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SENTINEL LYMPH NODE BIOPSY IN THICK MELANOMA PATIENTS (N=350): WHAT IS ITS PROGNOSTIC ROLE?

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Synopsis

Historically, thick melanoma patients have not been considered good candidates for SLNB because of the high risk of distant metastases and the related poor prognosis. The aim of this study is to assess the utility of SLNB and its prognostic role in this selected group of patients

Abstract

Background: Sentinel Lymph Node Biopsy (SLNB) is currently recommended for patients with intermediate-thickness melanomas (T2-T3). Historically, T4 melanoma patients have not been considered good candidates for SLNB because of the high risk of distant progression. However, some authors suggest that T4 melanoma patients could be considered as a heterogeneous group and that could benefit from SLNB. Methods: We retrospectively analyzed 350 patients with thick (>4 mm) melanomas between 1999 and 2011. Patients were stratified into three groups depending on the results of SLNB: 1) 94 SLNB negative; 2) 84 SLNB positive, 3) 172 SLNB not performed (observation group). The associations of clinical pathologic features with the result of SLNB, Disease Free Interval (DFI) and Disease Specific Survival (DSS) were analyzed. Results: Multivariate analyses confirmed a better prognosis for SLN-negative patients compared with observation patients (DSS HR 0.62, p=0.03; DFI HR=0.47, p<0.001). The observation group was shown to have the same prognosis as the positive SLN group, when adjusted for principal confounders in the model. Conclusions: We confirmed that thick melanoma patients are a heterogeneous group with different prognosis. In our experience, SLNB allowed for an appropriate stratification of patients in different survival groups. On the basis of our results, we strongly recommend the routine execution of SLNB in cases of primary melanoma thicker than 4 mm.

Key words: SLNB, observation patients, Thick melanoma

INTRODUCTION

Sentinel lymph node biopsy (SLNB) is strongly recommended in patients diagnosed with primary melanoma characterized by Breslow thickness between 1 and 4 mm. [1-3]. In contrast, when Breslow thickness is greater than 4 mm the role of SLNB is unclear [4-17]. Historically, this selected group of patients has not been considered good candidates for SLNB because of a high risk of distant progression and poor prognosis. However, recent studies identified Sentinel Lymph Node (SLN) status as an important predictive factor in patients with primary melanomas thicker than 4 mm (pT4, American Joint Committee on Cancer AJCC) [15-17]. The most recent guidelines of the American Society of Clinical Oncology and Society of Surgical Oncology, based on critical review of all available evidence, advocates offering SNB to patients with melanomas 1.0 mm or more to 4 mm suggesting that SNB may be recommended to patients with thick melanomas (>4 mm) only for staging purposes and to facilitate regional disease control [18].

Considering the conflicting literature data on SLNB role in this selected group of patients, we decided to retrospectively analyze a case series of primary melanomas thicker than 4 mm followed at our single center. We analyzed pattern and the time of progression comparing patients who underwent SLNB to patients who did not.

MATERIALS AND METHODS

SLNB was introduced in our institution in January 1999. The clinical records of 2,968 melanoma patients, diagnosed and followed-up at our center from 1999 to 2011, have been reviewed and reclassified according to the last American Joint Committee on Cancer (AJCC) staging system [19]. Patients with incomplete histo-pathological data, non-cutaneous, or unknown primary melanoma, clinically evident stage III melanoma (not detected with SLNB), and stage IV melanoma were excluded. Variables recorded were sex, age, date of diagnosis, site of primary melanoma,

Breslowthickness, Clark level, histological type, ulceration, histological regression, and site and type of progression.

