Correlation of Histologic Regression in Primary Melanoma With Sentinel Node Status

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IMPORTANCE The influence of regression on the status of the sentinel node (SN) is controversial. In many centers, the presence of regression in thin melanomas supports the performance of an SN biopsy.

OBJECTIVE To identify whether regression in primary melanoma has any influence on SN involvement.

DESIGN, SETTING, AND PARTICIPANTS Retrospective study of melanomas with a Breslow thickness greater than 0.75 mm and undergoing SN biopsy from January 1, 2003, through December 31, 2010, at Instituto Valenciano de Oncología, which receives melanoma patients from regional hospitals and dermatology practices. Only cases with paraffin blocks or histologic slides representative of the primary tumor and available for review were included in the study. Melanomas from 201 patients met these criteria and constitute the core of this study.

EXPOSURES Sentinel node biopsy in melanoma.

MAIN OUTCOMES AND MEASURES Presence or absence of regression in the primary melanoma, type (early vs late), and extension were correlated with the presence or absence of metastasis in the SNs. In addition, the main clinical and histologic characteristics of the primary melanoma were correlated with the status of SN and the regression features.

RESULTS Regression was found in 52 melanomas (25.9%). Regression did not show a statistically significant association with SN status. When melanomas were subdivided by Breslow thickness into 4 groups, those with regression had a lower frequency of positive SNs in 3 of the 4 groups (≤1.00, 1.01-2.00, and >4.00 mm), although differences did not reach statistical significance in any group. We found no influence by type of regression or its extension on the SN status. Regression was found more frequently in thin melanomas (≤1.00 mm), melanomas located on an axial site, and superficial spreading or lentigo maligna melanoma types (P = .02, P < .001, and P = .03, respectively).

CONCLUSIONS AND RELEVANCE Regression of the primary melanoma is not associated with a higher proportion of positive SNs. These data do not support the practice of performing SN biopsy in thin melanomas with regression in the absence of additional adverse prognostic characteristics.

Published online June 4, 2014.
Regression in melanoma is defined as an area within the tumor in which neoplastic cells have disappeared or become reduced in number from the dermis (and occasionally from the epidermis) and have been substituted by fibrosis with accompanying melanophages, new vessels, and a variable inflammatory infiltrate. Regression is found in melanoma with a frequency that ranges from 10% to 35%. The differences occur primarily because the diagnosis of regression does not depend on the presence of a single finding but on a constellation of features, most of them relying on subjective criteria. A recent review of the literature established that the best histologic characteristics to define regression are the presence of inflammatory infiltrate, fibrosis, melanophages, neovascularization, epidermal flattening, and apoptotic melanocytes or keratinocytes. Although all these features do not need to be present simultaneously, an additional essential criterion is the disappearance of the tumor or a reduction in the number of neoplastic cells in a more or less extensive area.

The influence of regression on the prognosis of melanoma has been a matter of great controversy for decades. Although several studies indicate that regression increases the likelihood of metastasis, other reports have found that regression is not associated with a change in the prognosis or that it may even behave as a protective factor. The interpretation given for the poor prognosis associated with regression is that the disappearance of a portion of the tumor may lead, at least in some cases, to an underestimation of the original Breslow thickness. For this reason, in many hospitals, thin melanomas (<1.00 mm) with histologic features of regression are considered candidates for sentinel node (SN) biopsy. The opposing view on the influence of regression on melanoma prognosis considers regression as a host immune response against its own tumor, and consequently a negligible effect or even a better prognosis should be anticipated. The effect of melanoma on SN status is also controversial. Although few studies have analyzed this relationship, controversy also surrounds its influence.

An additional area of debate is whether regression, independently of the percentage of the melanoma involved, should be considered equally relevant. Although Ronan et al found that regression is associated with a higher risk for metastasis when it involves 75% or more of the horizontal dimension of the melanoma, other investigators consider regression extensive and relate it to metastasis when at least 50% of the melanoma is affected.

