

## Significance of Primary Melanoma Regression on Local Infiltrate and Outcome

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**ABSTRACT Introduction:** The characteristics and the prognostic value of regression in primary melanomas are controversial.

**Objectives:** To further characterize “hot” and “cold” tumor’s stromas and to investigate the association between dermoscopy, pathology, and the prognostic implications of regression.

**Methods:** A 14-year-collection-based retrospective analysis was carried out on 40 patients with confirmed regressive melanomas.

**Results:** The extent of regression in dermoscopy was associated with the stage of the regression ( $P = 0.05$ ) and with the MelanA patterns in histology ( $P = 0.02$ ). Blue-gray and gray-brown color of the peppering ( $P = 0.01$ ), and the eccentric, multifocal character of the dermoscopic regression ( $P = 0.05$ ) were associated with “hot” stromas (CD8+, Granzym B+). Focal histologic regression (regressing melanomas) was associated with a good outcome ( $P < 0.001$ ), while a complete regression (regressed melanomas) was associated with melanoma-related death ( $P < 0.001$ ). “Hot” stromas (CD8+ were

significantly associated with survival at 10 years ( $P = 0.044$ ), while “hot” stromas (Granzyme B<sup>+</sup>) were associated with the locoregional extension ( $P = 0.016$ ), and the initial distant metastasis ( $P = 0.016$ ).

**Conclusions:** Dermoscopic features of regression in primary melanomas were associated with the stage of regression, its extent, and the “hot” or “cold” nature of the tumor stroma, with prognostic implications.

## Introduction

Histopathological features of regression, encountered in 10%-35% of primary cutaneous melanomas [1,2], classically appear on dermoscopy as white (or blue-white) scar-like areas (WSA) [3,4], variably admixed with blue-gray granularity (BGG) or “peppering”. Both WSA and BGG are unspecific features of regression, and are often regularly distributed on more than 50% of the surface benign lesions, while they are smaller and irregularly distributed in melanomas [3–6]. Recently, reticulated regression has been described in *in situ* or slow-growing invasive melanomas as a new dermoscopic feature of regression, and appears as a coarse blue-gray net, with thick gray-blue lines with large pink-colored holes [2,7]. Although classic histopathological features of primary melanoma regression have been described over the past decades, their clinical implications and prognostic value remain unclear and controversial [2,8–16].

New interest in the evaluation of the nature of the host response, and the subsequent regression features in malignant tumors, especially melanomas, came after the development of immunotherapy. Tumor stromas have been sub-classified into “hotly” and “coldly” infiltrated by immune cells [17], with the pathogenic hypothesis that “hot” tumors may respond better to immunotherapy, which stimulates the already present immune cells, whereas “cold” tumors should (or could) be initially stimulated by specific neo-adjuvant agents before the initiation of immunotherapy.

## Objectives

The primary aim of the present study was to further characterize “hot” and “cold” stromas in regressive melanomas based on dermoscopic and histopathologic criteria, and to preoperatively analyze dermoscopic features at different stages of regression. The secondary aim was to investigate the association between dermoscopy, pathology, and the prognostic implications of regression, with the ultimate goal of helping in the pre-therapeutic definition of “hot” tumors, which may benefit from postoperative adjuvant immunotherapy, and “cold” tumors, which could be included in potential neo-adjuvant clinical trials in priority before the excision of the primary tumor.

## Methods

The present study was approved by the Hospices Civils de Lyon ethics committee, project N°20-15 (2019). It is a collection-based retrospective study of a consecutive series of patients having cutaneous melanomas with both confirmed dermoscopic and histopathological changes of regression, over a period of 14 years (2006-2019), for whom a complete set of clinical dermoscopic photographs was available. All patients gave their written informed consent for the use of their clinical records, clinical and dermoscopic images, pathological specimen at the time of the primary excision of the tumor, and subsequent inclusion in the Centre de Ressources Biologiques (Institutional biobank) of the Hospices Civils de Lyon for research purposes.

