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The Sentinel Node Biopsy in Patients with Thick Melanoma: Outcome Analysis from a Single-institution Database

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Abstract. *Background: We examined the impact of sentinel lymph node (SLN) biopsy among patients with primary melanoma that exceeded 4.0 mm in Breslow thickness, treated in our Institution from 1998 until 2009. Patients and Methods: According to Kaplan-Meier statistics, overall survival (OS) and disease-free survival (DFS) were assessed in patients with: i) disseminated disease at diagnosis with respect to patients undergoing SLN biopsy and ii) positive SLN and negative SLN. The effect of age, thickness and number of positive SLN on survival was also calculated. Results: Forty-three patients with thick melanoma were included (29 men and 14 women; mean age 65±17 years, tumor thickness ranging from 4 to 20 mm). Thirteen patients (30%) were not eligible for SLN biopsy due to metastatic disease or poor clinical condition. Biopsy was performed on 30 patients: 14 with positive SLN (46.7%, group A) and 16 with negative SLN (53.3%, group B). Seven patients (50%) died in group A and 2 patients (13%) in group B (mean follow-up 28 and 59 months, respectively); all 7 patients in group A and no patient in group B died because of melanoma. OS and DFS were both significantly higher in group B than group A. Conclusion: Our experience demonstrates a high rate of positive SLNs in patients with thick melanoma, and significant differences regarding the general outcomes between those with positive and negative SLNs, the latter group having a good prognosis despite the thick primary tumor. This observation stresses the importance of SLN biopsy as a staging tool in patients with thick melanoma.*

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In 2005, the Multicenter Selective Lymphadenectomy Trial-I first reported a possible survival advantage when sentinel lymph node (SLN) biopsy is performed in patients with intermediate-thickness melanoma (1).

Apart from intermediate thickness, a debate currently exists regarding the utility of SLN biopsy in patients with both thin and thick primary melanomas. In agreement with the American Joint Committee on Cancer (AJCC) TNM staging system (2), those tumors whose thickness is less than 1.0 mm, or more than 4.0 mm, according to Breslow's depth of invasion, are debated. The controversy is based on the prognostic impact of SLN biopsy in these subgroups of patients; for patients comprising the thin melanoma group, the expected rate of diseased nodes is very low, while for patients with thick tumors, the high rate of distant metastasis leads to a poor prognosis. Thus, for contradictory reasons, the possible benefit expected by a SLN biopsy can be little.

The aim of this study was to contribute evidence to this debate from our personal experience, by examining the impact of SLN biopsy among patients with primary melanoma that exceeded 4.0 mm in Breslow thickness, who were treated in our Institution.

Patients and Methods

Patients. All patients with thick primary melanoma (≥4 mm) treated at the Department of Surgery, University of Perugia, Perugia General Hospital, Italy, from 1998 until 2009 were included in this study. No exclusion criteria were specified. All patients had provided informed consent to the treatment based on our Institution's approved protocol.

Methods. Patients with no distant metastasis and no nodal involvement at diagnosis underwent SLN biopsy, in the absence of other contraindications. Patients with positive SLNs underwent complete lymph node dissection (CLND). Our SLN biopsy technique and method of SLN evaluation have been described in previous papers (3, 4).

Table I. *Main characteristics of included patients.*

	Overall population	Group 1	Group 2
Patients, n (%)	43	13 (30)	30 (70)
Age (years)			
Mean±SD	65±17	76±20	61±13
Median	66	83	64
Range	28-98	36-98	28-81
Gender, M/F	29/14	10/3	19/11
Primary melanoma site, n (%)			
Head/neck	6	5	1
Trunk	15	3	12
Extremities	22	5	17
Melanoma thickness (mm)			
Mean ±SD	8±4	10±5	7±4
Median	6	10	6
Range	4-20	4-19	4-20
Follow-up (months)			
Mean ±SD	38±30	23±17	44±32
Median	25	15	29
Range	6-125	8-60	6-125
Overall death, n (%)	22 (51)	13 (100)	9 (30)
Death from melanoma, n (%)	17 (40)	10 (78)	7 (23)
Cardiovascular death, n (%)	3 (7)	2 (15)	1 (3)
Other cause of death, n (%)	2 (5)	1 (8)	1 (3)

Table II. *Main characteristics of patients with positive SLN and with negative SLN.*

