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Original Article

Sentinel lymph node biopsy for cutaneous melanoma: A 6 years study

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ABSTRACT

Background: The aim of this study was to evaluate the results of sentinel lymph node biopsy (SLNB) in cutaneous melanoma at our institution. **Materials and Methods:** 128 patients with primary cutaneous melanoma who underwent SLNB between April, 2004, and August, 2010 were studied. Univariate and multivariate analysis was performed to explore the effect of variables on mortality and sentinel node status. Survival analysis was performed using the Kaplan-Meier approach. **Results:** Positive SLNB were detected in 35 (27.3%) of 128 cases. Mean Breslow depths were 3.7 mm for SLNB positive patients and 1.99 mm for SLNB negative patients. False negative rate was 1%. The recurrence rate was 40% for positive patients and 6.5% for negative patients (odds ratio 9.7 [confidence interval 95 % 3.3-28.1]). 33 patients (29%) had an ulcerated melanoma, 12 (10.5%) in the positive group and 21 (18.5%) in the negative group. The disease recurred in a 48.5% of patients with ulcerated melanoma, but only in a 2.5% of patients with non-ulcerated melanoma. Upon multivariate analysis, only Breslow thickness ($P = 0.005$) demonstrate statistically significance for SLNB status. Multivariate analysis for clinicopathologic predictors of death demonstrate statistically significance for Breslow thickness ($P = 0.020$), ulceration ($P = 0.030$) and sentinel node status ($P = 0.020$). **Conclusions:** This study confirms that the status of the sentinel node is a strong independent prognostic factor with a higher risk of death and lower survival. Patients with ulcerated melanoma are more likely to develop recurrence, and also higher risk of death than patients with non-ulcerated melanoma.

KEY WORDS

Melanoma; sentinel node biopsy; sentinel node dissection

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INTRODUCTION

In the last 50 years, the incidence of melanoma has increased dramatically. It is estimated that 68,130 new cases of melanoma will be diagnosed and about 8,700 patients will die of the disease in the United States during 2010.[1] The high-level of clinical suspicion in detecting the disease in its early stages has restricted the increasing mortality of this disease (approximately 85% in stages I and II).[2]

The sentinel lymph node (SLN) is defined as the first node directly draining lymph from the primary melanoma. Since, its introduction by Morton in 1992,[3] sentinel lymph node biopsy (SLNB) has become a standard procedure in the staging and treatment of primary melanoma ≥1 mm and clinically negative nodes or melanomas <1 mm in thickness associated with the poor prognosis changes. Below this threshold, the expected number of positive SLN is too small to justify the use of this technique.

The value of SLNB in melanoma patients is controversial.[4] Numerous studies have shown that the status of the SLN is an important and independent prognostic parameter for overall survival and recurrence-free survival of melanoma patients.[5-7] It present a higher predictive accuracy than the standard prognosticators, such as Breslow thickness, Clark level, ulceration, age and sex.[8] SLNB has been declared as standard procedure in the treatment of melanoma patients by the World Health Organization.[9] With minimal morbidity, SLNB reliably detects subclinical nodal involvement,[10] provides accurate and cost-effective staging,[11] and identifies patients who may benefit from adjuvant therapy.[12] However, many authors do not generally recommend SLNB for routine use until further evidence shows an improvement in prognosis as a result of SLNB.[13,14]

There are three hypotheses about how SLNB could affect the prognosis of patients with melanoma. First, the prognosis does not change as melanoma cells metastasize simultaneously via lymphatic and haematogenous routes, and micrometastases in the SLN only indicate the metastatic potential of melanoma cells ("marker hypothesis"). Second, the prognosis improves because micrometastases are removed early, which impairs their ability for distant metastasization. This implies that melanoma cells metastasize primarily via the lymphatics and acquire the potential for distant metastases after a certain period of "incubation" time in the regional lymph node ("incubator hypothesis"). Third, the prognosis is impaired as melanoma cells are removed from an immunologically active environment, preventing an immune response against melanoma antigens.[15-17]

In our hospital, our department is responsible for carrying out the technique of SLN for melanoma. We perform between 20 and 25 annual interventions for melanoma SLN and we have an accumulated experience of 6 years using the technique. In those patients in whom the sentinel node contains metastases, surgery is completed with selective lymph node dissection (SLND) of the involved basin.

The purpose of our study is to evaluate all the patients with melanoma treated in our hospital using SLNB from April 2004 to August 2010, and assess what factors may be associated with Sentinel Node (SN) positivity and mortality.

MATERIALS AND METHODS

Study characteristics

A retrospective observational study was carried out. We included all patients with melanoma who underwent SLNB at the Universitary Hospital of Gran Canaria "Dr. Negrín", from April 2004 to August 2010.

