

Sentinel Lymph Node in Melanoma – a Study Conducted in the South of Brazil

Sentinelová uzlina u melanomu – studie provedená v jižní Brazílii

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Summary

Background: The presence or absence of lymph node metastases is a very important prognostic factor for survival and recurrence in patients with cutaneous melanoma. Controversies remain among specialists about whether it is advisable or not to perform a sentinel lymph node biopsy in patients with melanoma, although it is currently supported by most standard guidelines. We performed this study to identify which patients are more prone to having a positive lymph node test result in a population with high melanoma rates in the south of Brazil. **Materials and Methods:** We performed the study with 62 consecutive patients who underwent sentinel lymph node biopsies from 2003 to the early months of 2015 in the city of Blumenau – Santa Catarina, Brazil. **Results:** Breslow thickness, ulceration, nodular subtype, and Clark level IV were associated with positive sentinel lymph node group status ($p \leq 0.05$). **Discussion:** Although there is still a controversy over whether or not this procedure should be performed, most guidelines still support its application. To lower the economical and physical impact, however, it is worthwhile to determine which patients are more prone to acquiring positive lymph node at presentation and, perhaps, in the future, indicate surgery for this particular group, who could benefit most from further treatment options.

Key words

melanoma – sentinel lymph node biopsy – prognosis

Souhrn

Východiska: Přítomnost nebo nepřítomnost metastáz lymfatických uzlin je nejdůležitějším prognostickým faktorem pro přežití a recidivy u pacientů s kožním melanomem. Mezi odborníky se vedou spory, zda je vhodné či nikoli provést biopsii sentinelové uzliny u pacientů s melanomem, i když v současné době je tento názor podporován většinou standardních guidelineů. Provedli jsme tuto studii s cílem určit, kteří pacienti jsou náchylnější k pozitivnímu nálezů v populaci s vysokou mírou melanomu na jihu Brazílie. **Materiály a metody:** Provedli jsme studii u 62 po sobě jdoucích pacientů, kteří podstoupili biopsii sentinelové uzliny od roku 2003 do prvních měsíců roku 2015 ve městě Blumenau, Santa Catarina, Brazílie. **Výsledek:** Breslow tloušťka, ulcerace, nodulární podtyp a stadium Clark IV byly spojeny se stavem pozitivní sentinelové uzliny ($p \leq 0,05$). **Diskuze:** I když přetrvávají rozpory, zda tento postup provádět, většina guidelineů tuto indikaci stále podporuje. Abychom však snížili ekonomické i fyzické náklady, je nutné pokusit se vytipovat pacienty náchylnější k výskytu pozitivních lymfatických uzlin a ty pak případně v budoucnosti indikovat k operaci. Tato specifická skupina pacientů by mohla mít z další léčby největší benefit.

Klíčová slova

melanom – biopsie sentinelové uzliny – prognóza

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Introduction

Melanoma rates are increasing faster than any other malignancy in the world according to American and European sources [1,2]. In South America, the figures are not different, rising exponentially during the past years [3].

Even though many advances have been achieved lately in the field of metastatic melanoma [4–7], early diagnosis and appropriate surgical treatment remain critical to the cure.

The presence or absence of lymph node metastases is the most important prognostic factor for survival and recurrence in patients with cutaneous melanoma [8], leading to the development of a minimally invasive technique of lymph node assessment. This technique consists in sampling the first nodes on the most likely path of lymphatic spread of a primary cutaneous melanoma i.e., the sentinel lymph node (SLN) [9]. It has been shown by Morton et al. over 20 years ago that melanoma rarely metastasize to other nodules skipping the SLN [10]. Different surgical techniques may be performed and different tracers can be used, according to the surgeon's expertise [11]. This is a highly effective surgical procedure and maps the SLN in 98% of the times. If a positive SLN (PSLN) is detected, a surgical lymphadenectomy is then performed, according to the drainage area.

Lymphatic mapping has then become standard of care in most melanoma specialized centers in the world [12]. Clear prognostic information is obtained by this procedure, as a positive lymph node detection automatically places the disease in stage III. SLN commitment is strongly related to survival and recurrence rates and is a prognostic tool even in thick melanoma patients [13].

Nevertheless, some experts believe that the cost benefit ratio is not enough to advocate the procedure. A study comprising more than 2,000 patients fell short of displaying any survival benefit in five years [14]. The lack of an available active adjuvant treatment increases criticism of this method that does not lack complications, such as lymphedema, lymphocele and a calculated 96% rate of patients undergoing the SLN biopsy unnecessarily [15,16].