	Group A (SLN +)	Group B (SLN –)
Patients, n (%)	14 (46.6)	16 (53.3)
Age (years)		
Mean±SD	62±15	60±11
Median	65	64
Range	35-81	28-74
Gender, M/F	10/4	9/7
Primary melanoma site, n (%)		
Head/neck	0	1
Trunk	6	6
Extremities	8	9
Melanoma thickness (mm)		
Mean±SD	7±4	7±4
Median	6	5
Range	5-20	4-15
Follow-up (months)		
Mean±SD	28±19	59±34
Median	24	65
Range	9-73	6-125
Overall death, n (%)	7 (50)	2 (13)
Death from melanoma, n (%)	7 (50)	0
Cardiovascular death, n (%)	0	1 (6)
Other cause of death, n (%)	0	1 (6)
Patients without residual disease at follow-up, n (%)	4 (57)	12 (86)

Objectives. The primary objective of this study was to assess survival (overall survival and disease-free survival) in patients with: i) disseminated disease at diagnosis with respect to patients undergoing SLN biopsy; ii) positive SLNs and negative SLNs.

The secondary objective of this study was to investigate the effect of variables (age, thickness and number of positive SLNs) on survival.

Statistical analysis. Descriptive statistics (mean, standard deviation, median, ranges) and survival estimates [overall survival (OS) and disease free survival (DFS)] according to Kaplan-Meier were calculated. The log-rank test was used to calculate the hazard ratio in patients with disseminated disease at diagnosis and those undergoing SLN biopsy and in patients with positive SLNs and with negative SLNs. The Cox regression analysis was used to investigate the effect of variables (age, thickness and number of positive SLN) upon survival. The statistical analysis was performed by using StatsDirect 2.7.7.

Results

Overall, 43 patients presented with thick melanoma. They were 29 men and 14 women, with a mean age of 65±17. Tumor thickness ranged from 4 to 20 mm (mean 8±4 mm). Thirteen patients (30%) (group 1) did not undergo SLN biopsy for the following reasons: 5 patients presented with nodal involvement at diagnosis, 5 patients had distant metastases at diagnosis, 3 patients were in a poor clinical condition due to relevant comorbidities and died soon after the diagnosis. The 30 remaining patients, who were included in group 2, underwent SLN biopsy. Main characteristics of the included patients are shown in Table I. Overall, 13 patients (100%) died in group 1, and 9 patients (30%) in group 2 (mean follow-up 23 and 44 months, respectively). Ten patients (77%) in group 1 and 7 patients (23%) in group 2 died because of melanoma.

OS was higher in group 2 (mean survival time 87 months, 95% CI: 66 to 108 months), with respect to group 1 (mean survival time 23 months, 95% CI: 14 to 32 months) with a hazard ratio of 5.8, 95% CI: 2 to 17 months (Figure 1). Neither age nor thicknesses were predictors for OS.

In the subgroup of patients undergoing SLN biopsy, 14 patients had positive SLNs (46.7%, group A) and 16 patients had negative SLNs (53.3%, group B). Seven patients (50%) died in group A and 2 patients (13%) in group B (mean follow-up 28 and 59 months, respectively) (Table II). All 7 patients in group A and none patient in group B died because of melanoma.

OS was higher in group B (mean survival time was 111 months, 95% CI: 85 to 136 months) with respect to group A (mean survival time was 40 months, 95% CI: 23 to 58 months) with a hazard ratio of 7.1 (95% CI: 1.8 to 28.7) (Figure 2). DFS seems to be higher in group B (mean survival time 109 months, 95% CI: 80 to 137 months) with respect to group A (mean survival time 49 months, 95% CI: 24 to 74 months) with a hazard ratio of 4.9 (95% CI: 0.6 to 39.5) (Figure 3).