The criteria adopted for SLNB inclusion were previously reported [20-22]. Age above 75 years and significant comorbidities were exclusion criteria for this procedure. Due to the lack of specific guidelines, a multidisciplinary team has discussed each case analyzing pros and cons to give indication to SLNB. All decision were made at the best of physicians knowledge, considering the potential wrong indication in a field without evidence-based recommendations.All the patients signed a procedure informed consent. A total body CT scan was performed in all patients to exclude the presence of regional of distant metastases before SLNB. Only patients submitted to SLNB, whose node stage was known, were considered as candidates for immunotherapy, according to evidence based recommendations[23,24]. Each case was discussed by a multidisciplinary team considering performance status, comorbidities and life expectancy.

Patients were retrospectively stratified into two groups 1) SLNB performed (178) and 2) observation group (172) and subsequently into three groups depending on the results on SLNB: 1) 94 SLNB negative; 2) 84 SLNB positive, 3) 172 SLNB not performed (observation group). All patients with a positive SLNB underwent a consecutive complete lymph nodes dissection (CLND). Patients who developed nodal progression during follow-up underwent therapeutic lymph nodes dissection (TLND). The surgical approach used in the CLND and in TLND was the same [20-22]. All patients were followed-up according to the guideline criteria on the basis of AJCC classification (observation and negative SLN as stage II and positive SLN as stage III) [19,25-27].

Statistical analyses

Pearson's Chi square test and Student's t-test were preliminary performed to compare respectively categorical and continuous variables, and to evaluate potential differences in the variables' distribution among groups. The Disease-Free Interval (DFI) was calculated from the date of surgical excision of the primary melanoma to the date of first disease relapse or last check-up. Disease-

specific survival (DSS) was calculated from the surgical excision date of the primary melanoma to the date of melanoma death or last check-up. Survival distribution curves were plotted using the Kaplan-Meyer method and the statistical comparisons were performed using the log-rank test. Cox regression analyses were carried out on DFI and DSS to calculate crude and adjusted HRs and 95% CIs for the different study group. Cases lost to follow-up and cases with a non-melanoma related cause of death were censored at the last follow up control. Two different models were performed, one for the evaluation of the prognostic role of SLNB (performed vs observation, Model 1) and another evaluating the prognostic role of the SLN status (Observation, SLN negative and SLN positive, Model 2). Clinical variables analyzed were: gender, age at diagnosis, Breslow thickness, ulceration, histological type, histological regression and site of primary melanoma. The proportional hazard assumption was assessed with the Schoenfeld residuals. This did not give reason to suspect violation of this assumption. The nature of variables (continue/categorical) included in the model was evaluated considering literature reports and the results of the log-likelihood ratio test. Akaike information criterion (AIC) was used for model selection. All statistical tests were two sides. P-values < 0.05 were considered significant. Statistical analyses were performed using Stata/SE12.0 Statistical Software (STATA, College Station, TX)

Confounders

Available confounders for melanoma progression included age, Breslow thickness, histological subtype, primary tumor body site, ulceration, histological regression, gender. As recommended by the STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) guidelines, and to determine which confounders influence the significance of the three study groups, all available and appropriate confounders for each survival analysis were first separately tested at bivariate Cox models. Mitoses number, which is an important factor in the current AJCC staging system for thin melanoma, was excluded from our main analyses, as their role in the staging of

thick melanoma are not well known and this data was unknown for the 37% of cases, especially in the earlier years of the study.

RESULTS

Clinical features

We identified a total of 350 patients with a diagnosis of primary melanoma characterized by a Breslow thickness greater than 4 mm and at least a follow-up of 12 months between the disease-free group (25 patients with a follow up less than 1 year were excluded out of 375). Patients were diagnosed, treated and followed-up at the Dermatologic Clinic of Turin University Hospital from 1999 to 2011 (Table 1). In all patients a wide local excision of the primary tumor was performed at the diagnosis. SLNB was performed in 178 out of 350 patients (50.8%); 84 of them had positive SLNB and 94 were negative (giving a 47% of SLN positivity rate). In the remaining 172 patients (49.2%) the staging at diagnosis was performed with total body CT. All patients enrolled showed no evidence of distant metastases at diagnosis. Overall, 218 patients (62.3%) were male. The median age at diagnosis was 65.4 years (range 24.9-93). Superficial Spreading Melanoma (SSM) and Nodular Melanoma (NM) were the most represented histotypes. The majority of melanomas appeared on the trunk (n=138, 39.4%). Mean Breslow thickness was 7.00 mm ± 3.42. Most of the patients showed a Breslow between 6 and 8 mm (n=275, 78.5%). The 85.2% reported a Clark level of IV or V. Ulceration was present in 201 out of 350 patients (57.4%), and histological regression was present in 33 out of 350 (9.4%). During follow-up, 222 out of 350 patients (63.4%) developed a recurrence, 150 showed regional metastases, and 72 developed distant metastases as first site of relapse. As expected, the majority of regional lymph nodes involvement appeared in patients who did not undergo SLNB (p=0.006) (Table 1)

