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Biópsia do Gânglio Sentinela em Melanomas Espessos: Estudo Clínico Retrospectivo num Único Centro

Mariana Lemos[1], Ricardo Vieira[2], Ana Brinca[3], Américo Figueiredo[4]

[1]Aluna do Mestrado Integrado em Medicina/Medical Student, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[2]Professor Auxiliar/Associated Professor, Faculdade de Medicina da Universidade de Coimbra, Dermatology and Venereology Department, Coimbra University Hospital Center, Coimbra, Portugal

[3]Assistente Hospitalar/Consultant of Dermatology and Venereology, Serviço de Dermatologia dos Hospitais da Universidade de Coimbra, Portugal

[4]Professor e Director do Serviço de Dermatologia/Professor and Head of Dermatology Department, Centro Hospitalar e Universitário de Coimbra, Portugal

RESUMO – **Introdução**: A biopsia do gânglio sentinela é um procedimento genericamente aceite no estdiamento do melanoma. O valor prognóstico desta técnica parece ser mais relevante nos melanomas de espessura intermédia (1-4mm) do que nos melanomas espessos (>4mm). Objectivo: Avaliar o valor prognóstico do estado do gânglio sentinela em doentes com melanoma espesso. **Doentes e Métodos**: A sobrevivência livre de doença e a sobrevivência global foram estimadas pelo método de Kaplan-Meier e por um modelo de regressão de Cox numa amostra de doentes com melanoma espesso. **Resultados**: Foram incluídos 43 doentes (52.2% do sexo masculino) com uma média etária de 63,9 anos. A biopsia do gânglio sentinela foi positiva em 20 casos (46,5%). O tempo médio de seguimento foi de 40 meses. Os doentes em que não foram encontradas metástases no gânglio sentinela tiveram uma sobrevivência livre de doença aos 5 anos significativamente maior do que o grupo de doentes com gânglio sentinela positivo (63% versus 19%, $p<0.05$). A sobrevivência global aos 5 anos foi tendencialmente mais baixa em doentes com gânglio sentinela positivo (52% versus 79%), embora sem significado estatístico. **Conclusão**: O estado do gânglio sentinela não teve influência estatística na sobrevivência global dos doentes da nossa série de melanomas espessos, provavelmente devido ao risco elevado de metastização por via hemática. Porém, a biopsia do gânglio sentinela forneceu informação prognóstica relevante, uma vez que teve clara influência na sobrevivência livre de doença.

PALAVRAS-CHAVE – Biópsia do Gânglio Sentinela; Melanoma; Neoplasias da Pele; Prognóstico; Taxa de Sobrevida.

Sentinel Lymph Node Biopsy in Thick Melanoma: A Single-Centre Retrospective Clinical Study

ABSTRACT – ***Background:*** *Sentinel lymph node biopsy is widely accepted in the staging of melanoma. The prognostic value of this technique seems to be greater in intermediate-thickness melanoma (1-4 mm) than in thick melanoma (>4 mm). Objective: To assess the prognostic value of sentinel node status in patients with thick melanoma.* ***Patients and Methods:*** *The disease-free survival and the overall survival were estimated using Kaplan-Meier curves and a Cox regression model in a sample of patients with thick melanoma.* ***Results:*** *Forty-three patients were included (52.2% male) with a mean age of 63.9 years. Sentinel node biopsy was positive in 20 patients (46.5%). Mean follow-up was 40 months. Patients without sentinel node metastases had a 5-year disease-free survival rate significantly higher than those with positive sentinel node (63% versus 19%, $p < 0.05$). The 5-year overall survival rate was tendentiously lower in patients with positive sentinel node (52% versus 79%), lacking statistical significance.* ***Conclusion:*** *The sentinel node status was not able to predict the overall survival in our series of thick melanomas, probably due to the high risk of hematic spread. However, sentinel lymph node biopsy provided important prognostic information, since the sentinel lymph node status influenced the disease-free survival.*

KEY-WORDS – *Melanoma; Prognosis; Sentinel Lymph Node Biopsy; Skin Neoplasms; Survival Rate.*

