1	0,106		
	Male	578(48,3%)	44(56,6%)	1470 (0,920–2351)			
Site of primary melanoma							
	Head and Neck	51(4,3%)	1(1,3%)	1	0,384		
	Trunk	616(51,5%)	43(56,6%)	3,56(0,48–26,38)	0,214		
	Upper limb	145(12,1%)	6(7,9%)	2,10(0,24–17,95)	0,494		
	Lower limb	384(32,1%)	26(34,2%)	3,45(0,45–25,99)	0,229		
Ulceration							
	Not ulcerated	1154(96,6%)	67(89,5%)	1			
	Ulcerated	42(3,4%)	9(10,5%)	3691(1,72–7,89)	<0,001	2,94(1,36–6,31)	0,006
Mytosis							
	No Mitosis	267 (33,8%)	12(21,8%)	1	0,68		
	Mitosis>1	523(66,2%)	43(78,2%)	1,82(0,949–3,52)			
Breslow (continuous)		0,681(0,22)	0,788(0,17)	12,21(3,54–42,05)	<0,001	10,54(3,01–36,90)	<0,001
Breslow (categorial)							
	<0,75 mm	697(58,3%)	30(39,5%)	1			
	>0,75 mm	499(41,7%)	46(60,5%)	2,14(1,33–3,44)	0,001	2,02 (1,25–3,26)	0,004
Clark level							
	I	2(0,2%)	0	–			
	II	211(18,9%)	9(12,9%)	1			
	III	693(62%)	45(64,3%)	1522(0,73–3,16)	0,257		
	IV	211(18,9%)	16(22,3%)	1778(0,76–4,11)	0,174		
	V	1(0,1%)	0	–			

Table 4
Results of sentinel node biopsy according to the period and the apropriate AJCC edition. SNB: sentinel node biopsy.

cohort	n	stage	Negative SNB	Positive SNB
All patients	1272		1196(94%)	76(6%)
Cohort <2001	121	pT1 AJCC 5ˆ	24(96%)	1(4%)
		pT2 AJCC 5ˆ	92(95,8%)	4(4,2%)
Cohort 2002–2010	556	pT1a AJCC 6ˆ	425(95,5%)	20(4,5%)
		pT1b AJCC 6ˆ	101(91%)	10(9%)
Cohort 2011–2017	544	pT1a AJCC 7ˆ	117(94,4%)	7(5,6%)
		pT1b AJCC 7ˆ	390(92,9%)	30(7,1%)

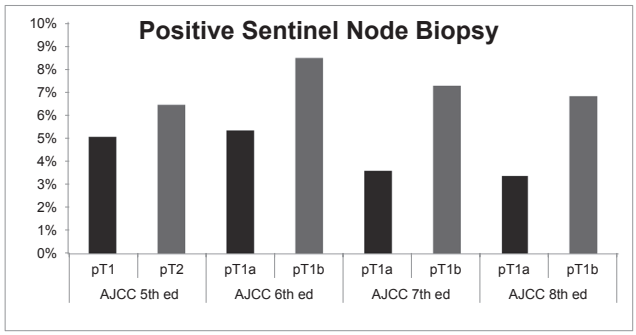

Fig. 1. Results of the sentinel node biopsy divided according to the various AJCC classifications.

staging system found that 14% of melanomas previously classified as T1b were re-staged as T1a and 15% of T1a were re-classified as T1b [19].

Oude Ophuis et al. stratified T1 patients by cohort according to AJCC edition: (1) 2003–2009 (6th) and (2) 2010–2014 (7th). They found that the overall proportion of pT1b had increased from 10.1% in Cohort 1–21.5% in Cohort 2; furthermore, they reported that the proportion of SNBs performed per cohort had increased for pT1b melanomas alone from 4.5% to 13.0%. The SNB positivity rate had decreased from 10.5% to 8.8% for the entire pT1 population, and for pT1b melanomas this reduction was from 11.3% to 8.6%. At 5-year follow-up, the relative survival rate was similar for pT1a and pT1b in both cohorts. The authors questioned the utility of the introduction of the mitotic rate criterion and suggested its reconsideration [20].

