Prognostic variables in patients with thick melanomas. Analysis of 362 cases

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Abstract

Background: Melanoma epidemiological and prognostic studies are based on Caucasian populations, in whom the predominant subtype is superficially-spreading melanoma and in whom thin melanomas (Breslow < 3 mm) predominate. Mexican patients show a predominance of thick melanomas (Breslow $\geq$ 3 mm), and the acral subtype is the most common. There are no publications on prognostic factors in thick melanomas. We hypothesize that we will identify factors that determine the prognosis in this group of patients. **Objective:** To identify clinical-pathological factors associated with the prognosis of patients with thick melanomas in the Mexican population. **Material and methods:** Data on melanomas with Breslow > 3 mm were collected from 2010 to 2015. The prognostic influence of various clinical-pathological factors was analyzed. **Results:** The most common subtypes were acral melanoma in 271 patients (74.9 %) and nodular melanoma in 49 (13.5 %). Median Breslow thickness was 7 mm. 56.6 % of the patients had lymph node metastases (clinical stage [CS] III), 269 (74.3 %) had ulceration, and surgical margins were positive in 15 (4.1 %). Elevated neutrophil: lymphocyte ratio ($\geq$ 2) was found in 188 (51.9 %). The variables associated with lower overall survival were CS ($p < 0.001$), Breslow thickness ($p = 0.044$), ulceration ($p = 0.004$), mitotic activity ($p < 0.001$), < 2-cm margin ($p < 0.001$) and an increased neutrophil: lymphocyte ratio ($p = 0.037$). In the multivariate analysis, the factors associated with overall survival were CS, mitotic activity, and surgical margin. **Conclusions:** In patients with thick melanomas, overall survival is influenced by mitotic activity, a positive margin, and clinical stage.

KEY WORDS: Melanoma. Breslow. Acral melanoma. Mitotic index. Prognosis.

Variables pronósticas de pacientes con melanomas gruesos. Análisis de 362 casos

Resumen

Antecedentes: Los estudios sobre factores pronóstico de melanoma están basados en poblaciones caucásicas, con predominio de melanomas delgados (Breslow < 3 mm). Los pacientes mexicanos muestran predominio de melanomas gruesos (Breslow $\geq$ 3 mm). **Objetivo:** Identificar factores asociados al pronóstico de pacientes con melanomas gruesos. **Material y métodos:** Se analizó la influencia pronóstica de factores clinicopatológicos en 362 melanomas gruesos. **Resultados:** La mediana de Breslow fue de 7 mm, 271 (74.9 %) pacientes tuvieron melanoma acral y 49 (13.5 %) melanoma nodular. El 56.6 % de los pacientes se encontró en etapa clínica [EC] III), 269 (74.3 %) tenía ulceración y 15 (4.1 %) márgenes positivos. Las variables asociadas con menor supervivencia global [SG] fueron la EC ($p < 0.001$), Breslow ($p = 0.044$), ulceración ($p = 0.004$), mitosis ($p < 0.001$) y margen < 2 cm ($p < 0.001$). En el análisis multivariante los facto-

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res que influyen en SG fueron la EC, mitosis y el margen quirúrgico. **Conclusiones:** En pacientes con melanomas gruesos la SG es influida por un margen positivo, mitosis y EC.

PALABRAS CLAVE: Melanoma. Breslow. Melanoma acral. Índice mitótico. Pronóstico.

Introduction

Cutaneous melanoma is a potentially aggressive malignancy the incidence of which continues to increase. In advanced cases, therapeutic options are limited, and there is a continuous search for novel prognostic factors and possible treatment goals. American Joint Committee on Cancer current TNM (Tumor, Node, Metastasis) staging system is based on multivariate survival analyses of nearly 39,000 melanoma patients.¹ According to these analyses, the most powerful prognostic indicators known in patients with localized melanoma are tumor thickness (Breslow thickness), ulceration, and mitotic count, in that order. However, known studies on these melanoma prognostic factors, as well as epidemiology and clinicopathological characteristics are based on populations of Caucasian origin, in whom the most common melanomas are strongly associated with sun exposure and are predominantly of the superficial dissemination type, in addition to showing a predominance of thin melanomas (Breslow < 3 mm).

Mexican melanoma patients have some distinctive clinicopathological differences, such as a predominance of the acral lentiginous subtype, as well as presenting with tumors with higher Breslow thickness.² Given that most patients in our population exhibit these unique clinical and pathological characteristics, and given that they are diagnosed at more advanced pathological stages, it is necessary for factors that allow better discriminating these patients' prognosis to be identified. Although the majority will be diagnosed at advanced pathological stages (pT3 and pT4) and intrinsically could have a poor prognosis, we believe that, even in this group of patients, overall survival may be influenced by pathological factors that allow identifying those patients with a poorer prognosis and thus being able to establish treatment strategies aimed at improving their life expectancy. In the literature, only two studies have explored pathological variables associated with prognosis in patients with thick melanomas;^{3,4} however, these are works aimed at finding specific markers (such as tumor-infiltrating lymphocytes) and in Caucasian populations. It is therefore necessary to identify

these factors in order to improve patient care, especially in Mexican patients, and this information could be extrapolated to Latin American populations, who share similar genetic backgrounds. The purpose of this work is to identify, in thick melanomas (Breslow > 3 mm), clinicopathological factors associated with patient prognosis. Our working hypothesis is that patients with thick melanomas have additional prognostic factors that allow stratifying them in risk groups.