Group comparison

Significant differences were seen when comparing our three study groups(Table 1): patients who did not undergo SLNB (observation group), SLNB-negative patients, SLNB-positive patients. Median age and Breslow thickness were lower in patients who underwent SLNB compared to the observation group. The trunk was the most common site of primary in observation patients, whereas lower limbs were more represented in patients who underwent SLNB. No differences in gender, ulceration, histological regression and histological subtype distribution were observed. Adjuvant immunotherapy was administered only in 42/178 SLNB staging patients. The median number of lymph nodes excised during SLNB was 1 (range:1-5). No difference in the number of excised lymph nodes was found between positive and negative SLN patients. The median number of positive lymph nodes at SLNB was 1 (range:1-3). Among them, the majority reported 1 SLN positive (69 out of 84, 82%). Furthermore, 49 patients out of 84 (60.5%) showed involvement of non-sentinel lymph nodes (NSLN) at CLND. The median number of overall positive lymph nodes, in patients submitted to SLNB and a CLND was 2 (range:1-14). Accordingly to AJCC, 19 patients were classified as Stage IIIA, 29 as Stage IIIB and 36 as stage IIIC (Table 1 supplemental).

Survival analyses

The median follow-up was 30.6 months (range 2.5-193.9 months). The median time to relapse across different groups was reported in Table 2 supplemental.

During the follow-up, 117 out of 172 (68%) observation patients, 50 out of 94 (53%) negative SLNB patients and 54 out of 83 (65%) positive SLNB patients showed a recurrence (Table 1). Most patients of the observation group recurred in regional lymph nodes or developed simultaneous skin and lymph nodes involvement (61 out of 117, 52%). The number of metastatic lymph nodes found during TLND in the observation group was higher than the overall number of positive nodes found during SLNB and CLND (3 lymph nodes (range 1-29) vs 2 lymph nodes (range 1-14), respectively).

On the basis of the number of metastatic nodes and/or presence of skin regional metastasis at first time to relapse, and the presence of ulceration, the patients were classified as 25 Stage IIIB and 69 IIIC patients according to AJCC Classification (Table 1 supplemental).

Regional lymph node recurrence was observed in 16 initial negative SLNB patients, accounting for a false negative rate of 16%. Distant metastases, as first site of progression, were observed in 20.5% of patients of the observation group, 42% of negative SLNB patients and 50% of positive SLNB patients.

In terms of DFI, there was a statistically significant difference between patients not submitted to SLN and patients who underwent this procedure (p=0.006) while it did not reach the significance for DSS (p=0.43). When stratifying in the 3 SLNB result groups (positive, negative, or observational) we observed a significant difference in DFI (p=0.0006) and in DSS (p=0.03) (Figure 1-2).

Patients with a positive SLNB and the observation group showed the same prognosis (Log-rank test DFI p=0.70; DSS p=0.39). Whereas, patients with a negative SLNB have a survival advantage compared to observation patients (Log-rank test DFI p=0.001; DSS p=0.04) and to positive SLN patients (Log-rank test DFI p=0.0025, DSS p=0.007).

