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The effect of time to sentinel lymph node biopsy on cutaneous melanoma survival

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Abstract

BACKGROUND: Whether timing of sentinel lymph node biopsy (SLNB) in cutaneous melanoma improves survival is not yet clear. The aim of this study was to investigate if the timing of SLNB influences long-term melanoma mortality.

METHODS: A 10-year retrospective cohort study was conducted on 748 cutaneous melanoma patients who underwent excision of the SLN. Hazard ratios and 95% confidence intervals were estimated from Cox proportional hazards models.

RESULTS: After adjusting for sex, age, Breslow thickness, mitotic rate, ulceration, and histologic type, patients who underwent early SLNB ($\leq$30 days) and resulted positive on final pathology had a 3 times decreased risk of melanoma mortality (hazard ratio = .29; 95%confidence interval = .11 to .77) in comparison to patients who underwent delayed SLNB ($\geq$31 days) and resulted positive on final pathology.

CONCLUSIONS: Our findings suggest that early SLNB ($\leq$30 days) improves melanoma survival.

Although cutaneous malignant melanoma is the least common form of skin cancer, it accounts for 95% of skin cancer deaths.[1] Metastasis to regional nodes has been shown to occur in approximately 20% of the patients with intermediate-thickness tumors (1.0 to 4.00 mm).[2,3] Lymph node metastasis is an indicator of poor prognosis for melanoma patients.[4,5] In 1978, Balch et al[6] suggested that patients with intermediate-thickness melanomas could benefit from early lymphadenectomy to prevent dissemination of regional metastases to distant sites. However, no clear therapeutic advantage, in terms of overall survival, for elective lymph node dissection was established.[7] In 1992, Morton et al[8] introduced the technique of lymphatic mapping and sentinel lymph node biopsy (SLNB) as an alternative to elective lymph node dissection for all patients with a high risk of metastasis. Sentinel lymph node (SLN) technique is performed with the use of blue dye and radiolabeled colloids and identifies the first node or nodes in the regional basin

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that receive lymph from the primary melanoma site. SLNB is recommended for patients with cutaneous melanomas with Breslow thickness from 1 to 4 mm at any anatomic site. In contrast, SLNB is not recommended for patients with thin melanomas (<1.0 mm) because of their low-overall risk of nodal metastasis or for patients with thick melanomas (>4.0 mm) due to the synchronous, occult distant metastases.[9] Although SLNB is considered a useful instrument for staging, to guide treatment decisions, and as entry criteria for clinical trials,[3] some controversies remain in terms of its therapeutic benefit. There is a continuing debate about whether removal of positive lymph nodes improves survival or whether nodal involvement is merely a marker of aggressive disease.[10] The aim of this study was to investigate if timing of SLNB influences long-term melanoma mortality.

Methods

A retrospective cohort study was conducted among 748 cutaneous melanoma patients from the same geographic area (Lazio), who underwent excision of a primary cutaneous melanoma (1.00 mm of Breslow thickness or more) lymphatic mapping and SLNB between January 1998 and December 2008. After having obtained informed consent, study subjects underwent wide excision, lymphatic mapping, and SLNB.[11] Patients with positive SLNB underwent selective lymphadenectomy. Data were merged from the Melanoma Registry of the Istituto Dermopatico dell'Immacolata, Rome. The histologic type, tumor thickness, ulceration, regression, and cellular types were recorded and followed the guidelines described elsewhere.[12–15] The *International Classification of Diseases Ninth Revision* was used to classify the anatomic site and cause of death. "Timing of SLNB" was defined as the time interval (number of days) between the date of the primary melanoma excision and the date of SLNB. "Early" and "delayed" were defined according to quartiles of the distribution of "timing of SLNB". The first quartile was considered as "early". The other quartiles were considered "delayed". Dichotomous variables were created for mitotic rate (<1 mitosis/mm^2 vs ≥1 mitoses/mm^2), ulceration (yes/no), SLNB status (positive/negative). Age was categorized in 4 classes (<30, 30 to 49, 50 to 69, and ≥70 years). Breslow thickness was categorized in 3 classes (1.0 to 2.0; 2.01 to 4.0; >4.0 mm). Histologic type was classified as superficial spreading melanoma, nodular, other (acral and desmoplastic). Anatomic site was classified as trunk, head/neck, upper limb, and lower limb. Tumor infiltrating lymphocytes (TILs) were categorized in 3 classes (low/moderate/marked). Files from the Registry Office of the Department of Epidemiology of the Lazio region were examined to obtain information on vital status and cause-specific mortality. The length of follow-up for each subject was the number of days from the diagnosis of primary melanoma to the date of death or to 31 December 2009, whichever came first. Patients who were alive or dead from other causes were considered censored.