A recent systematic review and meta-analysis assessed that the risk of sentinel node metastasis in thin melanomas is relatively low, with a pooled rate of 4.5% in melanomas <0.75 mm and 8.8% in melanomas >0.75 mm. Predictors of a positive SNB were: thickness ≥0,75 mm with a likelihood of SN metastases of 8.8%; Clark level IV/V with a likelihood of7.3%; ≥1 mitoses/mm2 with a pooled likelihood of 8.8%; the presence of microsatellites with a likelihood of 26.6%. Ulceration was not considered as an independent predictor: its presence did not significantly predict SN metastases at adjusted analysis [21].

During the present study period 1272 sentinel node biopsies were performed for thin (<1 mm) cutaneous melanoma with 76 (6%) positive SNBs. The Breslow's depth of infiltration and the presence of ulceration were significantly related to the presence of lymphatic metastasis, as confirmed at univariate and multivariate analysis. Presence and number of mitosis, Clark's level of infiltration, age, sex and site of the primary tumor were not associated with the presence of metastasis.

As shown in Tables 2 and 4 during the study period a great number of sentinel node biopsies were performed notwithstanding the usual criteria and the guideline recommendations for low-risk patients (stage pT1a according to the classification valid in the respective time period). These biopsies were performed for several clinical and organizational reasons: during the initial period of the study a great number of patients with a clinical diagnosis of melanoma made by dermatologists were sent directly to the surgeon for a primary excision and SNB at the same time. A number of biopsies were performed for selected patients on the basis of the surgeon's or dermatologist's judgment, in agreement with the patient. This could have led to a selection bias; patients with T1a melanoma who undergo SNB often represent borderline cases.

Nevertheless, performing a considerable number of theoretically non-indicated biopsies offers the possibility to describe the risk of lymph node metastasis in low-risk patients. In a subgroup analysis of low risk patients (no ulceration, stage pT1a according to the last edition of the AJCC classification), we found that 3,7% of patients had lymphatic metastasis.

Our data confirms the importance of the Breslow thickness and the presence of ulceration as a fundamental prognostic factor for lymphatic metastasis in thin melanoma. Moreover, the present data allows us also to analyze and "validate" the diagnostic performance of the last four editions of the AJCC classification for melanoma. Table 5 and Fig. 1 show the progressive improvement of diagnostic accuracy with an encouraging decrease of positive SNB rate among low risk patients (pT1a). However, it should be noticed that, despite convincing improvements and the reduction of positive biopsies among pT1a patients with the implementation of the new classifications a 10.71% rate among all positive nodes remains within the low-risk group, as classified with the last edition (Table 5).

The present study has two limitations: data regarding false negative biopsies cannot be provided due to the study design. Moreover a large proportion of the patients included had a "not recommended" nodal biopsy (low risk group, pT1a) but however are a small proportion of all the low risk patients. This represents a selection bias that could lead to a potential underestimation of the real incidence of nodal metastases in T1a melanomas. On the other

Table 5
Results of the sentinel node biopsy divided according to the various AJCC classifications. SNB: sentinel node biopsy.

		n	Positive SNB	%	% among all positive SNB
AJCC 5th ed	pT1	188	10	5,32%	17,86%
	pT2	667	46	6,90%	82,14%
AJCC 6th ed	pT1a	639	36	5,63%	64,29%
	pT1b	216	20	9,26%	35,71%
AJCC 7th ed	pT1a	269	10	3,72%	17,86%
	pT1b	586	46	7,85%	82,14%
AJCC 8th ed	pT1a	172	6	3,49%	10,71%
	pT1b	683	50	7,32%	89,29%
all		855	56	6,55%	100,00%

hand pT1a melanomas for which SNB was performed often represented borderline cases, leading to a potential contextual overestimation of the real incidence of nodal metastases in this subgroup. Despite these limitations, the present study represents one of the largest existing series of sentinel node biopsies for thin melanoma.

Conclusions

In conclusion, according to our results, the risk of lymph node metastasis in thin melanoma is 6% and should not be underestimated. Moreover, the Breslow thickness and the presence of ulceration are the only two factors which are significantly related to the presence of lymph node metastasis. The AJCC classification allows the stratification of the patients, but a relevant proportion of patients with thin melanoma could be underclassified. No recommendations can be drawn from the present study and more evidence and larger observation studies on thin melanoma are needed to better identify patients at risk of lymph node metastasis.

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Conflict of interest statement

All the authors have no conflict of interest to declare.

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