On the other hand, some authors have suggested an improvement in overall disease-free survival rates [17]. Also, it is well known that patients with micrometastasis show better survival rates than those with macroscopic involvement. Nevertheless, randomized clinical trials failed to demonstrate significant survival rates in patients that underwent lymphadenectomy after SLN detection.

In spite of all the controversies regarding the issue, the procedure is still recommended for melanoma whose thickness is more than 1 mm according to European cancer guidelines [18].

The objective of our study is to assess the epidemiologic profile of patients who underwent SLN biopsy in Blumenau – Santa Catarina, Brazil. This is the city with the highest melanoma rates in Brazil, according to a previous study conducted by Naser [3], in a Brazilian region that has melanoma incidences over ten times more frequent than the mean rates of the country [19]. Pathologic characteristics, demographic variables and the specific characteristics of patients with positive nodes are also discussed.

Methods

Data was assembled from 62 consecutive patients who underwent surgery from 2003 to the early months of 2015. The population is largely composed of people with European genetic background, as expected in this Brazilian region [20].

Data has been retrieved retrospectively from patients electronic charts. In case of missing data, we have reviewed directly the anatomical-pathological original report in order to be as accurate as possible.

Results

Data are summarized in Tab. 1 and 2.

In the negative SLN (NSLN) group, there was a predominance of female patients – 59.3%. On the other hand, in the PSLN group, most patients were males (75%). Nevertheless, this difference was not statistically significant (Tab. 1).

The primary lesion was most frequently found on the thorax in both positive and negative groups (Tab. 1).

As for the histopathological subtype, superficial spreading melanoma was more commonly found in the NSLN group (66.7%), while nodular melanoma prevailed in the PSLN group (62.5%) (Tab. 1). When we grouped the subtypes, nodular melanoma was significantly associated with positivity in SLN ($p = 0.00126$) than all the other subtypes together (Tab. 2).

Measurements of Breslow index were tested for normality, and by the Shapiro-Wilk test, the normality of each group was not confirmed. Therefore, a nonparametric test was performed – Mann-Whitney test. In this case, it showed that there are significant differences between the groups and the positive group showed a mean (or median in the case of this test) Breslow thickness significantly higher where DQ is the quartile deviation. While the median for the NSLN group was 1.25 ± 0.74 , the same measure for PSLN group was 3.5 ± 2.45 ; $p = 0.00022$ (Tab. 1, 2).

As for Clark levels, a level IV Clark level was associated with a positivity in SLN status, although the other levels were not ($p = 0.0257$) (Tab. 2). Breslow thickness correlates with metastatic affection of sentinel lymph node, meaning that thicker melanomas correlate with positivity of the exam. Nevertheless, in this study, Clark V was not correlated with positivity in the SLN status. This might be explained by the low number of patients with this measurement in NSLN (only 1) and none in PSLN group.

Although regression was not associated with lymph node status in the present study, ulceration was marginally associated with this feature ($p = 0.05$) (Tab. 1).

Discussion

Even though we would have expected many more patients in this sample, a few setbacks must be stated. First, as explained above, given the fact that the SLN biopsy is not associated with survival benefit, many physicians in the multidisciplinary teams, such as dermatologists, oncologists and cancer surgeons, do not indicate the procedure. Second, as the vast majority of Brazilian patients do not have private health insurance and the

Tab. 1. Demographic characteristics of the patients.

