Melanoma patterns of distant relapse: a study of 108 cases from a South Brazilian center*

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Abstract: Background: The incidence of cutaneous melanoma has increased over the last decades. Recurrences occur most frequently within the first 2-3 years after diagnosis but patients carry a lifelong risk of relapse. Nevertheless, there is no consensus in the literature on what screening tests patients should undergo.
Objectives: To evaluate the most common melanoma metastasis sites among a South Brazilian population from a city with one of the highest melanoma rates, and establish the best screening method for these patients.
Methods: A cross-sectional retrospective study of 108 consecutive melanoma patients followed up at a center from 2009 to 2013. Data were collected on demographic and tumoral characteristics, as well as the site of the first diagnosed metastasis.
Results: Patients were divided into 3 groups for analytical purposes: Non-visceral metastases (48% of patients), visceral metastasis (39%) and brain metastasis (13%). We tried to correlate age, gender, mean Breslow thickness, mitosis and death rates with the aforementioned groups but none showed any statistically significant association.
Conclusion: Melanoma patients must be monitored to detect early relapse and subsequent effective treatment but the best follow-up strategy remains to be established.
Keywords: Melanoma; Nevi and melanomas; Neoplasm metastasis; Skin neoplasms

INTRODUCTION

Cutaneous melanoma is one of the most aggressive forms of skin cancer. Its incidence is increasing faster than any other human malignancy.[1,2]

Until recently, the median survival time for advanced melanoma patients was 6-9 months from the time of diagnosis and only 15% of patients remained alive after 3 years. [3] Although some treatment options were available, such as chemotherapy and cytokines, they entailed poor response rates and no overall survival gain was achieved.[4] However, two landmark studies were recently presented and published concomitantly in the New England Journal of Medicine, demonstrating a significant survival benefit in well-designed Phase III trials.[5,6] However, the only hope of a cure for most patients lies in early diagnosis and subsequent surgery.

Even in patients treated with curative intent, about 20-30% experience relapse.[7] Recurrences are most frequently seen within the first 2-3 years after diagnosis but patients carry a lifelong risk of relapse.[8] Currently, no consensus exists on follow-up frequency and the use of imaging techniques after surgical resection, although many guidelines suggest that lesions under 1mm Breslow thickness carry a low risk

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of distant metastatis. Current follow-up guidelines are based on limited evidence or expert opinion solely, thus leading to great variability in the guidance provided. [9]

The purpose of this study is to evaluate the most common melanoma metastasis sites in a specific population from Blumenau, Santa Catarina, Brazil. According to previous studies, this city has one of the highest melanoma rates in the country.[10] These findings could help to improve screening strategies. This study has been approved by our Review Board (Ethics committee).

METHODS

This study is a cross-sectional, retrospective study based on medical records from 108 consecutive melanoma patients seen at *Hospital Santo Antonio*, Blumenau, from 2009 to 2013. Data were collected on demographic (age, sex) and tumoral (primary location, Breslow thickness, Clark level, regression, mitosis) characteristics, as well as the site of the first diagnosed metastasis. Among these 108 patients, 46 presented with or developed metastatic disease during the period of study. For analytical purposes, patients were divided into three categories: brain, visceral and non-visceral metastasis. Visceral metastasis included the lungs, liver, adrenal glands and gastrointestinal locations. Non-visceral metastasis included the skin, subcutaneous, soft tissues, bones and lymph nodes. Subsequently, we analyzed differences in mean age, sex, Breslow thickness and mitotic rate between these categories.

These data were analyzed with the Epi Info software version 7 (2013). In order to compare the three groups in accordance with the quantitative analysis, we applied the Variant analysis F-test (one factor ANOVA). Furthermore, a Chi-square was performed for the qualitative analysis and it was considered significant whenever $P < 0.05$.

RESULTS

Results are displayed in Table 1.

Among the 46 patients with metastatic disease, non-visceral metastases were the most common, affecting 48% of patients, followed by visceral metastasis (39%) and brain metastasis (13%).

The mean age varied between 59.67 ± 10.44 years for patients with brain metastasis, 57 ± 14.8 years for patients with visceral metastasis and 53.27 ± 16.72 years for patients with non-visceral metastasis. There was no statistically significant difference between the groups' mean ages ($p > 0.05$).

There was no difference between genders among the metastatic patients ($p > 0.05$).

The most common histological subtype among metastatic patients was nodular melanoma (32.6%), followed by superficial spreading melanoma (24%). Polipoid melanoma, a more aggressive form of nodular melanoma, was also found in 4.4% of patients. In situ melanoma was present in one patient as the sole site of disease apart the metastatic lesion (2.2%). Furthermore, in 13% of patients, the disease was already advanced at diagnosis and the primary lesion could not be found.

The trunk was the most commonly affected site (47.5%), followed by the inferior limbs (15.3%), superior limbs (13.1%) and head and neck (8.7%). One patient presented with primary mucosal melanoma (lips), another with primary ungueal melanoma.

The mean Breslow thicknesses for brain, visceral and non-visceral metastatic disease were 3.4 ± 0.72; 4.72 ± 3.58 and 4.39 ± 2.65, respectively. These differences were not statistically significant ($p > 0.05$).

The mean mitotic rate was high among all groups, varying from 9.14 ± 2.91 for non-visceral metastasis to 18.67 ± 6.11 in patients with brain metastasis. Nevertheless, there was no significant difference between the groups ($p > 0.05$).

There were very few deaths and relapses during the follow-up period. Statistical analyses were thus impaired and not performed in that time.

