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ORIGINAL ARTICLE – MELANOMAS

Sentinel Lymph Node Biopsy in Thick-Melanoma Patients (*N*=350): What is Its Prognostic Role?

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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 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; and (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 patients in the observation group (DSS hazard ratio [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-sentinel lymph node 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.

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 1.0–4 mm, suggesting that SNB may be recommended to patients with thick melanomas (>4 mm) for staging purposes only and to facilitate regional disease control.[18]

Considering the conflicting literature data on the role of SLNB 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 the pattern and time of progression, comparing patients who underwent SLNB with patients who did not.

S. Ribero and S. Osella-Abate have contributed equally to this work.

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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 AJCC staging system.[19] Patients with incomplete histopathological 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, Breslow thickness, 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 greater than 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 decisions were made to the best of the physician's knowledge, considering the potential wrong indication in a field without evidence-based recommendations. All patients signed a procedure informed consent. A total-body computed tomography (CT) scan was performed in all patients to exclude the presence of regional or 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). They were subsequently stratified into three groups depending on the results of the SLNB: (1) 94 SLNB-negative; (2) 84 SLNB-positive; and (3) 172 SLNB not performed (observation group). All patients with a positive SLNB underwent a consecutive complete lymph node dissection (CLND). Patients who developed nodal progression during follow-up underwent therapeutic lymph node dissection (TLND). The surgical approach used in both the CLND and 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 χ^2 and Student's t test were preliminary performed to compare categorical and continuous variables, respectively, and to evaluate potential differences in the distribution of variables 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–Meier 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 hazard ratios (HRs) and 95 % confidence intervals (CIs) for the different study groups. 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 sex, 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-sided. p Values <0.05 were considered significant. Statistical analyses were performed using Stata/SE12.0 Statistical Software (STATA Corporation, College Station, TX, USA).

Confounders

Available confounders for melanoma progression included age, Breslow thickness, histological subtype, primary tumor body site, ulceration, histological regression, and sex. 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, an important factor in the current AJCC staging system for thin melanoma, was excluded from our main analyses as its role in the staging of thick melanoma is not well known and this data was unknown for 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

TABLE 1 Patients' characteristics and distribution of clinicopathological features on the basis of sentinel lymph node biopsy status

		Thick-melanoma patients				
		Total	Observation patients	SLNB-negative	SLNB-positive	*p* value
Sex	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, years	Median (range)	65.4 (24.9–93)	71 (24.9–93)	63 (27.2–77)	58.8 (27.2–77.9)	<0.001
	≤65	175 (50)	63 (36.6)	54 (57.5)	58 (69.1)	<0.001
	>65	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
	NM	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[a]	6.2 ± 2.2[a]	6.7 ± 3.8	<0.05[a]
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)	

Data are expressed as *N* (%) unless otherwise specified

SLNB sentinel lymph node biopsy, *F* female, *M* male, *SSM* superficial spreading melanoma, *NM* nodular melanoma, *LMM* lentigo maligna melanoma, *ALM* acral lentiginous melanoma, *SD* standard deviation

[a] Bonferroni test (observation vs. negative sentinel lymph node)

greater than 4 mm and at least a follow-up of 12 months between the disease-free group (of 375 patients, 25 with a follow-up less than 1 year were excluded). 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 diagnosis. SLNB was performed in 178 of 350 patients (50.8 %); 84 had positive SLNB and 94 were negative (giving a 47 % SLN positivity rate). In the remaining 172 patients (49.2 %), 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, and most of the patients showed a Breslow thickness between 6 and 8 mm ($N = 275$, 78.5 %). A Clark level of IV or V was reported in 85.2 % of patients. Ulceration was present in 201 of 350 patients (57.4 %), and histological regression was present in 33 of 350 patients (9.4 %). During follow-up, 222 of 350 patients (63.4 %) developed a recurrence, 150 showed regional metastases, and 72 developed distant metastases as the first site of relapse. As expected, the majority of regional lymph nodes involved 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, and SLNB-positive patients. Median age and Breslow thickness were lower in patients who underwent SLNB compared with the observation group. The trunk was the most common site of primary tumor in patients in the observation group, whereas lower limbs were represented more in patients who underwent SLNB. No differences in sex, ulceration, histological regression, and histological subtype distribution were observed. Adjuvant immunotherapy was administered in only 42/178 SLNB-staging patients. The median number of lymph nodes excised during SLNB was 1 (range 1–5), and 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 these, the majority reported one positive SLN (69 of 84, 82 %). Furthermore, 49 patients 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 for SLNB and a CLND was 2 (range 1–14). According to the AJCC, 19 patients were classified as Stage IIIA, 29 as Stage IIIB, and 36 as Stage IIIC (electronic supplementary Table 1).

Survival Analyses

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

During follow-up, 117 of 172 (68 %) patients in the observation group, 50 of 94 (53 %) negative-SLNB patients, and 54 of 83 (65 %) positive-SLNB patients showed a recurrence (Table 1). Most patients in the observation group recurred in regional lymph nodes, or developed simultaneous skin and lymph node involvement

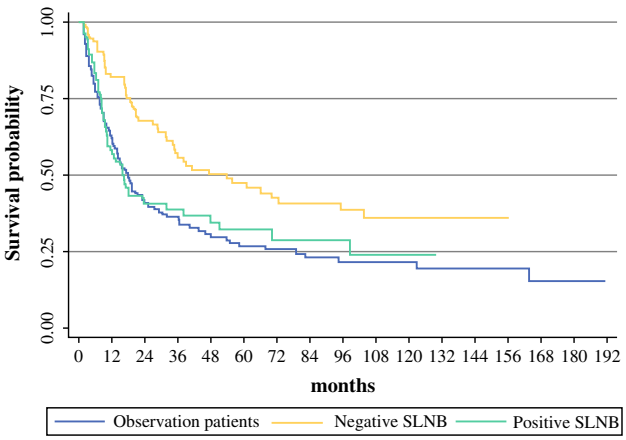

FIG. 1 Disease-free interval ($p < 0.001$) in the three groups stratified on the basis of sentinel lymph node management. *SLNB* sentinel lymph node biopsy

(61 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) versus 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, as well as the presence of ulceration, patients were classified as Stage IIIB (25 patients) and Stage IIIC (69 patients), according to the AJCC classification (electronic supplementary Table 1).