Material and methods

Data were retrospectively collected from the database of the Department of Pathological Anatomy of our institution, a national reference center. A total of 1,209 patients with histologically-confirmed melanoma diagnosis between 2010 and 2015 who had Breslow thickness > 3 mm were identified. All patients received full care and follow-up at our institution. Patients with previous treatments, recurrent disease, mucosal melanoma and melanoma in situ, as well as patients without follow-up, were excluded. The remaining 362 patients were analyzed in this study.

Demographic, preoperative, pathological and outcome variables were recorded. Clinical staging was performed by computed tomography, physical examination, and serum lactate dehydrogenase values. All patients were examined every three months for the first two years, and every six months thereafter. The outcome variables were divided as follows: surgery was considered adequate if the melanoma had been removed with appropriate surgical margins (which we defined as adequate if Breslow thickness > 2 cm).³ The primary outcome of our study was overall survival.

Data were analyzed using the SPSS 24.0 package for Windows (SPSS Inc., Chicago, IL, USA). The relationship between categorical variables was analyzed using the chi-square test, and for numerical variables, Mann-Whitney's U-test was used. The estimation of survival cumulative distribution in separate groups was calculated according to the Kaplan-Meier method, with the time of surgery as entry date. Differences in survival observed between the groups were tested using log-rank tests. Multivariate analysis was carried out using the Cox proportional hazards model with

forward progressive selection. All p-values were two-tailed, with hazard ratios (HR) and their corresponding 95 % confidence intervals (CI).

Results

Data from 1,219 patients are summarized in table 1; 713 patients (58.5 %) were females, and median age was 57 years (range, 15-92). Most common clinicopathological subtypes were acral lentiginous melanoma in 271 patients (74.9 %) and nodular melanoma in 49 (13.5 %). Median Breslow thickness was 7 mm. The most common Breslow group was that of lesions between 4 and 7 mm. All patients had sentinel lymph nodes and, out of them, 56.6 % had metastases. Ulceration was present in 269 patients (74.3 %), and surgical margins were inadequate in 15 (4.1%). The most common clinical stage was stage III. Elevated neutrophil: lymphocyte ratio (≥ 2) was found in 188 patients (51.9 %).

In the univariate survival analysis (Table 2), the variables that were identified to be statistically associated with lower overall survival were clinical stage ($p < 0.001$), positive sentinel lymph node ($p < 0.001$), Breslow thickness ($p = 0.044$), ulceration ($p = 0.004$), presence of mitotic activity ($p < 0.001$), inadequate margin ($p < 0.001$) and increased neutrophil: lymphocyte ratio ($p = 0.037$). In the multivariate analysis (Table 3), the factors that proved to be independently-associated with overall survival were clinical stage, mitotic activity, and surgical margin.

Discussion

In this study of 362 patients with thick melanomas, we identified that the most common subtype was acral melanoma and that the factors that were independently associated with overall survival were clinical stage, mitotic activity, and surgical margin. The univariate analysis showed that Breslow depth continues to be an important predictor of survival, with survival decreasing as Breslow thickness increases. In addition, an increased neutrophil: lymphocyte ratio was identified to decrease overall survival.

To the best of our knowledge, studies of prognostic markers in thick cutaneous melanoma are quite limited.^{4,5} In cutaneous melanoma evaluation, microscopic characteristics are crucial, not only for diagnosis but also for prognosis, including tumor thickness, ulceration and mitotic count, according to the latest TNM classification. Despite current knowledge on prognostic indicators in cutaneous melanoma, patient

Table 1. Clinical and pathological variables of 362 patients with melanoma

Variable	Values
Age (years), median (range)	58 (18-73)
Age groups, n (%)	
< 40 years	40 (11)
≥ 40 years	322 (89)
Gender, n (%)	
Females	207 (57.2)
Males	155 (42.8)
Clinical stage, n (%)	
II	157 (43.4)
III	205 (56.6)
Subtypes, n (%)	
Acral	271 (74.9)
Nodular	49 (13.5)
Superficial dissemination	42 (11.6)
Breslow thickness, mm, median (range)	7 (3-60)
Thickness groups (Breslow), n (%)	
3-4 mm	93 (25.7)
4.1-7 mm	119 (32.9)
7.1-10 mm	62 (17.1)
> 10 mm	88 (24.3)
Ulceration, n (%)	
No	93 (25.7)
Yes	269 (74.3)
Mitosis, median (range)	0 (0-60)
Mitosis, n (%)	
≤ 1 mitosis	225 (62.2)
> 1 mitosis	137 (37.8)
Surgical margin, n (%)	
Adequate	347 (95.9)
Inadequate (< 2 cm)	15 (4.1)
Longest diameter, mm, median (range)	26 (1-190)
Neutrophil:lymphocyte ratio, median (range)	2 (0.58-17)
Neutrophil:lymphocyte ratio, n (%)	
< 2	174 (48.1)
≥ 2	188 (51.9)
Average follow-up, median (standard deviation)	41.12 (39)
Outcome, n (%)	
Alive	264 (72.9)
Dead	98 (27.1)
5-year overall survival (%)	66.9 %