The criteria for SLNB were patients with primary melanoma ≥1 mm without palpable lymph nodes and no distant metastases. We also included other patients with melanomas <1 mm if Clark level was in a stage III-IV, were ulcerated, showed signs of regression or were young.

We did not include the variable mitoses/mm^2, because we started collection with National Comprehensive Cancer Network guidelines of 2010.

In our study, we consider recurrence of the disease when distant metastasis, lymph node, or local recurrence appears after excision of the lesion and SLNB.

Lymphatic mapping and surgical technique

The day before or the morning of surgery, all patients underwent preoperative lymphatic mapping with the injection of 0.5-1 mCi of Tc99 m injected in 4-6 intradermal points surrounding the site of primary melanoma. The SLN was identified by the nuclear physician using a handheld gamma probe and then marked on the skin with a permanent marker. All basins identified were explored through limited incisions directed by the same handheld gamma probe. The SLN was defined as any node with the highest radioactive count in the marker area. This node(s) was identified and removed, and it was sent in formaldehyde solution directly to the Department of Pathology. Any node(s) with >10% count rate of the most radioactive node was also removed and analysed. Intraoperative SLN study was not done on any patient. Before SLNB, a wide local excision was performed on the primary melanoma site with 1-2 cm margins, depending on its thickness.

Histologic analysis of surgical specimens

The submitted SLN were reviewed by routine histopathological study (Haematoxylin and Eosine) and by immunohistochemical methods (S-100 and Human Melanoma Black 45). If the histological analysis showed metastatic melanoma, a SLND was carried out in a second sitting.

Data and statistical analysis

Data used for the preparation of this article were obtained from the medical records of patients. We designed a database with Access software for storing patient data. These data were analysed using the SPSS version 15.0. The level of statistical significance was set for $\alpha = 0.05$.

From a descriptive standpoint, quantitative variables were treated by analysing the rates of centralization and dispersion: The arithmetic mean and standard deviation.

We calculated the odds ratio (OR) with a confidence interval (CI) of 95% for qualitative variables (gender, location, Breslow, Clark levels and ulceration).

A multivariate logistic regression model was performed to demonstrate the possible relationship between variables and SNB result. It included the variables: Sex, age, Breslow, ulceration (present vs. absent) and location (trunk vs. no trunk). We also performed a multivariate logistic regression to demonstrate the relationship between variables and death. The variables included were: Sex, age, Breslow, ulceration (present vs. absent) and sentinel node (positive vs. negative).

RESULTS

Between April 2004 and August 2010, 128 patients with primary skin melanoma underwent SLNB, 61 men (47.7%) and 67 women (52.3%). The mean patient age was 55.7 ± 16.3 years.

Clinicopathological features are shown in [Table 1]. Thirty-five patients (27.3%) had a positive SLNB. Seven of these (20%) had tumour-positive non-sentinel nodes identified at the time of SLND. The Breslow thickness of these patients was always >1.8 mm and in 71% it was more than 4 mm [Table 2]. Of 93 patients with a negative SLNB, only one patient developed a recurrence in a lymph node basin that was negative by SLNB (false negative rate of 1%).

Table 1: Clinicopathological features

	Positive sentinel node n=35 (%)	Negative sentinel node n=93 (%)	OR (95% CI)
Gender			
Male	21 (60)	40 (43)	0.5 (0.2-1.1)
Female	14 (40)	53 (57)	
Age (years)			
Mean (SD)	56.9 (14.9)	55.2 (16.8)	
Location			
Trunk	10 (28.6)	38 (40.9)	1.7 (0.7-4.0)
Upper limb	3 (8.6)	14 (15.1)	0.81 (0,19-3.4)
Lower limb	11 (31.4)	25 (26.9)	1.7 (0.62-4.5)
Acral	5 (14.3)	7 (7.5)	2.7 (0.7-10.4)
Head and neck	6 (17.1)	9 (9.7)	2.5 (0.73-8.8)
Breslow			
Mean (mm)	3.7	1.99	
0-1 mm	3 (8.6)	27 (29)	0.12 (0.29-0.50)
1.01-2 mm	13 (37.1)	33 (35.5)	0.43 (0.15-1.18)
2.01-4 mm	7 (20)	20 (21.5)	0.38 (0.12-1.22)
>4 mm	12 (34.3)	13 (14)	3.21 (1.29-7.9)
Clark levels			
I	1 (2.9)	1 (1.1)	1.25 (0.6-26.9)
II	1 (2.9)	16 (17.2)	0.08 (0.007-0.870)
III	12 (34.3)	48 (51.6)	0.31 (0.073-1.3)
IV	17 (48.6)	23 (24.7)	0.92 (0.22-3.9)
V	4 (11.4)	5 (5.4)	2.27 (0.57-9)
Ulceration			
Present	12 (42,4)	21 (24,7)	2.15 (0.89-5.23)
Absent	17 (58.6)	64 (75.3)	