This study has not been registered in a public trial registry because it does not prospectively assigns human subjects to intervention or comparison groups to evaluate the cause and effect relationship between a medical intervention and a health outcome. This study does not fall into the scope of the French Jardé law, of 16<sup>th</sup> November 2016 because it uses a preexisting cohort of patients and preexisting clinical records.

The exclusion criteria were the absence or the poor quality of the dermoscopic images and the non-confirmation of the presence of histopathological features of regression upon reevaluation of the original histopathological slides. Clinical history, clinical and dermoscopic images, histopathological reports, standard immunochemistry data (MelanA), and, when applicable, genotyping of BRAF mutations were directly collected from patient electronic records.

Dermoscopic images were analyzed by 3 independent experienced dermoscopists. Regression-associated features were recorded as well (WSA and BGG), and were specifically evaluated for their presence, their disposition (central, eccentric, unifocal, multifocal), and their surface extension (on less than 25%, between 25% and 50%, or on more than 50% of the lesion). The presence or absence of reticular regression was also recorded.

Histopathological and MelanA slides were evaluated independently by 4 dermatopathologists with no knowledge of the original histopathology report; the regression was sub-classified into 3 stages as reported in the literature [2]. Stage 1, or “inflammatory phase”, is characterized by a still recognizable tumor, with dense lymphocytic infiltrates admixed with nests of malignant melanocytes. Stage 2 or “regressing phase” is characterized by still recognizable

melanoma cells, with tumor reduction or disappearance in the overlying epidermis, while in the papillary dermis the malignant tissue is replaced by lymphocytes and fibrosis. An increased vascularity is also observed because of angiogenesis, and heavily pigmented macrophages can be observed. Stage 3 or “regressed melanoma” is characterized by the complete disappearance of the tumor that is replaced by a dense fibrotic tissue with vessels and melanophages in varying numbers, with few or no lymphocytes underneath a thinned epidermis. The extent of regression was also examined, and classified as focal if it involved a portion of the dermal component of the tumor, partial if it involved the entire dermal component, and complete if it involved the entire tumor [2].

Additional immunophenotypic studies (CD8, Langerin, Granzyme B, and PDL-1) and an Orcein stain were performed on formalin-fixed paraffin-embedded original pathological specimens. The proportion (%) of cells positive for CD8, Granzyme B, Langerin, and PDL-1 was evaluated in the area of the regression and in the tumor stroma, and categorized as covering < 5%, ≥5 and <10%, ≥10 and <25%, ≥25 and < 50%, ≥50 and >75%, or >75% of the whole inflammatory infiltrate. After discussion between the authors and a review of all the slides, tumors were considered as “hot” if their stroma was CD8+ on more than 25%, Granzyme B+ on more than 10% of the inflammatory infiltrate, PDL-1+ on more than 5%, or Langerin+ on more than 5%. Otherwise, they were considered as “cold”.

Following our clinical practice, BRAF mutation was tested only for primary tumors thicker than 1.00 mm.

### Statistical Analysis

Analyses were performed using the Statistical Package for the Social Studies software version 20. Quantitative variables were expressed as mean (± standard deviation, SD) and qualitative variables as count (percentage). Progression-free survival was defined as the number of months from the diagnosis to the identification of locally recurrent or metastatic disease in the lymph nodes or distant organs. Death was considered as melanoma-related in patients for whom the melanoma had progressed. A univariate analysis was performed to investigate the association between histological regression characteristics, inflammatory infiltrate status, and prognosis, using a chi-squared <sup>2</sup> test. A P value ≤0.05 was considered as significant.

## Results

Among the 98 patients from the collection database, only 40 were included (30 were excluded because of incomplete dermoscopy record, 28 were excluded because of the absence of clear-cut histopathological features of regression). The mean (SD) age of included patients was 63.6 (15.7) years, and 82.5% of them presented with melanomas in the local stage (I and II of the AJCC 2018 Melanoma staging; Table 1).