Univariate Cox analyses estimates were reported in Table 3 supplemental. Patients submitted to SLNB have a reduced incidence of progression compared to the observational group. When we stratified patients on the basis of SLNB results, we observed that negative SLNB patients have a reduced estimated incidence of both progression and death compared to the observational group.

Multivariate Cox analyses were performed to rule out possible confounders involved in melanoma prognosis; proportional hazard assumptions were maintained in both the models (Tables 2 and 3). Despite the adjustment, patients submitted to SLNB were protected in terms of DFI compared to the observation group (HR 0.59, p=001), while on DSS this difference did not reach the significance (HR=0.44, p=0.176). SLN-negative patients maintained a favorable prognosis in terms of DFI and DSS when compared to the observational group (DSS HR 0.62, p=0.03; DFI HR=0.47, p<0.001).

The positive SLN group did not show a different prognosis compared to the observational group when adjusted for confounders (Table 3). Breslow thickness, ulceration, histological regression and gender maintained their significance in the multivariate Cox analyses on DSS and DFI.

DISCUSSION

The management of patients diagnosed with a melanoma characterized by a Breslow thickness greater than 4 mm remains controversial due to the high risk of haematogenous metastases. The conflicting results of the previous studies might be due to the lack of guidelines for the management of these patients, resulting in not uniform patient cohorts [15, 16]. In our experience half of the thick melanoma patients (172 out of 350) did not undergo SLNB. This reflects the lack of guidelines for thick melanoma management.

The majority of previous studies compared patients treated with SLNB to observation or patients with a positive SLNB to patients with a negative SLNB. Recently, Morton et al. [2] reporting the final version of the Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) differentiated patients with intermediate thickness melanoma (1.20-3.5 mm) from patients with melanoma thicker than 3.5 mm. In this analysis Morton et al. reported a significant benefit in terms of DFS for thick primary melanoma patients who underwent SLNB compared to observation patients.

Our study had a lower power not being a prospective one, but it analyzed a group of thick melanoma at a higher risk (>4mm, median Breslow thickness 7 mm compared to 5.8 in the thicker group of analysis of Morton's Study) and confirmed the protective role of SLNB in terms of DFI. Previous studies, which compared SLN positive and negative patients, reported conflicting data. Caracò et al.[11] showed that SLNB provided accurate staging of nodal status in T1-T4 melanoma patients who had no clinical evidence of metastases. However, in thick melanomas, the survival curves did not show significant differences between negative and positive-SLN patients. Essner et al. [5] confirmed that in T4 melanoma the SLN status was not correlated with patients' overall

survival. At the contrary, in several other studies the SLN status was shown to be an important prognostic factor in T4 patients [4,7,15, 28]. In our experience median survival in terms of DFI and DSS in negative SLN patients with T4 melanoma (47.3 and 118 months, respectively) was higher than in the positive SLN group (14 and 28 months, respectively). This finding was recently confirmed in a recent meta-analysis [16].

To the best of our knowledge, this is the first study which performed a prognostic analysis of patients stratified in observation, SLN negative and SLN positive group. The first finding of our study was that negative SLN patients showed a better DFI and DSS, not only compared with positive SLN patients, but also compared to observation patients. Multivariate Cox regression analyses confirmed different prognoses for these groups in terms of DFI and DSS (Table 3). Negative SLNB patients showed a lower risk of recurrence and death compared to observation patients, even when adjusted for the most important prognostic factors. Furthermore, no clinical outcome differences were shown between observation and positive SLN patients.

In the same model we identified gender, tumor thickness and the presence of ulceration as independent prognostic factors for DFI and DSS. Similar results were reported by Scoggins et al. [15] on DFS and OS; in their experience ulceration reported a significant value only for OS.

Histological regression has been previously related to poor prognosis in thick melanoma patients [7, 15, 29]. In our experience, histological regression maintained a significant favorable prognostic role on DFI and DSS after adjusting for confounders. These findings seem to confirm the positive prognostic role previously reported in I-II stage melanoma patients [30].