outcomes can be unpredictable. Distant metastases can appear in cases with thick primary tumors with no other known unfavorable prognostic characteristics; in contrast, no recurrence or death can be observed in cases of thick primary tumors at long-term follow-up.

Table 2. Clinical variables associated with survival in 362 melanoma patients

Variable	Mean survival (months)	5-year overall survival	p-value
Gender			
Males	110.5	61.2	0.523
Females	93.7	70.2	
Age			
< 40 years	126.4	74.9	0.144
≥ 40 years	104.4	65.8	
Clinical stage			
IIA	106.857	85.7	< 0.001
IIB	139.230	85.7	
IIC	103.028	69.6	
IIIA	89.919	78.4	
IIIB	110.367	77.8	
IIIC	75.370	67.2	
Subtype			
Acral	103.8	63.4	0.093
Nodular	128.5	84.4	
Superficial dissemination	107.2	71.4	
Sentinel lymph node			
Negative	127	78	< 0.001
Positive	89.4	57.1	
Breslow groups			
3-4 mm	122.818	76.9	0.044
4.1-7 mm	107.898	70.2	
7.1-10 mm	82.720	54.6	
> 10 mm	91.613	56.7	
Ulceration			
No	NC	82.7	0.004
Yes	NC	61.9	
Mitosis			
No	121.3	77.3	< 0.001
Yes	90.0	50.8	
Margin			
Adequate	110.6	68.9	< 0.001
Inadequate (< 2 cm)	27.1	12.9	
Neutrophil:lymphocyte ratio			
< 2	116.1	72.2	0.037
≥ 2	98.5	61.6	

NC = not calculated.

In this context, there is a demand for better prognostic accuracy and more appropriate treatment and follow-up. In our population, as shown by our results, patients generally present with large tumors at advanced stages, where prognosis would appear to be bleak. In existing studies, known prognostic factors are associated with poorer survival.⁴ However, in our patients, ulceration was not associated with poorer prognosis.

Table 3. Multivariate analysis of factors associated with survival in 362 cases of melanoma

Variable	Hazard ratio	95 % confidence interval	p-value
Mitosis (≥ 1 vs. < 1)	2.491	1.644-3.755	< 0.001
Stage (stage II vs. III)	1.349	1.169-1.556	< 0.001
Neutrophil:lymphocyte ratio (< 2 vs. ≥ 2)	1.222	0.809-1.846	0.340
Breslow groups (4 groups; reference: 3-mm Breslow)	1.131	0.941-1.361	0.190
Ulceration (absent vs. present)	0.685	0.379-1.237	0.210
Margin (adequate vs. inadequate [< 2 cm])	0.315	0.154-0.646	0.002

Interestingly, in the univariate analysis we found that an increased neutrophil: lymphocyte ratio was associated with a poorer prognosis and, although it did not maintain this association in the multivariate analysis, the fact of being a marker associated with inflammation could provide some prognostic information in our patients, perhaps as an indirect marker of the inflammatory response associated with melanoma.^{6,7}

Surgical resection with sufficient margin is a component of surgical standard of care for primary cutaneous melanomas susceptible to surgery. Determining the extent of excision has been a considerable focus of analysis since the earliest melanoma descriptions. In 2011, the Swedish Melanoma Study Group and the Danish Melanoma Group published the results of their Scandinavian collaborative trial, which randomized 936 patients with cutaneous melanoma > 2 mm Breslow thickness to undergo resection with surgical margins of 2 or 4 cm. The authors concluded that resection margins of 2 cm were sufficient and safe for patients with > 2 mm thick melanomas.⁸ Our findings confirm this, since even with very large Breslow thicknesses (half of our population has Breslow thickness > 7 mm), a negative margin is independently associated with better overall survival (HR = 0.315, 95 % CI: 0.154-0.646, p = 0.002).

The limitations of our study are those inherent to its retrospective nature and to the fact that it is not a population-based study, but rather a study based on a referral center. In this context, there is generally a presentation bias (more advanced disease or recurrence); however, the results were determined only by the evaluation of those patients who were initially treated at the center.

In conclusion, we identified that, in patients with stage II and III melanomas with Breslow thickness > 3 mm, survival is influenced by mitotic activity, positive margin, and clinical stage (presence of lymph node metastases). Our univariate analysis suggests a role for the neutrophil: lymphocyte ratio in the prognosis of patients with thick melanomas, a role that should be further investigated. A negative margin in this type of patients is associated with a significant increase in overall survival.

Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

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