Within the regression area of the tumor, WSA were observed in 55% of lesions, blue-WSA in 45%, BGG in 97.5% (Figures 1-3). Reticular regression was observed in 75% of cases, and was associated with the polychromatic character of the lesion (P = 0.047) and the stage 2 of the regression in histology (P = 0.049).

**Table 1. Descriptive Analysis of Patients Included in the Present Study**

Total population n = 40	N (%)
Mean age, years (SD)	63.6 (15,7)
Sex, male	24 (60)
Lymph node metastasis	6 (15)
Metastatic melanoma	6 (15)
<b>Dermoscopic regression variables</b>	
<b>Blue-white areas</b>	
Blue-white	18 (45)
White	22 (55)
<b>Blue –white areas characteristics</b>	
Central	2 (5)
Eccentric	37 (92,5)
<b>Coverage of the lesion</b>	
Less than 25%	14 (35)
25-50%	10 (25)
More than 50%	16 (40)
Peppering	39 (97,5)
Focal	37 (92,5)
Total	2 (5)

Table 1 continues

**Table 1. Descriptive Analysis of Patients Included in the Present Study (continued)**

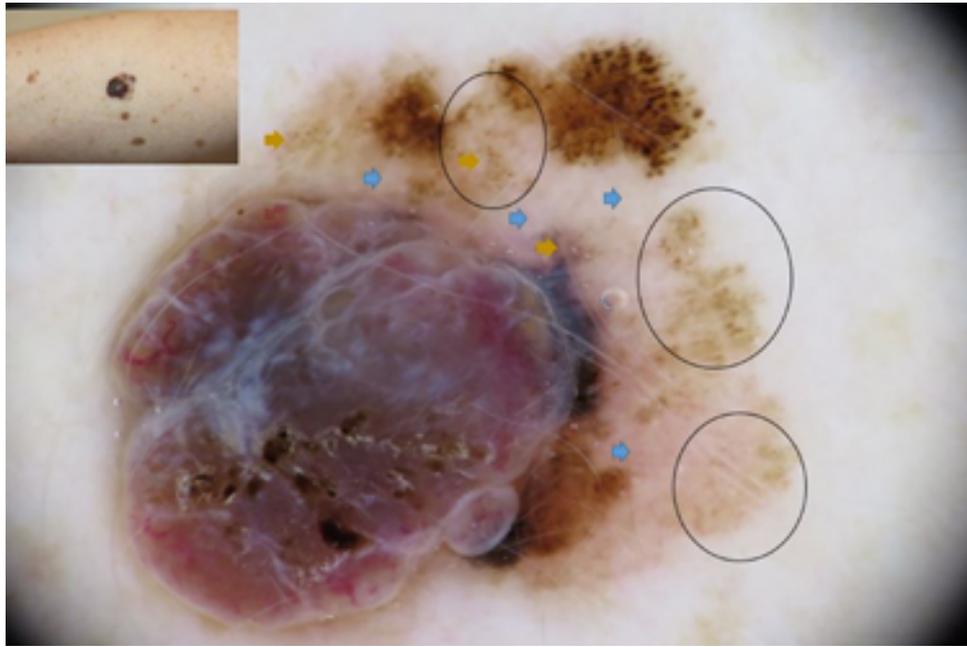
Total population n = 40	N (%)
Color of the lesion	
Brown-gray	13 (32.5)
Grey-blue	14 (35)
Grey-blue and brown-gray	12 (30)
Reticular regression in less palpable area	30 (75)
Grey-blue lines	20 (50)
Brown-gray lines	10 (25)
Vascularization	
Polymorphic vessels	25 (62.5)
Linear irregular	2 (5)
<b>Histopathology and immunochemistry</b>	
Melanoma histological subtype	
SSM	25 (62.5)
Regressive unclassifiable	7 (17.5)
LM	6 (15)
ALM	2 (5)
Stage of the regression	
1	3 (7.5)
2	24 (60)
3	13 (32.5)
Extent of regression	
Complete	1 (2.5)
Focal	27 (67.5)
Partial	12 (30)
MelanA	
Normal (stage 1 of regression)	1 (2.5)
Reduced in the dermis, reduced in the epidermis	26 (65)
Absent in the dermis, reduced in the epidermis	13 (32.5)
Orcein in the regression area	
Repressed, condensed, horizontal	35 (87.5)
Repressed, not condensed, horizontal	5 (12.5)
<b>Immunochemistry (Hot stromas)</b>	
CD8+	37 (92.5)
Granzyme B+	22 (55)
Langerin +	21 (52.5)
PDL1+	14 (35)
Mutation BRAF V600 E	5 (12.5)
Melanoma staging AJCC 2018	
I and II (local)	33 (82.5)
III (loco-regional)	2 (5)
IV (Metastatic)	5 (12.5)
Evolution after 2 years of treatment	
Death	2 (5)
Stable without clinical or radiologic evolution	6 (15)
Complete remission after more than 2 years	30 (75)