The main aim of the present study is to examine the influence of regression on the status of the SN. The melanomas that constitute the core of this study were reviewed separately by 2 dermatopathologists (R.B.-E. and V.T.) following preestablished criteria for regression. Regression was further classified as early or late and by the percentage of the melanoma it involved. We sought to understand the influence of regression on SN status and its relationship to other relevant clinical and histologic prognostic characteristics of melanoma more precisely.

### Methods

Melanomas with a Breslow thickness greater than 0.75 mm and undergoing SN biopsy from January 1, 2003, through December 31, 2010, at the Instituto Valenciano de Oncología were considered eligible for this study. Mucosal melanomas were excluded. The starting point was selected because, in our institution, SNs were routinely studied with hematoxylin-eosin and at least 2 immunohistochemical stains from that date. Patients were selected from our melanoma database, the characteristics of which are detailed elsewhere. Inclusion criteria of the present study required melanomas with paraffin blocks or histologic slides representative of the primary tumor to be available for review to evaluate regression according to our preestablished criteria. The study was approved by the institutional review board of the Instituto Valenciano de Oncología, which receives melanoma patients from regional hospitals and dermatology practices. Patients provided oral informed consent.

### Clinical and Histologic Features

The clinical characteristics evaluated included patient sex and age (≤65 vs >65 years) and tumor location. The anatomic location was identified as axial (head/neck or trunk) or the extremities. Histologic variables of melanomas included Breslow thickness (grouped according to the American Joint Committee on Cancer AJCC staging system ≤1.00, 1.01-2.00, 2.01-4.00, or >4.00 mm), ulceration (present vs absent), tumor mitotic rate (expressed as 0, 1-5, 6-10, or >10 mitoses/mm²), tumor-infiltrating lymphocytes (absent, nonbrisk [sparse], or brisk [dense]), microscopic satellitosis (defined as the presence of melanoma cell nests of >0.05 mm separated from the tumor mass by a layer of collagen or subcutaneous fat ≥0.30 mm thick [present vs absent]), and regression (described in detail below).

### SN Status

Biopsy of the SN is performed at our institution in all melanomas with a Breslow thickness greater than 0.75 mm; all melanomas with a Breslow thickness of 0.75 mm or less that have ulceration, angiolymphatic invasion, or regression; and all melanomas in which an inadequate excision precludes a correct assessment of Breslow thickness (the presence of ≥1 mitosis/mm² was considered an additional criterion after the publication of the 2009 AJCC melanoma classification). Although regression is described and quantified by horizontal extension in the histologic report of our center (<50% or ≥50% of the horizontal width of the whole tumor), a minimum degree of regression or the area involved is not required to establish an indication for SN biopsy. We selected 0.75 mm as the thickness cutoff for the SN biopsy recommendation because, in our hospital, we have maintained the 1988 melanoma AJCC staging system that was in use in 1996, when we started performing this technique. To avoid selection bias, we considered for this study only those melanomas with a thickness greater than 0.75 mm.
In our institution, for SN biopsy, the node is bisected longitudinally and 250-μm levels are obtained until the node is exhausted. Three sections of 4 μm are obtained for each level and processed for hematoxylin-eosin and immunohistochemical (S-100 protein and HMB-45 antigen) staining.

Regression
All the melanomas included in this series were removed with an excisional biopsy. Histologic slides from all melanomas undergoing SN biopsy were studied separately by 2 dermatopathologists (R.B.-E. and V.T.). Subsequently, a conjunct review of all cases was undertaken, and cases in which disagreement persisted were reviewed by a third specialist (C.R.). Special attention was paid to the presence or absence of regression. The presence of regression was evaluated according to criteria previously established by a detailed review of the dermatologic literature\(^2\) and our own experience as follows:

1. Small or large areas with a decrease or an absence of melanoma cells in the dermal component of the tumor
2. Fibrosis
3. Inflammatory infiltrate
4. Melanophages
5. Neovascularization
6. Epidermal flattening
7. Colloid bodies (apoptosis of keratinocytes/melanocytes)

Early regression was defined by criteria 1 (usually small foci), 2 (to some degree), and 3 (dense inflammatory infiltrate) with any combination of criteria 4 through 7. Late regression was defined as criteria 1 (usually medium to large areas) and 2 (very evident) with any combination of criteria 3 through 7.