Furthermore, our results highlighted that patients undergoing CLND following a positive SLNB have a smaller burden of regional disease compared to patients undergoing TLND (for a disease progression in observed patients subgroup). This suggests that SLNB could also help in regional disease control.

In conclusion, we are aware that our study was not randomized and was based on a hospital monocentric dataset of patient, but we were able to confirm that pT4 melanoma patients are a heterogeneous group with different prognoses. In our experience, SLNB allowed for an appropriate stratification of patients in different survival groups. On the basis of our results, we recommend the routine execution in clinical practice of SLNB in cases of primary melanoma thicker than 4 mm.

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DISCLOSURES The authors declare no conflicts of interest

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Table 1: Patients' characteristics and distribution of clinico-pathological features on the basis of SLNB status

			Thick melanoma patients			
		Total	Observation patients	SLNB Negative	SLNB Positive	p
Gender	F	132 (37.7%)	75 (56.8%)	29 (22.0%)	28 (21.2%)	0.08
	M	218 (62.3%)	97 (44.5%)	65 (29.8%)	56 (25.7%)	
Age	median	65.4 (24.9-93)	71 (24.9- 93)	63 (27.2-77)	58.8 (27.2-77.9)	<0.001
	≤65 years	175 (50%)	63 (36.6%)	54 (57.5%)	58 (69.1%)	<0.001
	>65 years	175 (50%)	109 (63.4%)	40 (42.5%)	26 (30.9%)	
Histotype	SSM	143 (40.8%)	62 (36.0%)	40 (42.6%)	41(48.8%)	0.46
	MN	143 (40.8%)	77 (44.7%)	38 (40.4%)	28 (33.3%)	
	LMM	19 (5.5%)	13 (7.6%)	3 (3.2%)	3 (3.6%)	
	ALM	31 (8.9%)	13 (7.6%)	9 (9.6%)	9 (10.7%)	
	other	14 (4.0%)	7 (4.1%)	4 (4.2%)	3(3.6%)	
Site of primary	Head/neck	51 (14.6%)	30 (17.4%)	15 (16.0%)	6 (7.1%)	0.02
	Trunk	138 (39.4%)	66 (38.4%)	40 (42.6%)	32 (38.1%)	
	Upper extremities	35 (10%)	23 (13.4%)	8 (8.5%)	4 (4.8%)	
	Lower extremities	126 (36%)	53 (30.8%)	31 (32.9%)	42 (50%)	
Breslow thickness	mm±SD	7. 00±3.42	7.5±3.7*	6.2±2.2*	6.7±3.8	<0.05*
Breslow	4<br≤6	202 (57.7%)	85 (49.4%)	61 (64.9%)	56 (66.7%)	0.04
	6<br≤8	73 (20.9%)	41 (23.8%)	21 (22.3%)	11(13.1%)	
	8<br≤10	34 (9.7%)	20 (11.7%)	5 (5.3%)	9 (10.7%)	
	>10	41 (11.7%)	26 (15.1%)	7 (7.5%)	8 (9.5%)	
Clark level	III	52 (14.8%)	21 (12.2%)	19 (20.2%)	12 (14.3%)	0.19
	IV	199 (56.9%)	94 (54.7%)	55 (58.5%)	50 (59.5%)	
	V	99 (28.3%)	57 (33.1%)	20 (21.3%)	22 (26.2%)	
Ulceration	No	149 (42.6%)	77 (44.8%)	44 (46.8%)	28 (33.3%)	0.14
	Yes	201 (57.4%)	95 (55.2%)	50 (53.2%)	56 (66.7%)	