SSM=Superficial spreading melanoma

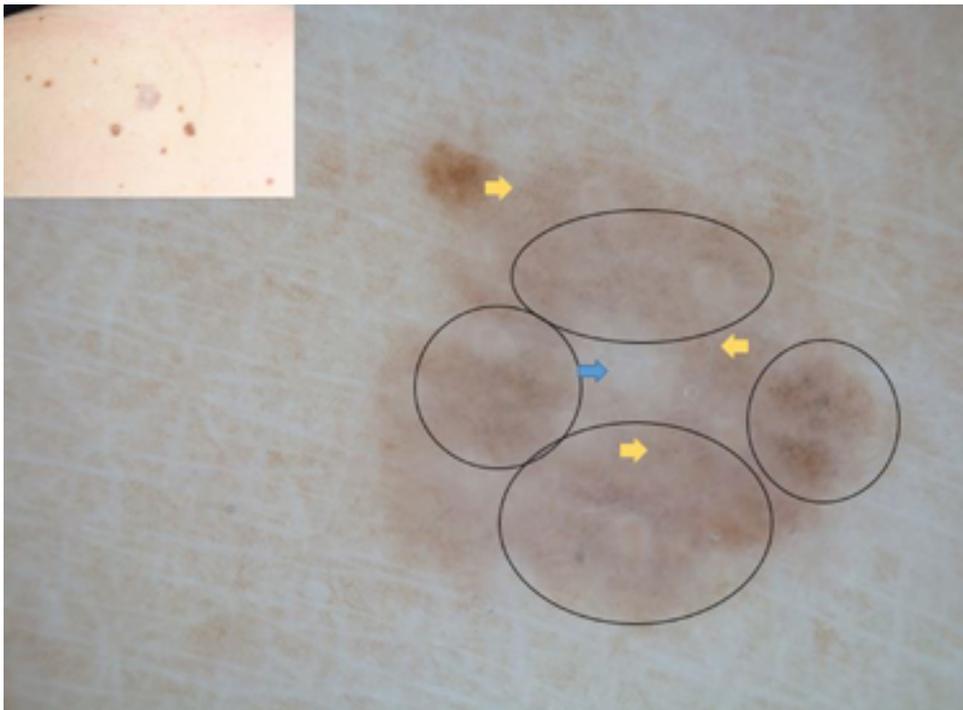
LM: Lentigo maligna

ALM=Acral lentiginous melanoma

AJCC =American Joint Committee on Cancer



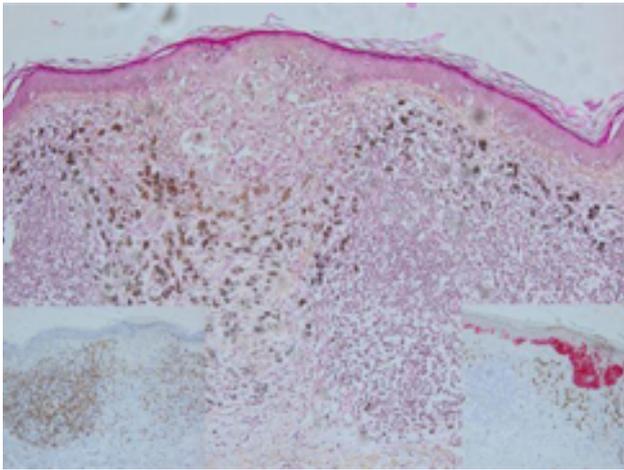
**Figure 1.** Clinical and dermoscopic images of a regressing melanoma. Multicomponent pattern with multiple peripheral eccentric white scar-like areas (blue arrow) covering less than 50% of the lesion, with reticular regression (black circle). Focal peppering (brown arrow).



**Figure 2.** Clinical and dermoscopic images of a regressed melanoma. White-blue scar-like areas (blue arrow), and extensive peppering (brown arrow) covering more than 75% of the lesion, with reticular regression (black circles).

Peppering was associated with thin melanomas (< 1mm,  $P = 0.012$ ) and positive BRAF mutations ( $P = 0.028$ ). WSA were associated with follicular migration in histology ( $P = 0.014$ ). The extent of regression in dermoscopy was associated with the stage of regression ( $P = 0.05$ ) and to MelanA patterns in histology ( $P = 0.023$ ). Chaotic lesions were associated

with stage 1 and 2 of regression ( $P = 0.035$ ), irregular thick reticular lines ( $P = 0.049$ ) and blue white veil ( $P = 0.014$ ) were associated with stage 2 of regression. Annular granular pattern was associated with stage 2 and 3 of regression ( $P = 0.009$ ). Skin fissures exaggeration in dermoscopy ( $P < 0.001$ ), the presence of eccentric globules ( $P = 0.027$ ), blue-white area



**Figure 3.** Hot stroma in a regressive melanoma. Stage 2 of histologic regression with the corresponding melanA pattern as reduced in the dermis and reduced in the epidermis, and CD8<sup>+</sup> immunochemistry on more than 50% of the inflammatory infiltrate (magnification x10).

veil ( $P = 0.038$ ), and perifollicular circles ( $P = 0.045$ ) were associated with focal regression in histology. The loss of normal elastic fiber architecture in Orcein stain was associated with the WSA with peppering ( $P = 0.001$ ; Table 2).