Correspondência: Ricardo Vieira
Serviço de Dermatologia - Hospitais da Universidade de Coimbra
Praceta Mota Pinto - 3000-075 Coimbra, Portugal
Tel.: 00351239400420 - Fax: 00351239400490
E-mail: ricardo.jdc.vieira@gmail.com

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INTRODUCTION

Sentinel lymph node biopsy (SNB) is a safe and minimally invasive technique that provides relevant information about the sentinel lymph node status, which is one of the most important prognostic factors for patients with localized cutaneous melanoma.[1]

Although the prognostic value of this technique is largely established in intermediate thickness melanoma (1 to 4mm), there is still some controversy regarding its efficiency and reliability in thick melanoma (> 4mm). This is mainly due to the fact that this subset of patients has a high risk of hematic spread of the disease regardless the sentinel lymph node status.

Data about the prognostic impact of sentinel lymph node status in thick melanoma are conflicting in several studies. In the latest report of the MSLT-I trial (Multicenter Selective Lymphadenectomy Trial), consisting of a 10-year review, Morton *et al*[2] observed that the SNB-based staging in primary thick melanoma provided important prognostic information and was correlated with a significant increase in disease-free survival (DFS), although this was not true for overall survival (OS). Fairbairn *et al* achieved similar results in their study.[3] Several other authors[4-12] have been successful in correlating the SNB--based staging with improved DFS and OS, advocating its use in this subset of patients. The results presented by Vermeeren *et al*[13] suggest that the only relevant prognostic factor regarding patients with thick melanoma is SNB and this procedure can be used to stratify patients according to the risk of recurrence. Conversely, Rhodes[14] and Oliveira Filho *et al*,[15] stated that SNB status does not contribute with relevant prognostic information in patients with thick melanoma and, therefore, SNB should not be recommended due to the lack of prognostic information.

The aim of this retrospective clinical study was to assess the prognostic value of sentinel lymph node status in patients with thick melanoma and to determine its usefulness as a staging procedure.

MATERIALS AND METHODS

This study reviewed medical files of patients with cutaneous melanoma (thickness higher than 4.0 mm) in whom SNB was successfully performed in the Department of Dermatology, Coimbra University Hospital Center, Coimbra, Portugal, between January 2004 and December 2010. The data were collected during 2015.

The sentinel lymph node identification was performed by lymphoscintigraphy. The radiotracer used was 99mTc-albumin nanocolloid that was injected intradermally in 4 different points around the primary tumor or around the scar of the excisional biopsy. This injection occurred 18-24 hours prior to surgery. The imaging was taken by a gamma camera and the localization of the sentinel lymph node was marked on the skin. A gamma probe was used to detect the sentinel lymph node during surgery. The first lymph node receiving the radiotracer in a given basin were considered the sentinel node, as well as those nodes which had at least 10% of the radioactive count of the hottest sentinel node detected intraoperatively in that basin. The sentinel nodes were formalin fixed, paraffin embedded and systematically sectioned under a "breadloafing" technique. Classical stain with hematoxylin-eosin and immunostains with HMB-45 and S-100 were performed.

The patients were assigned to two study groups: group A (patients with positive SNB), and group B (patients with negative SNB).

In both groups the following variables were studied: demographic variables (age and gender), variables related to melanoma and its progression (melanoma subtype, thickness, presence of ulceration, location, average follow-up time, tumor recurrence, DFS, melanoma-related death and OS) and sentinel lymph node status. Mitotic rate was not included, since the patients were collected before 2010, previous to the inclusion of the mitotic rate in the staging system of the American Joint Committee on Cancer.

Descriptive statistic measures were applied to all the study variables: mean, standard deviation, median and interquartile intervals (percentile 25 to percentile 75).

Variables were compared recurring to methods of inferential statistics, using chi-square test for nominal variables and Pearson's correlation test for quantitative variables.

DFS and OS were calculated and interpreted by the method of Kaplan-Meier, which produced survival curves. Hazard ratios (HR) were determined from a Cox regression analysis, which was also used to access the effect of the different variables in DFS and OS.

A *p* value under 0.05 was defined as statistically significant.