Statistical methods

The main outcome of interest was death from melanoma. Survival estimates were generated using the Kaplan-Meier method. The log-rank test was used to compare the survival curves in patients' subgroups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from Cox proportional hazards models. The likelihood ratio test was used to decide whether to keep each covariate in the model and to test for interaction. The following confounding factors considered in the analysis were: sex, age, Breslow thickness, mitotic rate, ulceration, TILs, histologic type, anatomic site, year of primary melanoma diagnosis. Because there is no clinically acceptable "cut-off point" for time to SLNB, we categorized data at fixed percentiles. Using the 2 to 4 quartiles as the reference category (≥31 days), HR and 95% CI were estimated. Other cut-offs based on percentiles and the median of the distribution of time to SLNB were also tested. Effect modification by sex, Breslow thickness, year of diagnosis, mitotic rate and ulceration, and SLNB status was also considered. Data were analyzed with STATA software (Stata 11.0; StataCorp LP, College Station, TX).

Results

In the study population there were 149 deaths, 100 of which were due to melanoma. Ten-years all-cause survival was 68.5%. Ten-year melanoma specific survival was 78.7%. Of the 748 patients with cutaneous melanoma, 141 patients were positive for nodal metastasis (18.9%) and 607 cases (81.1%) were negative. The mean age of melanoma patients participants was 54.7 years (standard deviation = 16.6), and slightly more than half of the patients were men (54.1%). The median time to SLNB was 41 days.

Table 1 shows the 10-year melanoma survival by clinical and histologic characteristics and HRs for death from melanoma and 95% CIs. Survival decreased with increasing age ($p_{trend} < .001$) and Breslow thickness ($P < .0001$). Ten-year survival of patients with node metastasis was 51.3%. Patients with node metastasis had 5 times an increased risk of mortality (HR = 5.37; 95% CI = 3.62 to 7.96). The most powerful predictors of prognosis, after SLN status, were Breslow thickness (HR = 3.71; 95% CI = 2.45 to 5.62) followed by mitotic rate (HR = 2.78; 95% CI = 1.72 to 4.48) and ulceration (HR = 2.43; 95% CI = 1.59 to 3.71).

Table 2 shows the characteristics of the patients by SLN status. Patients that resulted positive on final pathology had a higher frequency of tumors with more than 2 mm of Breslow thickness (66.7% vs 31.8%, $P < .0001$), with the presence of ulceration (26.2% vs 15.3%, $P = .002$) high-mitotic rate (61.2% vs 32.3%, $P < .0001$) than patients that resulted negative on final pathology. No difference was found for sex, age and anatomic site, and SLNB status.

Table 1 Demographic, histologic, and clinical characteristics of the patients: Kaplan-Meier estimates for melanoma survival and crude hazard ratio for melanoma mortality and 95% confidence intervals

	Subjects (n = 748)	Deaths	Survival		
Characteristics	n* (%)	n*	%†	P value‡	HR (95%CI)§
Sex					
Females	343 (45.9)	48	77.5		1
Males	405 (54.1)	52	80.3	.73	.93 (.63–1.38)
Age group, y					
<30	58 (7.8)	3	92.2		1
30–49	233 (31.1)	24	82.1		1.97 (.59–6.55)
50–69	294 (39.3)	45	76.3		3.15 (.98–10.1)
≥70	163 (21.8)	28	73.3	<.001‖	4.12 (1.25–13.6)
Breslow thickness (mm)					
1.00–2.00	461 (61.6)	34	86.2		1
≥2.01	287 (38.4)	66	65.9	<.0001	3.71 (2.45–5.62)
Mitotic rate					
Low (<1 mitosis/mm^2)	329 (62.3)	28	85.8		1
High (≥1 mitoses/mm^2)	199 (37.7)	42	66.5	<.0001	2.78 (1.72–4.48)
Presence of ulceration					
No	618 (82.6)	69	81.6		1
Yes	130 (17.4)	31	64.7	<.0001	2.43 (1.59–3.71)
Histologic type					
SSM	547 (73.8)	57	82.7		1
Nodular	177 (23.9)	38	67.6		2.07 (1.38–3.13)
Other¶	17 (2.3)	3	…	<.001	…
Anatomic site					
Trunk	286 (38.2)	36	80.0		1
Head/neck	53 (7.1)	9	73.2		1.55 (.75–3.23)
Upper limb	166 (22.2)	20	80.1		.92 (.53–1.59)
Lower limb	243 (32.5)	35	76.9	.49	1.22 (.76–1.94)
Tumor-infiltrating lymphocytes					
Low/moderate	192 (25.7)	28	80.5		1
Marked	51 (6.8)	4	89.0	.18	.48 (.17–1.38)
SLNB status					
Negative	607 (81.1)	50	86.2		1
Positive	141 (18.9)	50	51.3	<.0001	5.37 (3.62–7.96)