On the other hand, red milky areas ( $P = 0.033$ ), irregular thick reticular lines ( $P = 0.044$ ), polygons ( $P = 0.044$ ), and blue-gray and gray-brown color of the peppering granules ( $P = 0.011$ ) were associated with “hot” Granzyme B<sup>+</sup> tumors, while “hot” CD8<sup>+</sup> stromas were associated with skin fissures exaggeration ( $P = 0.043$ ) and with the eccentric and multifocal character of regression in dermoscopy ( $P = 0.05$ ). “Cold” PDL1<sup>+</sup> stromas were associated with inversed network in dermoscopy ( $P = 0.05$ ) and eccentric globules ( $P = 0.044$ ), while “cold” Langerin<sup>+</sup> stromas were associated with the multicomponent pattern ( $P = 0.032$ ), peripheral structureless area ( $P = 0.026$ ), and the rhomboidal pattern ( $P = 0.049$ ) (Table 2).

**Table 2. Univariate Analysis**

Variables		P value
Immunodepression	Stage 3 of regression	0,000
Elevated lesion (plaque ou nodular)	Hot stroma Granzyme B+	0,038
Lesion color (polychromatic or achromic)	BRAF mutation	0,035
	Regression extent	0,041
	Reticular regression in an area les palpable than the other areas	0,014
Loco-regional metastasis	Dermoscopic regression (Blue-white areas (scar like))	0,041
	Focal regression in histology	0,004
	Hot stroma Granzym B +	0,016
Peppering	Focal regression (focal peppering)	0,000
	Low risk of recurrence after complete remission after surgery	0,029
Extent of regression in dermoscopy	MelanA expression	0,023
	Regression stages in histology	0,05
Eccentric character of regression in dermoscopy	Stage 2 and 3	0,012
	Hot stroma CD8 +	0,05
Granules color	Hot stroma Granzym B +	0,011
Reticular type of regression	Regression stage 2	0,049
Annular granular pattern	Stage 2 and 3 of regression	0,009
	Good outcome with complete remission, and no evolution after treatment	0,001
Irregular thick reticular lines	Stage 2 of regression	0,049
	Hot stroma Granzyme B +	0,044
Skin fissures exaggeration	Focal regression in histology	0,000
	Hot stroma CD8 +	0,043
	Good outcome with complete remission, and no evolution after treatment	0,002
	Good response to immunotherapy	0,003