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 in 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 significance for DSS ($p = 0.43$). When stratifying in the three SLNB groups (positive, negative, or observational), we observed a significant difference in DFI ($p = 0.0006$) and DSS ($p = 0.03$) (Figs. 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 had a survival advantage compared with patients in the observation group (log-rank test DFI $p = 0.001$, DSS $p = 0.04$) and positive-SLN patients (log-rank test DFI $p = 0.0025$, DSS $p = 0.007$).

Univariate Cox analysis estimates are reported in electronic supplementary Table 3. Patients submitted to SLNB had a reduced incidence of progression compared with the

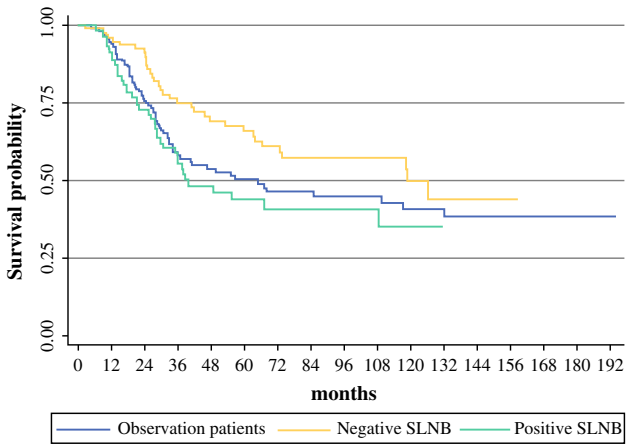

FIG. 2 Disease-specific survival ($p = 0.03$) in the three groups stratified on the basis of sentinel lymph node management. *SLNB* sentinel lymph node biopsy

observational group. When we stratified patients on the basis of SLNB results, we observed that negative-SLNB patients had a reduced estimated incidence of both progression and death compared with the observational group.

Multivariate Cox analyses were performed to rule out possible confounders involved in melanoma prognosis; proportional hazard assumptions were maintained in both models (Tables 2 and 3). Despite the adjustment, patients submitted to SLNB were protected in terms of DFI compared with the observation group (HR 0.59; $p = 001$), while on DSS this difference did not reach significance (HR 0.44; $p = 0.176$). SLN-negative patients maintained a favorable prognosis in terms of DFI and DSS when compared with the observation 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 with the observation group when adjusted for confounders (Table 3). Breslow thickness, ulceration, histological regression, and sex maintained their significance in the multivariate Cox analyses on DSS and DFI.

TABLE 2 Multivariate Cox regression analyses on disease-free interval and disease-specific survival (Model 1)

	DFI			DSS		
	HR	CI	*p* value	HR	CI	*p* value
Age >65 years	1.03	0.78–1.37	0.833	1.08	0.76–0.54	0.662
Sex (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	0.61	0.35–1.06	0.082	0.44	0.19–1.00	0.050
Sentinel node biopsy versus 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
Upper extremities	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 $p = 0.33$)

DFI disease-free interval, *DSS* disease-specific survival, *HR* hazard ratio, *CI* confidence interval

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 hematogenous metastases. The conflicting results of the previous studies might be due to the lack of guidelines for the management of these patients, resulting in patient cohorts that are not uniform.[15,16] In our experience, half of the thick-melanoma patients (172 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 with patients in the observation group, or patients with a positive SLNB with patients with a negative SLNB. Recently, Morton et al.[2], when 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 a 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 with patients in the observation group.

Our study had a lower power, not being a prospective study, but it analyzed a group of thick-melanoma patients at a higher risk (>4 mm, median Breslow thickness 7 mm compared with 5.8 in the thicker group analysed in the study of Morton et al.), 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. On the contrary, in several other studies the SLN status was

TABLE 3 Multivariate Cox regression analyses on disease-free interval and disease-specific survival (Model 2)

	DFI			DSS		
	HR	CI	*p* value	HR	CI	*p* value
Age >65 years	1.05	0.79–1.40	0.72	1.11	0.78–1.58	0.57
Sex (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	0.32–0.98	0.04	0.40	0.17–0.93	0.03
Staging						
Observation patients	1			1		
SLNB-negative	0.47	0.33–0.68	<0.001	0.62	0.39–0.96	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
Upper extremities	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 $p = 0.22$)

DFI disease-free interval, *DSS* disease-specific survival, *HR* hazard ratio, *CI* confidence interval, *SLNB* sentinel lymph node biopsy

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 groups. 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 with patients in the observation group. 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 with patients in the observation group, even when adjusted for the most important prognostic factors. Furthermore, no clinical outcome differences were shown between patients in the observation group and positive-SLN patients.

In the same model, we identified sex, 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 for OS only.

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 stage I–II melanoma patients.[30]

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

CONCLUSIONS

We are aware that our study was not randomized and was based on a hospital monocentric dataset of patients, but we were able to confirm that patients with pT4 melanoma 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 of SLNB in clinical practice in cases of primary melanoma thicker than 4 mm.

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