These criteria also enabled us to establish whether regression was early (regressing melanoma) or late (established regression or regressed melanoma). An essential feature in considering the existence of any type of regression (early or late) was the observation of a focal decrease or a clear-cut absence of the tumor. To be classified as early, regression needed to show a dense inflammatory infiltrate in areas in which the tumor had disappeared or in which an objective decrease in the number of melanoma cells was observed compared with surrounding areas and at least some degree of fibrosis (Figure 1A). Late regression was characterized by focal or large areas without melanoma in the dermis and occasionally in the epidermis accompanied by evident and sometimes large areas of fibrosis (Figure 1B). Other characteristic histologic criteria of regression (melanophages, neovascularization, epidermal flattening, and colloid bodies resulting from apoptosis of keratinocytes/melanocytes) could be appreciated in early and late regression, and their presence or absence was evaluated in each case. Extension of regression was considered as the percentage of melanoma in a horizontal dimension with features of regression. Three groups were established depending on whether regression involved less than 25%, 25% to 50%, or greater than 50% of the total width of the melanoma. Apart from undergoing evaluation globally in the melanoma present in each slide, the inflammatory infiltrate was also characterized within the areas with regression as absent, non-brisk, or brisk, and its cellular composition was described with particular attention to the presence of plasma cells.

Regression characteristics (presence or absence, early vs late, and extension) were correlated with the presence or absence of metastasis in the SNs. In addition, for each patient, the following clinical and histologic characteristics of the primary melanoma were analyzed regarding its correlation to the status of SN and regression characteristics: sex, age, location of the tumor, clinicopathologic type, Breslow thickness, ulceration, tumor mitotic rate, and microscopic satellitosis.

Statistical Analysis
The variable response was SN positivity. Binary variables included age, sex, tumor location, ulceration, tumor-infiltrating lymphocytes, presence of regression, and regression type; categorical variables, Breslow thickness, mitotic index, clinicopathologic type, and extension of regression. In a
second analysis, the variable selected was regression, that is, presence or absence, type, and extension. Regression was correlated with the rest of the variables of the primary melanoma. Association was performed using the χ² test, the Fisher exact test, or univariate logistic regression analysis. Based on the Wald method, we calculated odds ratios (95% CIs) for each variable. Forward and backward stepwise multiple logistic regression analysis was performed to identify independent predictors of SN positivity. Significance level was set at P = .05. We used commercially available software (SPSS, version 15.0; SPSS, Inc.) to perform the statistical analysis.

Results

During the study period (January 1, 2003, through December 31, 2010), 765 melanomas were treated definitively in our hospital. Our melanoma committee recommended the performance of an SN biopsy in 377 patients. Two hundred and eighteen melanomas belonging to 218 patients fulfilled the selection criteria. The SN biopsy was not performed in 7 patients owing to contraindications for anesthesia (n = 3) or because the patient did not give informed consent (n = 4). In 10 of 211 patients (4.7%), an SN was not identified. Therefore, this correlation study is based on a final figure of 201 melanomas in 201 patients. Median age of the patients was 55 (interquartile range, 42-67) years. Table 1 summarizes the clinical and pathologic characteristics of the patients.

SN Status

The number of SNs identified per patient was as follows: 1 SN in 102 patients, 2 SNs in 67 patients, 3 SNs in 23 patients, 4 SNs in 6 patients, 5 SNs in 2 patients, and 6 SNs in 1 patient. The SN procedure was restricted to 1 lymph node basin in 159 patients, 2 basins in 39 patients, and 3 basins in 3 patients.