*Table 2 continues*

**Table 2. Univariate Analysis (continued)**

Variables		P value
Blue-white area (veil)	MelanA pattern: reduced in the dermis, reduced or normal in the epidermis	0,010
	Stage 2 of regression	0,014
	Focal regression in histology	0,038
Pseudopods	Good outcome with Complete remission, and no evolution after treatment	0.033
Peripheral focal irregular network	Good outcome with a complete remission, and no evolution after treatment	0.05
Polygons	Hot stroma Granzym B+	0,044
Melanoma stage (AJCC 2018)	The extent of regression	0.01
	Hot stroma CD8+	0.038
Regression stage	Stage 2   local extension	0.030
	Stage 3   melanoma specific death (at 2 years, 5 years of initial treatment)	p=0.048/ p=0.020
Immunotherapy response	Hot stroma CD8 +	0.032
Progression free survival	Regression extent	0.005
	Hot stroma CD8+	0.044
Melanoma specific death	Regression extent	0.000

Focal regression was associated with good outcome ( $P < 0.001$ ) and the immunotherapy response ( $P < 0.001$ ), while complete and partial regression of histology were associated with melanoma-related death ( $P < 0.001$ ), regression stage 3 of histology was associated with melanoma-related death at both 2 years ( $P = 0.048$ ) and 5 years ( $P = 0.020$ ) since initial treatment. “Hot” CD8<sup>+</sup> stromas were associated with a good response to immunotherapy ( $P = 0.032$ ), and with the survival at 10 years ( $P = 0.044$ ). Also, “hot” Granzyme B<sup>+</sup> stromas were associated with locoregional extension ( $P = 0.016$ ), and initial distant metastasis ( $p=0.016$ ) (Table 2).

The local extension (in transit metastasis) of these regressive melanomas was associated with the stage 2 of regression ( $P = 0.030$ ), while locoregional extension and initially distant metastasis were associated with WSA in dermoscopy ( $P = 0.041$ ) and with focal regression in histology ( $P = 0.008$ ; Table 2).

## Conclusions

In the present study we were able to further characterize “hot” and “cold” stromas in the context of melanoma regression based on dermoscopic criterias and the inflammatory infiltrate status. Indeed, we found an association of many and specific dermoscopic features with “hot” Granzyme B<sup>+</sup> and “hot” CD8<sup>+</sup> stromas, or “cold” PDL1<sup>+</sup> and “cold” Langerin<sup>+</sup> stromas. This further characterization of the previous sub-classification of “hot” and “cold” stromas in melanomas [17] based on the immunopathology nature of the inflammatory

infiltrate had interesting prognostic implications, as CD8<sup>+</sup> stromas were significantly associated with a good response to immunotherapy, and to the disease free survival at 10 years, which confirms a study that has previously reported an association between CD8 T-cell infiltration and better prognosis [14]. Also, “hot” Granzyme B<sup>+</sup> stromas were associated with locoregional extension and the initial distant metastasis, while no prognostic implication of Langerin or PDL-1 expression around the tumor and in the regression were found in the present study. The prognostic value of PDL-1 is controversial, as some authors have failed to observe a correlation between PDL-1 expression in sentinel lymph node metastases and the outcome (which is consistent with our results), while others have reported PDL-1 as an independent negative prognostic marker in conventional melanoma, and, in contrast, others have reported PDL-1 expression in mucosal melanomas as correlated with longer recurrence-free survival [18].