CI: Confidence interval, OR: Odds ratio, SD: Standard deviation

Table 2: Relationship between Breslow and positive sentinel node and positive non sentinel node

Breslow	Positive sentinel node (n/%)	Positive non-sentinel node (n/%)
0-1 mm	3 (8.6)	0 (0)
1.01-2 mm	13 (37.1)	2 (28.6)
2-4 mm	7 (20)	0 (0)
>4 mm	12 (34.3)	5 (71.4)

A total of 294 sentinel nodes were removed. The mean number of sentinel nodes taken at each operation was 2.28 (range 1-6).

Mean Breslow tumour thickness for all primary melanomas was 2.46 mm. Mean Breslow thickness of 3.7 mm (CI 95% 2.5-4.9) for SLNB positive melanomas was significantly greater than 1.99 mm (CI 95% 1.68-2.30) for negative melanomas. All patients with a positive SLNB had a Breslow thickness ≥1 mm.

To date, 10 patients (8%) have died from melanoma, eight of them from the positive group (mortality rate 22.9%) and only two patients from the negative group (mortality rate 2.2%). Therefore, in this study,

positive patients are 13.5 times more likely to die from their disease than negatives, OR = 13.5 (CI 95% 2.7-67.3). The mean survival rate of 58.3 months (CI 95% 48.6-68.1) for positive patients was significantly lower than 73.3 months (CI 95% 71.9-76.6) for negative patients ($P < 0.001$) [Figure 1].

Of 128 patients, 20 (15.6%) develop disease recurrence. In the group of patients with positive SLNB, 14 (40%) of 35 patients developed recurrence. In patients with a negative SLNB, only 6 patients (6.5%) developed recurrence. Therefore, there is a 9.7-fold greater chance of melanoma recurrence if the sentinel node is positive when compared to having a negative result (OR 9.7; CI 95% 3.3-28.1) [Table 3].

In our study, 33 patients (29%) had an ulcerated melanoma, 12 (10.5%) in the positive group and 21 (18.5%) in the negative group. In 48.5% of patients with ulcerated melanoma the disease recurred, while it only recurred in a 2.5% of the patients with non-ulcerated melanoma. Therefore, patients with ulcerated melanoma are 37.1 times more likely to develop recurrence than patients with non-ulcerated melanoma (OR 37.1; CI 95% 7.8-177).

In this series, 11 patients (88.6%) showed pattern of regression, all of them from the negative SLNB group (OR 0.88; CI 95% 0.82-0.95%).

Multivariate logistic regression for clinicopathological predictors of SLN status [Table 4] demonstrated statistical significance only for Breslow thickness (OR 1.27; CI 95% 1.02-1.57; $P = 0.005$). Multivariate logistic regression for clinicopathological predictors of death [Table 5] demonstrated statistical significance for Breslow thickness (OR 1.53; CI 95% 1.05-2.23; $P = 0.020$), ulceration (OR 65.96; CI 95% 1.5-2917.77; $P = 0.030$) and SLN status (OR 11.9; CI 95% 1.67-85.3; $P = 0.020$).

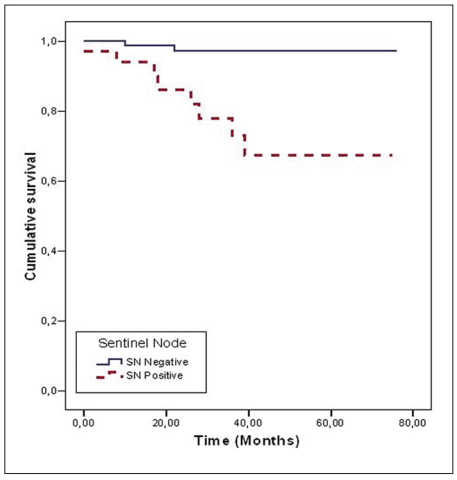

Figure 1: Kaplan-Meier plot of survival in patients with positive SN and negative SN ($P < 0.001$; log-rank test)

DISCUSSION

Our cohort, 128 patients, presents some variables, either clinical or pathological, similar to other series described in the literature.

In the current study, the rate of positive SLN was 27.3%, which is slightly higher than other studies[1-3,6-8] which ranged between 15% and 23%. In the group of patients with positive sentinel node, the positivity rate of non-sentinel nodes found in lymphadenectomy was 20%, comparable with other series,[1-3,6,8] which ranged from 7.8% to 33%.