Statistical analysis was performed using the software program IBM® SPSS® Statistics 20.

RESULTS

A total of 43 patients with thick melanoma were included: 21 women (48.8%) and 22 men (51.2%), with a mean age of 63.9 years. SNB was positive in 20 (46.5%) patients (group A) and negative in 23 (53.5%) patients (group B). The mean follow-up was 40 months.

The characteristics of both groups are summarized in Table 1.

Fifteen patients (35%) suffered melanoma-related death, with 9 patients belonging to group A (45%) and 6 belonging to group B (26%). No significant differences were observed between both groups respecting the risk of suffer an event of melanoma-related death.

A total of 22 patients (51%) suffered disease recurrence, with 14 patients (70%) belonging to group A and 8 patients (35%) belonging to group B. Despite this tendency, no statistically significant differences were found.

Overall, DFS (Fig. 1) was longer in group B (average of 55 months, 95% confidence interval: 41 to 68 months), when compared with group A (average of 28 months, 95% confidence interval: 15 to 41 months), with a 5-year disease-free survival rate of 63% in group B and 19% in group A. This difference between the two groups was statistically significant ($p=0.02$ by log rank test). The hazard ratio was 2.7 with 95% confidence interval of 1.1 to 6.6 ($p<0.05$).

Overall survival (Fig. 2) was higher in group B (average of

Table 1 - Characteristics of patients with thick melanoma according with sentinel lymph node status.

	TOTAL	Positive SNB (Group A)	Negative SNB (Group B	*P* value
Patients, n (%)	43	20 (46.5)	23 (53.5)	
Age (years) • Mean + SD • Median • Interquartile Range (25-75)	 64 ± 16 69 23	 62 ± 15 67 25	 66 ± 17 69 19	NS
Gender, M/F	22 / 21	12 / 8	10 / 13	NS
Melanoma Location, n (%) • Head/Neck • Trunk • Upper Limb • Lower Limb	 4 (9) 13 (30) 4 (9) 22 (51)	 0 7 (35) 2 (10) 11 (55)	 4 (17) 6 (26) 2 (9) 11 (48)	NS
Melanoma Type, n (%) • Superficial Spreading Melanoma • Nodular Melanoma • Acral-Lentiginous Melanoma • Other Types	 1 (2) 13 (30) 18 (42) 11 (26)	 0 6 (30) 9 (45) 5 (25)	 1 (4) 7 (30) 9 (39) 6 (26)	NS
Tumor Thickness (mm) • Mean + SD • Median • Interquartile Range (25-75)	 7.47 ± 4 6.62 3	 7.89 ±4 7 2	 7.1 ± 3 6 3	<0,001
Ulceration, nr (%) • Yes • No • Unknown	 28 (65) 11 (26) 4 (9)	 14 (70) 4 (20) 2 (10)	 14 (61) 7 (30) 2 (9)	NS
Disease Recurrence, n (%) • Yes • No	 22 (51) 21 (49)	 14 (70) 6 (30)	 8 (35) 15 (65)	NS
Follow-up Time (months) • Mean + Stand. deviation • Median • Interquartile Range (25-75)	 40 ± 26 34 45	 33 ± 24 27 33	 44 ± 27 48 51	NS
Melanoma-related death, n (%)	15 (35)	9 (45)	6 (26)	NS

NS – Non significant; SD – Standard deviation.

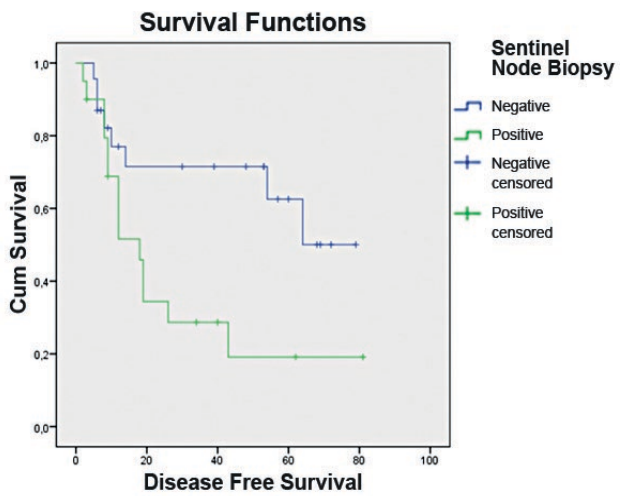

Figure 1 - Disease-free survival in patients with thick melanoma according with sentinel lymph node status.