A preoperatively comparison of various dermoscopic features of regressive melanoma at different stages of regression was made, and the association between dermoscopy, pathology, and the prognostic implications of regression was investigated. Peppering was found as significantly associated with thin melanomas in histology, this refines knowledge about peppering that has been described as an expression of melanophages in the dermis [2], and has been significantly associated with BRAF mutation [2], confirming that regression may be a hallmark of BRAFV600 melanomas. In addition, in primary melanomas, mutated BRAF has been

described as an adverse prognostic factor [20]. In the present study, even though BRAF mutation status was not found in many patient records because most had thin melanomas, it was significantly associated to rapidly growing melanomas, which were polychromatic, chaotic, or with a multicomponent pattern in dermoscopy, or with signs of horizontal growth and local extension. As a result, BRAF mutation may be a prognostic factor in regressive melanomas. Also, the dermoscopic extent of regression (WSA with peppering) was significantly associated with regression stages in histology and enabled us to evaluate the aggressiveness of the tumor, since the results presented herein demonstrated an association between advanced stages of regressive melanomas and the extent of regression, and between stage III melanoma and melanoma-related death. In addition, the presence of dermoscopic signs associated with hot stromas CD8+ or Granzyme B + ( rRed milky areas, irregular thick reticular lines, polygons, the peppering granules' color, and the eccentric, multifocal character of regression), supports the idea that further dermoscopic investigations of the regression in primary melanomas would be of great help in the pre-excision therapeutic evaluation and predictable therapeutic response.

Reticular regression in a clinically less palpable area, which has been recently reported [7,19], was frequent in patients who had stage 2 of regression in thin melanomas. This type of regression may be correlated with the remaining junctional component and the heterogeneous dermal regression in stage 2 before the complete disappearance of the dermal tumor.

Remarkably, MelanA red immunostaining could be a good tool to confirm, characterize, and probably classify the histologic regression, especially when histologic regression is not so obvious. Despite contradictions in the literature, patients with thin melanomas who show partial regression cannot be included in the "low-risk" group if the extent of regression is more than 50% [16,21,22]. Completely regressive lesions represent a factor of delay in diagnosis, and of development of locoregional and distant metastasis, as it has been reported in some case reports and studies [21,23]. This was also confirmed with the results herein as melanoma-related death was associated with regressed melanomas (stage 3 and complete regression).

The data herein suggest that the prognostic role of regression depends on the stage of melanoma, the stage of regression and its extent (regressing or regressed melanomas), and the "hot" or "cold" nature of the CD8+ and Granzyme B+ tumor stroma, which may explain the controversies found in the literature concerning regression [2] as it has not been precisely sub-classified previously.

Due to the retrospective nature of this study, many important data were missing from the patient records: for example, the BRAF status that was not determined for all patients, especially because most melanomas were thin, it

was therefore not possible to draw conclusions about the prognostic value of BRAF mutation in regressive melanomas. However, even though this aspect would have been interesting to determine, and for future studies, it was not among our main objectives. Also, the small number of patients was due to the retrospective collection of the records and to the dermoscopic images themselves that were often not found or of poor quality, leading to the exclusion of some patient. Additionally, some patients were excluded after review by experienced pathologists because regression was not objectively observed.

The present study provides a better characterization of regression in primary melanomas, and a better comprehension of the "hot" or "cold" character of the stroma. An important outcome of the study is that regressing melanoma (early stages of regression) is associated with favorable outcome whereas regressed melanoma (complete regression stage 3) is associated with a worse outcome. Further studies with a prospective design could help in confirming and investigating these results, especially the importance of dermoscopy in predicting the immunophenotypic host response, with the ultimate goal to help in the pre-therapeutic definition of "hot" tumors that may benefit of postoperative adjuvant immunotherapy, and "cold" tumors in which inclusion in potential neo-adjuvant clinical trials could be proposed in priority before excision of the primary tumor.

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