CI = confidence interval; HR = hazard ratio; SLNB = sentinel lymph node biopsy; SSM = superficial spreading melanoma.
*Totals may vary because of missing values.
†Estimated by Kaplan-Meier method.
‡Log-rank test.
§Estimated by Cox's proportional model.
‖Log-rank test trend.
¶Acral and desmoplastic melanoma.

We also investigated if prognostic factors differ by timing of SLN (early vs delayed) and sentinel-node status. No statistical difference was observed between the main prognostic factors (sex, age, Breslow thickness, mitotic rate, presence of ulceration, histologic type, and anatomic site) and time to SLNB by SLNB status (data not shown).

Because a statistical interaction was observed between time to SLNB and SLNB status (P = .002), a stratified analysis was conducted. Table 3 shows the effect of time to SLNB on mortality by SLNB status. After adjusting for sex, age, Breslow thickness, mitotic rate, ulceration, and histologic type, patients who underwent early SLNB (≤30 days) and resulted positive on final pathology, had a 3 times decreased risk of melanoma mortality (model 1, HR = .29; 95% CI = .11 to .77) in comparison to patients who underwent SLNB after 30 days and resulted positive on final pathology.

We also controlled 1 at a time in the model 1 for other potential prognostic factors such as TILs, anatomic site of the tumor, year of diagnosis, number of positive lymph nodes, and the results did not change. No statistically significant effect of time to SLNB was found for patients that resulted negative on final pathology (data not shown).

An additional analysis was conducted using different cut-offs of time to SLNB. When we categorized the time to SLNB into quintiles (≤28 vs ≥29 days; HR = .18, 95% CI = .05 to .62) and deciles (≤20 vs ≥21 days; HR = .09, 95% CI = .01 to .66), the effect of early vs delayed remained. However, when we considered the median as the

Table 2 Characteristics of the patients by sentinel lymph node biopsy status

	SLNB status (n = 748)		
	Positive (n = 141)	Negative (n = 607)	
Characteristics	n	n	P value*
Sex			
Females	61 (43.3)	282 (46.5)	
Males	80 (56.7)	325 (53.5)	.49
Age, y			
Mean (SD)	55.8 (16.4)	54.5 (16.7)	
Median (IQR)	58.3 (42.9–68.8)	55.4 (40.8–68.3)	.44†
Breslow thickness (mm)			
Mean (SD)	3.36 (2.11)	2.18 (1.82)	
Median (IQR)	3.0 (1.6–4.0)	1.5 (1.2–2.5)	.0001
1.00–2.00	47 (33.3)	414 (68.2)	
≥2.01	94 (66.7)	193 (31.8)	<.0001
Mitotic rate			
Low (<1 mitosis/mm^2)	38 (38.8)	291 (67.7)	
High (≥1 mitoses/mm^2)	60 (61.2)	139 (32.3)	<.0001
Presence of ulceration			
No	104 (73.8)	514 (84.7)	
Yes	37 (26.2)	93 (15.3)	.002
Histologic type			
SSM	85 (60.7)	462 (76.9)	
Nodular	51 (36.4)	126 (21)	
Other‡	4 (2.9)	13 (2.2)	<.0001
Anatomic site			
Head/neck	7 (5.0)	46 (7.6)	
Trunk	46 (32.6)	240 (39.5)	
Upper limb	31 (22.0)	135 (22.2)	
Lower limb	57 (40.4)	186 (30.6)	.13

IQR = interquartile range; SD = standard deviation; SLNB = sentinel lymph node biopsy.
*Chi-square or Fisher's exact test, where appropriate.
†Kruskal-Wallis test.
‡Acral and desmoplastic melanoma.

cut-off (≤41 days vs ≥42 days), the effect disappeared (HR = .79; 95% CI = .44 to 1.45).