None of our patients presented a positive sentinel node when dealing with a Breslow thickness lower than 1 mm. Moreover, when the primary cutaneous melanoma had a Breslow index inferior to 1,8 mm we did not find additional positive nodes in the lymphadenectomy. The low incidence of positive non-sentinel nodes after lymphadenectomy shown in our and other studies may indicate that this procedure could be unnecessary in

Table 3: Comparison of mortality and recurrence between positive sentinel node and negative sentinel node

Died			Recurrence		
Positive SN (%)	***Negative SN (%)***	***OR (95% CI)***	***Positive SN (%)***	***Negative SN (%)***	***OR (95% CI)***
8 (22.9)	2 (2.2)	13.5	14 (40)	6 (6.5)	9.7
27 (77.1)	91 (97.8)	(2.7-67.3)	21 (60)	87 (93.5)	(3.3-28.1)

CI: Confidence interval, SN: Sentinel node, OR: Odds ratio

Table 4: Multivariate analysis of clinicopathologic characteristics predictive of sentinel lymph node metastases

Clinicopathologic characteristics	OR (95% CI)	*P* value
Breslow	1.27 (1.02-1.57)	0.005
Ulceration	1.47 (0.54-3.99)	0.087
Gender	2.3 (0.9-6.1)	0.195
Age	1 (0.97-1.03)	0.298
Location	1.37 (0.48-3.83)	0.333

CI: Confidence interval, OR: Odds ratio

Table 5: Multivariate analysis of clinicopathologic characteristics predictive of death

Clinicopathologic characteristics	OR (95%CI)	P value
Gender	0.67 (0.1-4.9)	0.689
Age	1.01 (0.93-1.09)	0.811
Breslow	1.53 (1.05-2.23)	0.02
Ulceration	65.96 (1.5-2917.77)	0.03
Sentinel node	11.9 (1.67-85.3)	0.02

CI: Confidence interval, OR: Odds ratio

patients with thin melanomas,[4,5,18] suggesting that metastases in those patients are confined exclusively to the sentinel node.

We only found one case of negative SN who suffered a nodal recurrence, establishing our false negative rate close to 1%, which is less than other large series studies with recurrence rates between 4% and 32%.[6]

Significantly, the mean Breslow thickness in the sentinel node positive patients in our study is 3.7 mm, higher than in other series.[7-10] This aspect may indicate that patients seek help in a more advanced stage of the disease, pointing consequently to the failure of our prevention strategies and early diagnostic measures.

There were 10 cases (8%) of death directly related to melanoma, which is similar to other series.[8,10,12] Eight of the cases belong to the SN positive group. It follows that having positive SN increases 13.5-fold the possibility to die from the disease, reflecting the importance of SN as a prognostic factor.

About 15% of all recruited patients suffered recurrence. This figure is comparable with other series, with rates ranging from 5% to 24%.[9] The recurrence rate in SN positive patients (40%), with a mean follow-up of 34 months, was significantly higher than the SN negative group (6.5%). Many other studies have shown similar results.[10,11]

The ulceration rate in our study was 29%, which is again similar to other groups.[5,7,8,15] A relevant finding of our study is the relationship between ulceration and recurrences. Fifty per cent of patients with ulcerated melanoma presented recurrent disease, 37-fold higher than in non-ulcerated patients. Multivariate logistic regression showed that ulceration is related to positive SN and a higher risk of recurrence. Nevertheless, these aren't statistically significant results. This finding, also presented in other series,[7,19] suggests that patients with ulcerative melanoma have a higher risk for occult metastases. This is the reason to perform SLNB in patients who present these histological characteristics independently of their tumour thickness, and suggests ulceration is a strong independent marker of bad prognosis.[20]

All the patients who showed a regression pattern presented negative SN. This aspect supports the consideration of this phenomenon as a defence mechanism. However, one patient with a regression pattern and a negative sentinel node developed visceral recurrence and subsequently died.

In our study, we have seen that positive SN is indicative of a higher risk of death and lower survival.

It is important to emphasize the role of the ulceration, because almost 50% of the patients with ulcerated melanoma have developed disease recurrence as well as a higher risk of death. These are both statistically significant results.

CONCLUSIONS

The presence of a positive sentinel node is associated with poor prognosis, higher risk of recurrence and death.

In our study, patients with ulcerated melanoma are statistically associated with a higher rate of recurrence and death.

Patients with Breslow index under 1.8 mm and a positive sentinel node did not show any other node affects in the lymphadenectomy. These patients could benefit from not doing the lymphadenectomy, but this requires further investigation.

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