Histological Regression	No	317 (90.6%)	159 (92.4%)	84 (89.4%)	74 (88.1%)	0.48
	Yes	33 (9.4%)	13 (7.6%)	10 (11.6%)	10 (11.9%)	
Immunotherapy	No	308 (88%)	172 (100%)	76 (80.8%)	60 (71.4%)	0.001
	Yes	42 (12%)	0	18 (19.1%)	24 (28.6%)	
First site of relapse	none	128 (36.6%)	55 (32%)	44 (46.8%)	29 (34.5%)	<0.001
	regional	150 (42.8%)	93 (54.1%)	29 (30.8%)	28 (33.3%)	
	distant	72 (20.6%)	24 (13.9%)	21 (22.3%)	27 (32.2%)	
Distribution of regional site metastases	Skin	66 (44%)	32 (34.4%)	13 (44.8%)	21 (75%)	0.006
	Lymph nodes	75 (50%)	55 (59.1%)	14 (48.3%)	6 (21.4%)	
	Both	9 (6%)	6 (6.5%)	2 (6.9%)	1 (3.6%)	

*Bonferroni test (observation vs negative SLN)

Legend: SSM : Superficial Spreading Melanoma; MN Nodular melanoma; LMM LentigoMaligna Melanoma; ALM AcralLentiginous Melanoma

Table 2: Multivariate Cox Regression analyses on DFI and DSS (Model 1)*

		DFI			DSS		
		HR	CI.	P	HR	CI	p
Age>65		1.03	0.78-1.37	0.833	1.08	0.76-0.54	0.662
Gender (Male vs Female)		1.34	1.00-1.80	0.049	1.59	1.10-2.31	0.014
Breslow		1.05	1.01-1.08	0.008	1.06	1.02-1.10	0.004
Ulceration		1.60	1.20-2.12	0.001	1.57	1.10-2.22	0.012
Histological Regression		.61	0.35-1.06	0.082	0.44	0.19-1.00	0.050
Sentinel node biopsy *vs* observation		0.59	0.43-0.79	0.001	0.77	0.53-1.12	0.176
Immunotherapy		1.49	0.96-2.32	0.072	1.38	0.83-2.31	0.211
Primary site	Head neck	1			1		
	Trunk	1.57	1.00-2.45	0.048	1.59	0.89-2.86	0.116
	Upperextremities	1.44	0.81-2.54	0.208	1.19	0.55-2.58	0.660
	Lower extremities	1.41	0.90-2.22	0.132	1.46	0.81-0.62	0.205

*The proportional hazard assumption was assessed with the Schoenfeld residuals DFI p=0.67, DSS p=0.33.

Table 3: Multivariate Cox Regression analyses on DFI and DSS (Model 2)*

		DFI			DSS		
		HR	CI.	P	HR	CI	p
Age>65		1.05	0.79-1.40	0.72	1.11	0.78-1.58	0.57
Gender (Male vs Female)		1.32	0.98-1.77	0.05	1.57	1.08-2.28	0.02
Breslow		1.04	1.00-1.08	0.03	1.05	1.01-1.09	0.02
Ulceration		1.58	1.19-2.10	0.001	1.57	1.11-2.23	0.01
Histological Regression		0.56	0.32-.98	0.04	0.40	0.17-0.93	0.03
Staging	Observation patients	1			1		
	SLNB Negative	0.47	0.33-.68	<0,001	0.62	0.39-.96	0.03
	SLNB Positive	0.78	0.54-1.12	0.18	1.03	0.66-1.62	0.87
Immunotherapy		1.46	0.94-2.26	0.09	1.33	0.80-2.22	0.27
Primary site	Head neck	1			1		
	Trunk	1.57	0.98-2.46	0.06	1.58	0.88-2.84	0.13
	Upperextremities	1.42	0.80-2.51	0.23	1.17	0.54-2.54	0.70
	Lower extremities	1.32	0.84-2.09	0.23	1.38	0.76-2.48	0.29

*The proportional hazard assumption was assessed with the Schoenfeld residuals, DFI p=0.59, DSS p=0.22).

Figure Legend

Figure 1: Disease Free Interval (DFI) ($p<0.001$) in three groups stratified on the basis of SLN management.

Figure 2:Disease Specific Survival (DSS) (p=0.03) in three groups stratified on the basis of SLN management.