An SN was positive in 40 of the 201 cases (19.9%). Metastases were detected with hematoxylin-eosin staining in 33 cases (16.4%), and immunohistochemical staining was needed to identify 7 additional cases (3.5%). Lymphadenectomy was performed in 39 of the 40 cases (1 patient denied permission after being informed). Additional metastatic nodes were identified in 4 patients (1 node in 3 and 2 nodes in 1).

As an initial approach, we correlated the status of the SN with the clinical and histologic characteristics of the primary melanoma (Table 1). Of all these variables, only ulceration, Breslow thickness, mitosis, and clinicopathologic type showed a statistically significant correlation with SN status. In the multivariable analysis, only Breslow thickness maintained a statistically significant relationship (P = .02).

Regression

Regression was found in 52 melanomas (25.9%). Regression was considered early in 15 cases (7.5%) and late in 37 (18.4%). Regarding extension, regression involved less than 25% of the whole melanoma in 20 cases (10.0%), from 25% to 50% in 19 (9.5%), and more than 50% in 13 (6.5%).

The presence or absence of regression in the primary melanoma did not show a statistically significant association with the status of the SN (Table 1). Nevertheless, a higher percentage of positive SNs were found when regression was absent. When melanomas were subdivided by Breslow thickness into 4 groups (<1.00, 1.01-2.00, 2.01-4.00, and >4.00 mm), those with regression had a lower frequency of positive SNs in 3 of the 4 groups (<1.00, 1.01-2.00, and >4.00 mm), although differences did not reach statistical significance in any group (Figure 2). The type of regression and its extension had no influence on SN status (P = .53 and P = .37, respectively).

Apart from SN status, we examined whether regression was associated with any other characteristic of the primary melanoma (Table 2). Location of the primary melanoma (axial vs extremities) was statistically associated with regression (P < .001); melanomas on an axillary location (head/neck or trunk) were more prone to develop regression. The different clinicopathologic types of melanoma had a dissimilar frequency of regression (P = .03). In lentigo maligna melanoma and superficial spreading melanoma, regression was more frequently identified. Regarding Breslow thickness, an inverse correlation was observed because the percentage of melanomas with regression was high in the group with a thickness of 1.00 mm or less (41.5% [17 of 41]) and very low in the group of melanomas with a thickness greater than 4.00 mm (10.5% [4 of 38]). Histologic characteristics that have repeatedly demonstrated a relationship with melanoma prognosis, such as ulceration and mitosis, did not show any relationship to regression.

We evaluated the composition of the inflammatory infiltrate in the regression areas with special attention to the presence of plasma cells. No correlation was found between the existence of a prominent number of plasma cells and SN status or regression. After testing the relationship of plasma cells with the main clinical and pathologic characteristics of the melanoma, we only found a statistically significant association with the presence of ulceration (P = .01), with plasma cells present in 4 of 145 nonulcerated melanomas (2.8%) and in 7 of 56 ulcerated melanomas (12.5%).

Discussion

The greatest difficulty of studies related to regression pertains to the subjective nature of its evaluation. Retrospective studies are therefore more exposed to the diverse interpretation of the regression phenomena by different pathologists. Our interest in this intriguing phenomenon led us to review the literature pertaining to the histologic findings previously defined as characteristic of regression. Based mainly on studies by Kang et al., who divided regression in 3 phases, and Massi and Leboit, who adopted a 2-phase staging, we developed our own set of criteria to identify regression and classify it into the categories of early regression or regressing melanoma and late or established regression or regressed melanoma. A prospective evaluation of the 201 cases included in this study was performed independently by 2 dermatopathologists, then all cases were reviewed conjointly and disagreements solved with the opinion of a third expert. This exhaustive procedure was arranged to improve the objectivity of the evaluation. Even with these precautions, we ac-
knowledge the intrinsic difficulty involved in the diagnosis of early regression. Differentiation may be almost impossible between areas with dense (brisk) inflammatory infiltrate vs areas in the initial stages of regression development with a questionable decrease in the number of neoplastic cells without fibrosis and with only a hint of increased vascularization and isolated melanophages. In the present study, when confronted with difficult cases, we restricted the diagnosis of regression to clear-cut cases with evident histologic findings of regression.