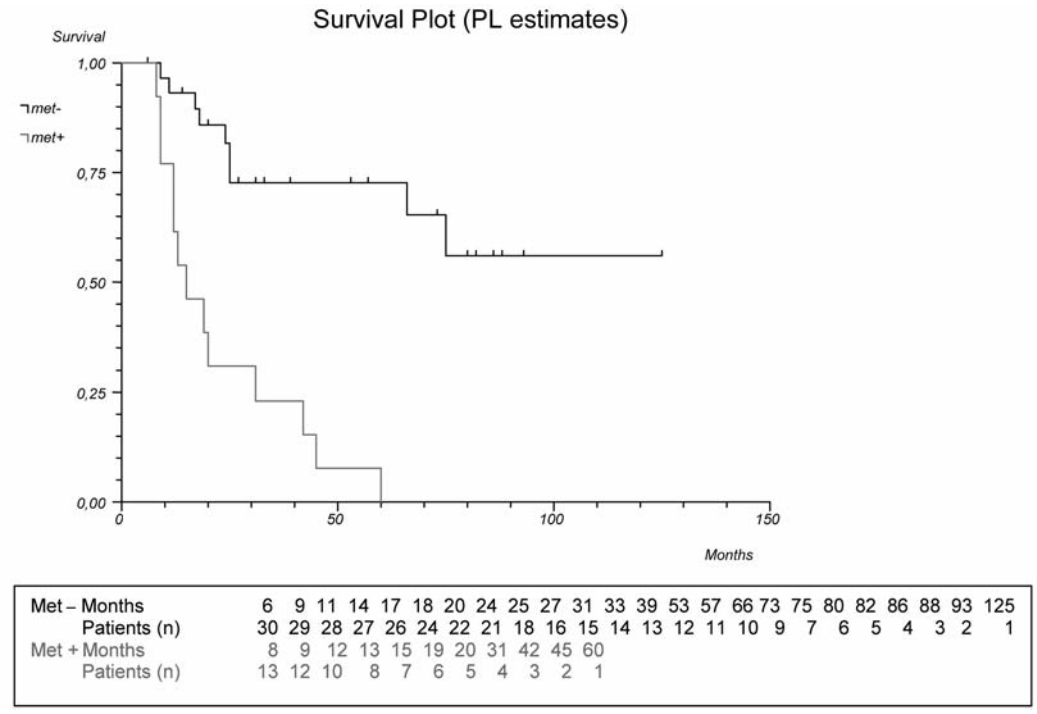

Figure 1. *Overall survival in patients with disseminated disease at diagnosis and in patients undergoing SLN biopsy.*

Neither age nor thicknesses were predictors for OS or DFS. In the subgroup of patients with positive SLN, the number of nodes involved was not a predictor for OS.

Discussion

In recent years, SLN biopsy has become a procedure that is accepted worldwide for the management of patients with melanoma. The procedure has the goal of granting prognostic and staging information, thus addressing the patient with a positive SLN to an early CLND, which has been proven beneficial, at least in subsets of melanoma patients (1).

However, many clinicians still question whether SLN biopsy is beneficial or not in patients with thick melanoma because these patients have a high rate of both regional and systemic occult disease at the time of presentation (5). This is why an accurate pre-operative work up is required for these patients, and a relevant number of patients will not be candidates SLN biopsy. During the presented trial, for 30% (13 patients out of 43) comprised such a group. Unfortunately, those patients who are excluded from SLN biopsy, mainly because of evidence of metastasis or due to poor clinical conditions, have a poor general outcome. We registered 100% of deaths with a mean survival time of 23 months, in which 77% of deaths were caused by melanoma, in comparison with a mean survival time of 87 months in the SLN-biopsy group.

As is expected, there is a good probability of harvesting a positive SLN from patients with thick melanoma, since we found a positive SLN in 47% of biopsied patients. This rate is higher than that reported in melanomas of intermediate thickness (6-11) and we believe that the rate of positive SLNs is increasing according to primary tumor thickness (9, 12-14).

Additionally, in the subset of T4 patients, SLN retains its value as a staging tool. Negative SLN-biopsy patients had a better OS, with a mean survival time of 111 months, whereas when the SLN was positive, the mean survival time was 40 months. DFS was also higher in this group of patients (109 months *versus* 49 months).

The overall death rate was 50% (7/14 patients) among patients with positive SLNs in comparison with 13% (2/16 patients) in the other group.

Another paint of interest comes to light if we analyze the causes of death in the two separate groups of patients. All patients in the SLN-positive group but none in SLN-negative group died because of melanoma. This is a very strong message that is in part limited by the short follow-up period, 28 and 59 months respectively, for the two groups.

Ten years after the paper written by Gershenwald *et al*. (15), who first stated that the pathological status of the SLN in patients with thick primary melanoma was the most important prognostic factor for survival, other reports (16-18) have failed