Comments

Although SLNB has been the gold standard for accurate staging and has been routinely used in clinical practice for 20 years, the therapeutic effect of SLNB on melanoma survival is debated.[10] Our study conducted in a large reference dermatological Italian hospital, showed that patients who underwent early SLNB within 1 month from the diagnosis of the primary melanoma and that resulted positive on final pathology had 3 times decreased risk of 10-year melanoma mortality, after controlling for all possible confounders. The findings of this study

Table 3 Cox regression model-hazard ratio for melanoma mortality for timing of SLNB by SLNB status HRs (95%CI)

	Sentinel lymph node biopsy status			
	Negative (n = 607)		Positive (n = 141)	
	Timing of SLNB, days		Timing of SLNB, days	
	Delayed (≥31)*	Early (≤30)	Delayed (≥31)*	Early (≤30)
Models	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 0†	1	1.87 (1.04–3.36)	1	.36 (.14–.92)
Model 1‡	1	1.77 (.97–3.26)	1	.29 (.11–.77)

CI = confidence interval; HR = hazard ratio; SLNB = sentinel lymph node biopsy.
*Reference category.
†Model 0: crude HR.
‡Model 1: HR adjusted for sex, age, Breslow thickness, mitotic rate, ulceration, and histologic type.

suggest that early SLNB impeded the growth and dissemination of disease and consequently increased patients' survival.

The prevalence of nodal metastasis in our population, across all Breslow thickness, was 18.9% which is comparable to other studies published elsewhere.[9,16] According to the recommendation of American Society of Clinical Oncology and Society of Surgical Oncology, SLNB is recommended to patients with intermediate-thickness melanomas (from 1.0 to 4 mm of Breslow).[9] In our study, we included all melanoma patients with 1.0 mm or more of Breslow thickness who underwent SLNB. To follow recommendations by American Society of Clinical Oncology and Society of Surgical Oncology in terms of inclusion criteria for SLNB, we excluded patients with Breslow thickness of 4.00 mm or more and re-ran the models, but the results did not change. Because SLN is technically more challenging when the primary melanoma is in the head and neck area,[17] we also controlled in the multivariable analysis for the anatomic site of the melanoma, and the results did not change.

There are only 2 studies so far that investigated the effect of the timing of SLNB on survival in melanoma patients and they showed contradictory results.[18,19] The study of Parrett et al[18] conducted on 492 melanoma patients showed that a delay time of SLNB (40 days or more) was not related to overall survival, whereas a more recent study showed that early SLNB (40 days or less) was associated with a worse melanoma 5-year specific survival.[19] However, there are many factors that might have influenced the results of these studies such as the lack of data on melanoma specific mortality of the study of Parrett (2012) and the high number of persons lost in the follow-up in the study of Tejera-Vaquerizo (2015).

By using different cut-offs of timing of SLNB based on percentiles and the median, we observed that the therapeutic effect of SLNB was only present when SLNB was performed within 1 month from the primary melanoma excision but not after that date. When we considered in our study, the median as the cut-off of early SLNB (41 days) the protective effect of timing of SLNB disappeared (HR = .79; 95% CI = .44 to 1.45).

Our study has some strength and limitations. The strength of our study is the complete and long-follow-up time (10 years) and the inclusion of all known prognostic factors for melanoma in the multivariate model. The limitation of our study is the type of design which is observational and not a randomized clinical trial that yields similar groups at the start of the investigation. However in our study, we showed no statistical difference between the main prognostic factors and timing of SLNB. Thus, the survival benefit found in our study of early SLNB cannot be explained by the high prevalence of patients with thin Breslow thickness and/or low-mitotic rate and/or no ulceration.

Conclusions

The results of our study suggest that early SLNB ($\leq$ 30 days) improves melanoma survival. Further observational studies to confirm our findings are warranted.

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