Based on the results of the present study, the presence of regression in melanomas with a Breslow depth greater than 0.75 mm does not imply a higher likelihood of SN involvement. When primary melanomas were stratified according to Breslow thickness, some differences in the percentage of SN positivity between melanomas with or without regression appeared, but they were not statistically significant. In fact, of the 4 groups of Breslow thicknesses considered, melanomas with regression had a lower frequency of SN metastasis than melanomas without regression in those with Breslow thicknesses of 1.00 mm or less, 1.01 to 2.00 mm, and greater than 4.00 mm. We confirmed the observation made by other authors regarding the lower depth of melanomas with associated regression.

### Table 1. Correlation of the Main Clinical and Histologic Characteristics of the Primary Melanoma With SN Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>SN Findings, No. (%) of Melanomas</th>
<th>Univariate Analysis, P Value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Negative (n = 161)</td>
<td>Positive (n = 40)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 77 (47.8)</td>
<td>20 (50.0)</td>
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<tr>
<td></td>
<td>Female 84 (52.2)</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td>≤40 42 (26.1)</td>
<td>5 (12.5)</td>
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<tr>
<td></td>
<td>41-60 56 (34.8)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;60 63 (39.1)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Axial 87 (54.0)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td></td>
<td>Extremities 74 (46.0)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Clinicopathologic type</td>
<td>LMM 5 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SSM 91 (56.5)</td>
<td>11 (27.5)</td>
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<tr>
<td></td>
<td>NM 32 (19.9)</td>
<td>23 (57.5)</td>
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<tr>
<td></td>
<td>ALM 16 (9.9)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td></td>
<td>Other 17 (10.6)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Breslow thickness, mm²&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤1.00 40 (24.8)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td></td>
<td>1.01-2.00 68 (42.2)</td>
<td>8 (20.0)</td>
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<td></td>
<td>2.01-4.00 31 (19.3)</td>
<td>15 (37.5)</td>
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<td></td>
<td>&gt;4.00 22 (13.7)</td>
<td>16 (40.0)</td>
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<tr>
<td>Ulceration</td>
<td>No 124 (77.0)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td></td>
<td>Yes 37 (23.0)</td>
<td>19 (47.5)</td>
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<tr>
<td>Tumor mitotic rate, mitosis/mm²</td>
<td>0 27 (16.8)</td>
<td>3 (7.5)</td>
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<tr>
<td></td>
<td>1-5 109 (67.7)</td>
<td>22 (55.0)</td>
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<tr>
<td></td>
<td>6-10 20 (12.4)</td>
<td>10 (25.0)</td>
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<tr>
<td></td>
<td>&gt;10 5 (3.1)</td>
<td>5 (12.5)</td>
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<td>Microscopic satellitosis</td>
<td>No 160 (99.4)</td>
<td>39 (97.5)</td>
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<td></td>
<td>Yes 1 (0.6)</td>
<td>1 (2.5)</td>
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<td>Regression</td>
<td>No 116 (72.0)</td>
<td>33 (82.5)</td>
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<tr>
<td></td>
<td>Yes 45 (28.0)</td>
<td>7 (17.5)</td>
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<tr>
<td>Tumor-infiltrating lymphocytes</td>
<td>Absent 83 (51.6)</td>
<td>26 (65.0)</td>
</tr>
<tr>
<td></td>
<td>Nonbrisk (sparse) 67 (41.6)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td></td>
<td>Brisk (dense) 11 (6.8)</td>
<td>0</td>
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</tbody>
</table>

Abbreviations: ALM, acral-lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; OR, odds ratio; SN, sentinel node; SSM, superficial spreading melanoma.

<sup>a</sup> Percentages have been rounded and might not total 100.

<sup>b</sup> Includes 8 spitzoid, 5 desmoplastic, 1 polypoid, and 5 melanomas in which the clinicopathologic type was not specified.