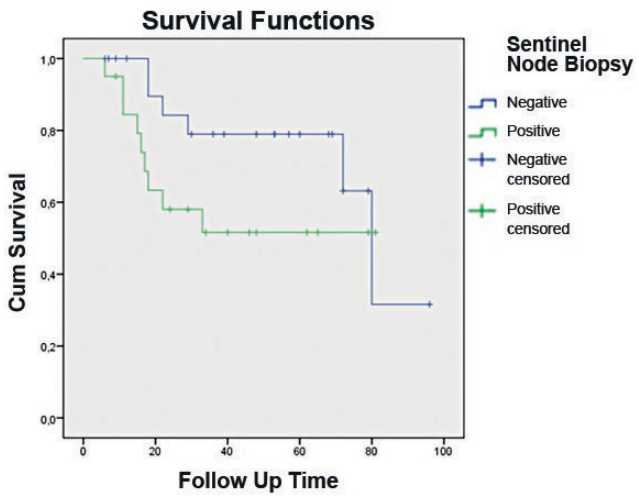

Figure 2 - Overall survival in patients with thick melanoma according with sentinel lymph node status.

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72 months, 95% confidence interval: 57 to 86 months) when compared with group A (average of 50 months, 95% confidence interval: 35 to 65 months). The hazard ratio for death in patients with positive sentinel lymph node was 2.2, with a 95% confidence interval of 0.8-6.1, which was non-significant ($p=0.146$). The 5-year survival rate corresponded to 79% in group B versus 52% in group A ($p=0.132$, log rank test). However, using Wilcoxon's generalized test, we were able to achieve statistical significance ($p=0.041$).

The only other variable which significantly influenced DFS in thick melanoma was melanoma thickness ($p\leq0.001$). This variable showed also significant influence in the risk of melanoma-related death ($p\leq0.001$).

DISCUSSION

According with the results reported by Morton *et al* in the MSTL-1 trial,[2] there was a clear disparity in terms of DFS but not OS between patients with thick melanoma having a positive or negative SNB result. Nevertheless, this study stratified patients in two different groups, matching the tumor's Breslow thickness: patients with intermediate thickness melanoma (1.20 to 3.50mm) and patients with thick melanoma (over 3.5mm). This is conflicting with the AJCC staging, which considers the cutoff of 4.0mm in the definition of thick melanoma. This stratification may create some concerns when comparing different studies. We should point out that several authors[4-12] stated that sentinel lymph node status predicts DFS as well as OS in patients with thick melanoma.

According to our results, lymph node metastases were identified by SNB in 46.5% of the patients, a finding consistent with other studies.[8,16] DFS was longer in patients with negative SNB, when compared with patients with positive SNB but there was no significant difference in terms of OS in the two groups. The impossibility to obtain significant differences in terms of OS can be explained by the morphology of the survival curves ("banana shaped" curves). These curves represent a survival superiority in the SNB negative group in early follow-up period (which may explain the significant Wilcoxon test, that focus on early events). Over time, probably due to the high hematic metastases rate, characteristic of thick melanomas, this survival superiority vanishes, and mortality rates become similar in both groups. Thus, the fact that no survival differences were found in both groups in the later follow-up might explain the non-significance of the Log Rank test, which is focused on later events. Despite the shorter follow-up period, these results are consistent with those obtained by Morton *et al*[1] and Fairbarn *et al*.[3]

Concerning the prognostic value of other variables, only melanoma thickness had a significant influence in DFS and in OS. These results are similar to those obtained by Fairbarn *et al*,[3] in which tumor thickness was the only significant prognostic factor that influences OS in thick melanoma.

In conclusion, despite its inability to predict overall survival, SNB is a recommended procedure in patients with thick melanoma, as it provides an inestimable value in terms of staging and prognosis.

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