Factors	Sentinel lymph node		p	Factors	Sentinel lymph node		p
	negative (n = 54)	positive (n = 8)			negative (n = 54)	positive (n = 8)	
Gender							
female	32 (59.3%)	2 (25%)	0.0753	superficial spreading, radial growth phase	1 (1.9%)	0 (0%)	
male	22 (40.7%)	6 (75%)		nodular phase	1 (1.9%)	0 (0%)	
Local [1]				lentigo maligno	1 (1.9%)	0 (0%)	
head and neck	10 (19.2%)	1 (12.5%)	invasive, VG phase	1 (1.9%)	0 (0%)		
upper limbs	9 (17.3%)	0 (0%)	nodular with fusocellular component, VG phase	1 (1.9%)	0 (0%)		
lower limbs	11 (21.2%)	2 (25%)	desmoplastic, positive margins	1 (1.9%)	0 (0%)		
thorax	21 (40.4%)	5 (62.5%)	not informed	4 (7.4%)	0 (0%)		
torsum and upper limb	1 (1.9%)	0 (0%)					
Local [2]				Breslow	(median ± ± DP) = (1.71 ± 1.34)	(median ± ± DP) = (5.33 ± 3.34)	0.00022
axilla	12 (22.2%)	1 (12.5%)		(median ± ± DQ) = (1.25 ± 0.74)	(median ± ± DQ) = (3.5 ± 2.45)		
inguinal	10 (18.5%)	3 (37.5%)					
right axilla	4 (7.4%)	2 (25%)					
left axilla	5 (9.3%)	0 (0%)					
cervical	6 (11.1%)	0 (0%)					
bilateral axilla	4 (7.4%)	1 (12.5%)					
right inguinal	3 (5.6%)	0 (0%)					
supraclavicular	2 (3.7%)	0 (0%)					
neck	0 (0%)	1 (12.5%)					
right cervical	1 (1.9%)	0 (0%)					
parotideal	1 (1.9%)	0 (0%)					
cervical bilateral	1 (1.9%)	0 (0%)					
inguinal and axilla	1 (1.9%)	0 (0%)					
cervical and left axilla	1 (1.9%)	0 (0%)					
parotideal and cervical	1 (1.9%)	0 (0%)					
left axilla and left inguinal	1 (1.9%)	0 (0%)					
not informed	1 (1.9%)	0 (0%)					
Type				Clark			
superficial spreading	36 (66.7%)	3 (37.5%)	I	1 (1.9%)	0 (0%)		
nodular	4 (7.4%)	5 (62.5%)	II	12 (22.2%)	0 (0%)		
lentigo	1 (1.9%)	0 (0%)	III	18 (33.3%)	2 (25%)		
NA (shaving)	1 (1.9%)	0 (0%)	IV	15 (27.8%)	6 (75%)		
acral VG	1 (1.9%)	0 (0%)	V	1 (1.9%)	0 (0%)		
lentiginous	1 (1.9%)	0 (0%)	II/III	1 (1.9%)	0 (0%)		
			NA	3 (5.6%)	0 (0%)		
			not informed	3 (5.6%)	0 (0%)		
			Regression				
			no	39 (72.2%)	8 (100%)	0.1640	
			yes	11 (20.4%)	0 (0%)		
			NA	1 (1.9%)	0 (0%)		
			not informed	3 (5.6%)	0 (0%)		
			Ulceration				
			no	37 (68.5%)	3 (37.5%)	0.0500	
			yes	13 (24.1%)	5 (62.5%)		
			NA	1 (1.9%)	0 (0%)		
			not informed	3 (5.6%)	0 (0%)		

P value of Fischer's exact test, in some cases it was not possible to calculate p value, because there were too many frequencies under 5. To compare Breslow thicknesses Mann-Whitney test was performed.

Observation one: From the patients on the negative group, seven didn't present the Breslow thickness measure.

VG – vertical growth, NA – non evaluable, DS – superficial dissemination, DP – standard deviation, DQ – quartile deviation

Tab. 2. Factors associated with lymph node positivity.

Factors	Sentinel lymph node		p
	negative (n = 54)	positive (n = 8)	
Type			
nodular	4	5	0.00126
others	46	3	
Clark			
IV	15	6	0.0257
others	33	2	
Clark			
III or IV	33	8	0.0672
others	15	0	

costs of the operation are not covered by the public health system, not many melanoma patients have access to the procedure, lowering expected figures.

Another interesting feature is that there are many differences in the anatomopathological descriptions of the primary lesions. This reflects the fact that they were analyzed by different pathologists, so a standardization of this data could not be achieved.

One of the most important reasons for choosing not to perform the SLN biopsy in melanoma a few years ago was not only the lack of any spectacular benefit in adjuvant therapy but also the associated toxicities of this treatment [21]; moreover, very poor clinical results achieved by then standard chemotherapy in the advanced setting, i.e., once a patient was classified as high risk or even metastatic, the treating oncologist could do little to change the tumor natural history. However, as targeted therapy [22] and immunotherapy [23,24] more and more grow in the field of melanoma, it is expected that one might be able to change the course of the disease by either selecting more appropriate patients to receive adjuvant treatment, as it is suggested in a subgroup analysis in a paper by Eggermont et al. [25]. Given the post hoc nature of the findings from the aforementioned paper, however, it is not to be taken as ultimate evidence

but as hypothesis generating, deserving to be tested in prospective randomized trials with pre-planned subgroup analysis.

Although controversies remain on whether or not to perform the procedure, most guidelines still support its indication. In order to lower the economical and physical impact, however, it would be a wise choice to try to determine which patients are more prone to present with a PSLN in the procedure and, perhaps, in the future, try to indicate the surgery to this particular group, which could benefit from further treatment options.

In the present paper, Breslow thickness, ulceration, nodular subtype and Clark level IV were associated with PSLN status. Further studies are necessary in order to determine if this particular group of patients will most benefit from the procedure.

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