<sup>c</sup> Grouped according to the American Joint Committee on Cancer staging system.<sup>20</sup>

<sup>d</sup> Maintained a statistically significant relationship with SN status and entered multivariate analysis. For tumors from 1.01 to 2.00 mm, the OR was 4.0 (95% CI, 0.4-34.4; <i>P</i> = .20); for 2.01 to 4.00 mm, 12.5 (1.4-109.9; <i>P</i> = .02); and for greater than 4.00 mm, 16.9 (1.8-154.3; <i>P</i> = .01). Tumors of 1.00 mm or less constituted the reference group.
the group of melanomas with a Breslow thickness of 0.75 mm or less. As we mentioned in the Methods section, SN biopsy is performed in our institution in this group of melanomas only when certain high-risk features are present. Regression was also regarded as a criterion of adverse prognosis, so we performed SN biopsy in melanomas of 0.75 mm or less when regression was present, independently of its extension or type. Nevertheless, this group of thin melanomas was not included in the present study because melanomas of comparable Breslow thickness and without adverse prognostic criteria were not subjected to SN biopsy. Of interest, among the group of 41 melanomas with a Breslow thickness of 0.76 to 1.00 mm included in the present study, 1 case had SN involvement.

In 2008, Morris et al12 published an extensive study addressing this same subject. They were able to correlate the presence of regression with the status of the SN in 943 patients with melanomas. They found a higher proportion of SN positivity in melanomas without regression, and this difference was statistically significant. Knowing that regression is found more frequently in thinner melanomas, they stratified patients by Breslow thickness and found that patients with regression had lower rates of SN positivity in all groups. A previous study by Fontaine et al17 disclosed similar results, that is, they found the same rate (29%) of SN positivity in melanomas with and without regression. Kaur et al18 performed a detailed study correlating regression with SN status. They proposed a 3-stage classification for histologic regression and reviewed the slides of 146 consecutive melanomas in which SN biopsy was performed. They found that regression had a favorable effect and was associated with SN negativity. A recent article by Ribero et al14 also found that regression had a favorable effect on overall and disease-free survival in AJCC stages I and II and was related to a lower proportion of SN positivity. Unfortunately, the evaluation of the influence of regression vs nonregression on SN status was hampered in these studies by the heterogeneous composition of the group of thin melanomas (≤1.00 mm).14,18 A high proportion of cases with regression are thin melanomas, a group usually associated with good prognosis and negative SN. Melanomas with a Breslow thickness of 1.00 mm or less without regression or adverse prognostic factors did not undergo SN biopsy. In 2003, Oläh et al19 published the only study that has found a negative association between regression and SN status. They studied 134 patients with melanomas of 2.00 mm or less in whom an SN biopsy was performed. They found a higher risk of SN metastasis in the group of melanomas with regression (64%) than in the group without regression (15%).

An expected result of our correlation study was that regression was found more frequently in melanomas present in an axial location and in certain clinicopathologic types. When melanomas with regression were subdivided by clinicopathologic type, lentigo maligna melanoma and superficial spreading melanoma were overrepresented compared with melanomas without regression; conversely, nodular and acral-lentiginous melanomas were underrepresented in the presence of regression. Previous publications on the subject of regression already found a higher proportion of regression in melanomas located on the trunk and in those with a radial growth phase, particularly superficial spreading melanoma.3,14–25 Future molecular studies should investigate the dissimilar rates of melanomas with and without regression regarding location and clinicopathologic type.

The pathogenesis of regression is not well understood. Traditionally, regression been considered an immunologically mediated phenomenon based on the inflammatory infiltrate that in different degrees characterizes regression. In fact, early regression may display a very dense lymphocytic infiltrate reminiscent of that present in a halo nevus. Nevertheless, an alternative hypothesis was entertained by Bastian,26 who proposed that, at some point, melanoma cells could enter a phase of telomere crisis and genome remodeling. As a consequence, numerous apoptotic bodies would be generated and attract T lymphocytes. In that way, the inflammatory infiltrate could be only an epiphenomenon. In a time dominated by target therapies, many of which are directed against regulatory T cells to increase the immune response against melanoma, we should improve our knowledge of the mechanisms that lead to the spontaneous disappearance of this tumor.