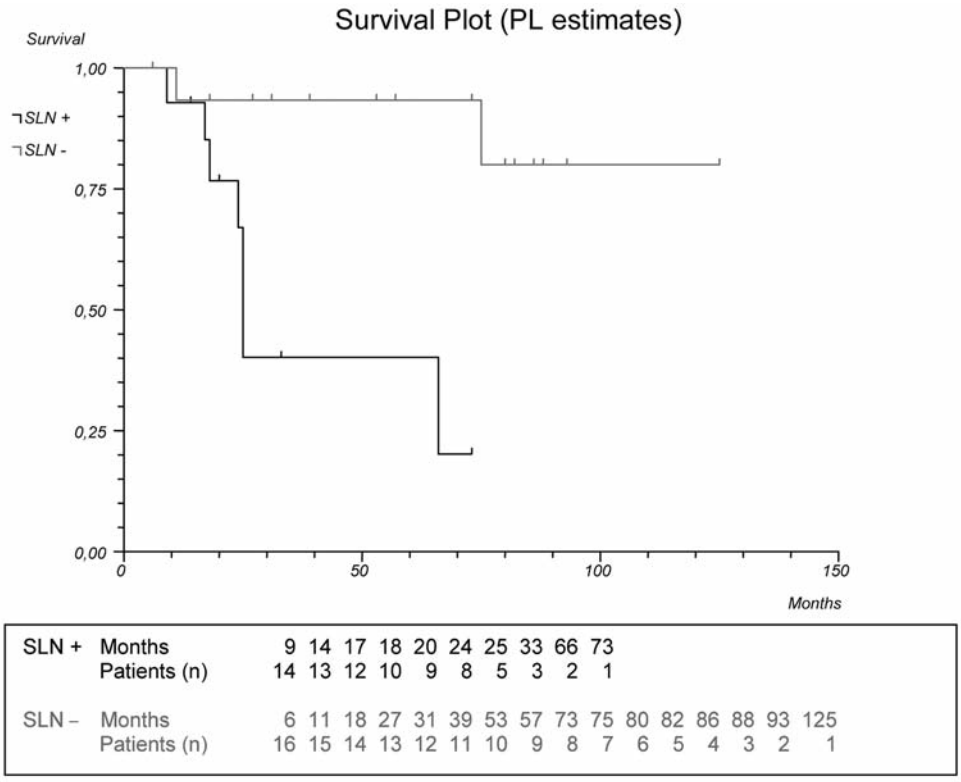

Figure 2. *Overall survival in patients with positive and negative SLNs.*

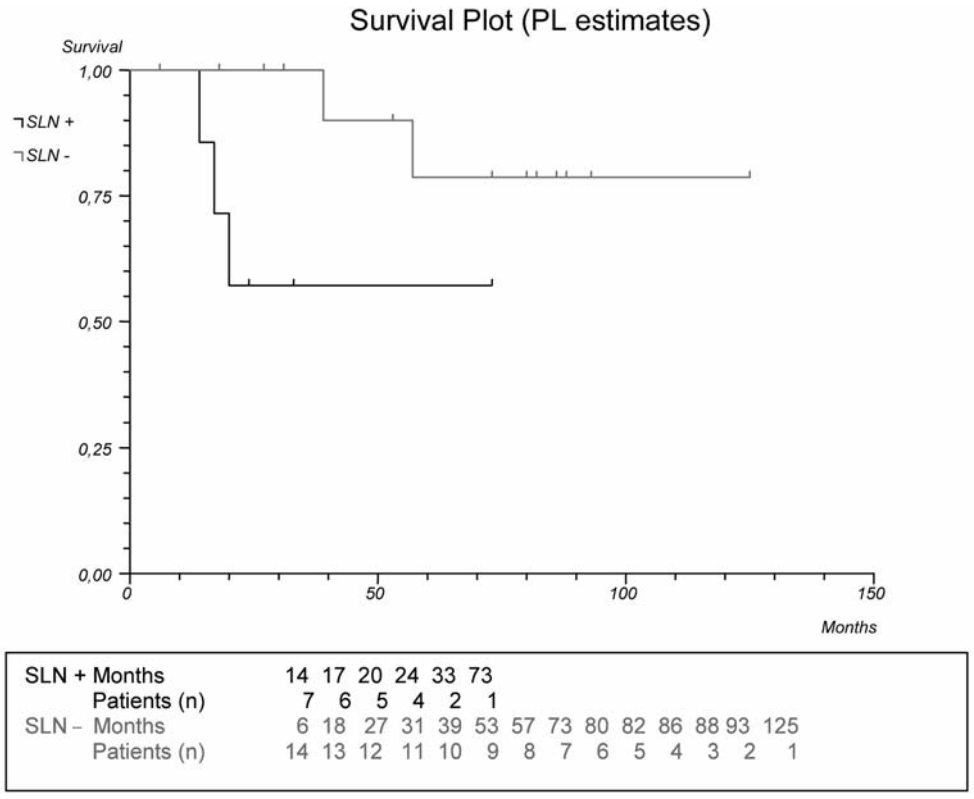

Figure 3. *Disease-free survival in patients with positive and negative SLNs.*

to show significant results in favor of SLN-negative patients, therefore raising doubts about the prognostic role of SLN biopsy in this subgroup of patients.

To date, there is still a debate regarding the real meaning that SLN biopsy has for patients with T4 melanoma (19). In our experience, patients with a thick melanoma (T4 according to AJCC staging system) and a negative SLN had a significantly better DFS and OS compared with those with metastasis to the SLN, with a median follow-up of 59 months.

In conclusion, the results of our study demonstrate significant differences with regards to the general outcome between SLN-positive and -negative patients, the latter group having a good prognosis despite the thick primary tumor, thus stressing the role of SLN biopsy as a standard method of staging in patients with thick melanoma also.

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