DISCUSSION

Melanoma rates are increasing in many countries. This phenomenon also affects southern Brazil, where melanoma rates have increased exponentially over the past 30 years. [11]

No consensus exists on which follow-up strategy is currently best for resected melanoma. It is well-known that lesions up to 1mm in Breslow carry a lower lifetime risk of distant relapse and lately there has been a tendency not to submit these patients to any invasive tests; however, lesions over 1mm in Breslow thickness entail a higher risk of distant relapse. Until recently, no regimen had produced any meaningful benefit in the adjuvant setting but many associated toxicities were noted. Further, it is only latterly that the cytotoxic regimen has demonstrated any observable survival gain in metastatic patients.[4,12] These factors made close follow-up highly debatable. Nevertheless, the recent launch of new active drugs against metastatic disease, such as ipilimumab and vemurafenib, with proven survival benefits, has shed new light on the subject. Early diagnosis of metastatic disease may help to improve management of these patients.[13-16]

An early study failed to demonstrate any significant clinical benefit of more intense or more frequent follow-up strategies in stage III patients as regards resectability of first relapse or overall survival in multivariate analysis. In fact, according to this study, almost

Table 1: Metastatic melanoma

Characteristic	Metastasis				P
	Brain ± ST (I) (n = 6)	Visceral ± ST (n = 18)	Non-visceral ±ST (n = 22)	Total ±ST (n = 46)	
Age (Mean ± ST)	(59,67 ± 10.44)	(57 ± 14.8)	(53.27 ± 16.72)		0.58794(II)
Gender					
Female	2 (33.3%)	9 (50%)	10 (45.5%)	21 (45.7%)	0.7771 (III)
Male	4 (66.7%)	9 (50%)	12 (54.5%)	25 (54.3%)	
Histological subtype					
Superficial Spreading	2 (33.3%)	5 (27.8%)	4 (18.1%)	11 (24%)	-
In situ	-	1 (5.6%)	-	1 (2.2%)	
Nodular	-	5 (27.8%)	10 (45.5%)	15 (32.6%)	
Polipoid	-	-	2 (9%)	2 (4.4%)	
Metastatic	1 (16.7%)	2 (11.1%)	3 (13.6%)	6 (13%)	
NA	3 (50%)	5 (27.8%)	2 (9.1%)	10 (21.7%)	
Localization of primary lesion					
Trunk	2 (33.3%)	6 (33.3%)	16 (54.5%)	20 (47.5%)	-
Inferior Limbs	-	2 (11.1%)	5 (22.6%)	7 (15.3%)	
Superior limbs	1 (16.7%)	1 (5.6%)	3 (13.6%)	6 (13.1%)	
Head and neck	-	2 (11.2%)	2 (9%)	4 (8.7%)	
Lips	-	1 (5.6%)	-	1 (2.2%)	
Ungueal	-	1 (5.6%)	-	1 (2.2%)	
NA	2 (33.3%)	5 (27.8%)	-	7 (15.2%)	
Clark level					
I	-	1 (5.9%)	-	1 (2.4%)	-
II	1 (16.7%)	-	-	1 (2.4%)	
III	1 (16.7%)	4 (23.5%)	4 (21.1%)	9 (21.4%)	
IV	1 (16.7%)	4 (23.5%)	7 (36.8%)	12 (28.6%)	
NA	3 (50%)	8 (47.1%)	8 (42.1%)	19 (45.2%)	
Breslow Thickness (Mean ± ST)	(3.4 ± 0.72)	(4.72 ± 3.58)	(4.39 ± 2.65)		0.79297(II)
Regression					
Yes	-	1 (5.6%)	1 (4.5%)	2 (4.3%)	
No	3 (50%)	8 (44.4%)	11 (50%)	22 (47.8%)	
NA	3 (50%)	9 (50%)	10 (45.5%)	22 (47.8%)	
Relapsing					
Yes	-	3 (16.7%)	3 (13.6%)	6 (13%)	
No	3 (50%)	8 (44.4%)	7 (31.8%)	18 (39.1%)	
NA	3 (50%)	7 (38.9%)	12 (54.5%)	22 (47.8%)	
Mitosis per 10 (Mean ± ST)	(18.67 ± 6.11)	(11 ± 6.99)	(9.14 ± 2.91)		0.07327(II)
Death					
Yes	1 (16.7%)	4 (22.2%)	5 (22.7%)	10 (21.7%)	
No	4 (66.7%)	11 (61.1%)	15 (68.2%)	30 (65.2%)	
NA	1 (16.7%)	3 (16.7%)	2 (9.1%)	6 (13%)	

I – ST: Standard Deviation.
II – P: P-value for the Analysis of Variance (ANOVA) F-test.
III – P: P-value for the Chi-square test of independence.

half of the systemic relapses and as much as 62% of local and in transit recurrences were discovered by patients and relatives, showing how intricate this issue is.[17]

We studied 108 melanoma patients who were seen at a single center, of which 46 (approximately 43%) presented with metastasis. For analytical purposes, patients were divided into three groups: non visceral metastasis, visceral metastasis and brain metastasis. We tried to correlate age, gender, mean Breslow thickness, mitosis and death rates with the aforementioned groups but none showed any statistically significant association. The small number of patients with metastatic disease may have contributed to these findings.

CONCLUSION

In our study, non-visceral metastasis prevailed, followed by visceral and brain metastasis. We could not find any correlation between the variables studied and the metastasis sites. More studies, perhaps with a higher number of patients, are necessary in order to show which screening strategy, if any, is best for melanoma patients.❑

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