**Conclusions**

The finding of histologic regression in a melanoma with a Breslow thickness greater than 0.75 mm does not imply a higher likelihood of metastasis in the SN. Although having data from the group of melanomas measuring 0.75 mm or less that are usually not subjected to SN biopsy would be of interest, the low rate of SN positivity in this group implies that a large study would be necessary to have statistical power to solve the question of the influence of regression. Nevertheless, the present data support the conclusion that regression should not have any influence in melanomas of 0.75 mm or less because regression did not influence melanomas in the next thickness.
groups (0.76-1.00 and 1.01-2.00 mm). Therefore, the presence of regression does not justify the performance of an SN biopsy in melanoma. Future studies should investigate the mechanisms that underlie this phenomenon and the preferential involvement of melanomas located on the axis and the superficial spreading and lentigo maligna melanoma types.

ARTICLE INFORMATION
Accepted for Publication: November 19, 2013.

Author Contributions: Drs Botella-Estrada and Nagore had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Botella-Estrada, Requena, Nagore.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Botella-Estrada, Traves, Requena, Nagore.
Critical revision of the manuscript for important intellectual content: Botella-Estrada, Traves, Requena, Nagore, Guillen-Barona, Nagore.
Statistical analysis: Nagore.
Administrative, technical, or material support: Botella-Estrada, Requena.
Study supervision: All authors.

Conflict of Interest Disclosures: None reported.

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NOTABLE NOTES

Divine Skin

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Variation in skin color around the world is a prime example of divergent evolution in humans, with darker skin serving a greater benefit around the equator and lighter skin providing an advantage closer to the poles. Although latitude may roughly correlate with skin pigmentation in our species, the color of the gods we worship is a different discussion entirely!

Hinduism encompasses a tremendous diversity of regional beliefs and interpretations of God, but some physical and iconographic features are widely accepted. The god Vishnu is described in early texts, such as the Kurma Purana, as red-eyed and colorless, but later texts portray him as blue. Rama and Krishna are the 2 most frequently described avatars (incarnations) of Vishnu, and they inherit his blue skin in various scriptures and epics. These descriptions are carried forth literally by most modern Hindu artwork and poetry, which illustrate Vishnu, Rama, and Krishna with light blue skin that is likened to the color of the sky or ocean. But many believe the color blue is simply a euphemism for dark skin, a common characteristic in the Indian subcontinent. In fact, the word “Krishna” translates from Sanskrit to “dark” or “black.”

Of the monotheistic religions, Christianity has been the most prolific in producing religious art. The Western Church initially forbade the physical depiction of God for hundreds of years, but the Renaissance saw God’s portrayals gradually emerge in paintings, frescoes, and sculpture. Perhaps the best known of these is Michelangelo’s Creation of Adam, in which God is an elderly man with a gray beard and wrinkled, white skin, an interpretation carried forth into the later Renaissance and Baroque periods. But the most frequently depicted figure in Christian art is Jesus Christ of Nazareth. While anthropologists believe the man resembled a Middle Eastern Jew with olive skin and dark hair, there are few textual references to Christ’s appearance, save for 1 passage in Revelation 1:15 (“his feet shone like burnished bronze”) and a description in the Islamic Hadith of Jesus as “red,” seen as a euphemism for fair skin.2 The classic and most familiar portrayal of Christ with fair skin, dark, flowing hair, and beard was popularized by sixth-century icons of Christ Pantocrator (“Christ the Ruler of All”); a specific depiction of Christ and gained ubiquity in the Middle Ages.3 Local Christian traditions, however, give Christ their own attributes, such as dark skin and curly hair in Ethiopia or blonde hair in Scandinavia.

Belief systems around the world all have something different to say regarding God’s physical appearance. Some ascribe superhuman attributes to their deity, whereas others favor a human image. Still others deny physicality to God entirely. But perhaps we can agree on one thing: if God has skin, it must be nothing less than divine!

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