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# Prediction of Sentinel Lymph Node Positivity by Growth Rate of Cutaneous Melanoma

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**Objective:** To determine whether growth rate (GR) of cutaneous melanoma predicts the histological sentinel lymph node (SLN) positivity.

**Design:** Retrospective cohort study.

**Setting:** Two tertiary melanoma referral centers.

**Patients:** A total of 698 patients with invasive primary cutaneous melanoma in whom the SLN was identified between January 1, 2000, and June 30, 2010.

**Main Outcome Measure:** Based on previous studies, a surrogate measure for GR in primary invasive melanoma was calculated as the ratio of Breslow thickness to time to melanoma development.

**Results:** The SLN was positive in 20.2% of patients. Multivariate logistic regression analysis revealed that GR, Breslow thickness, and the presence of microscopic satellitosis were independently associated with SLN positivity. The probability of SLN positivity was 8.2% for slow-growth melanomas (<0.10 mm/mo) compared with 19.8% for intermediate-growth melanomas (0.10-0.50 mm/mo) and 37.7% for fast-growth melanomas (>0.50 mm/mo). Growth rate was not an independent predictive factor for survival.

**Conclusion:** Growth rate of primary cutaneous melanoma, together with Breslow thickness and the presence of microscopic satellitosis, predicts the histological SLN positivity.

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GROWTH RATE (GR) OF CUTANEOUS melanoma, defined as the increase in Breslow thickness per unit of time, has been proposed as an important biological feature of this tumor. Clark et al[1] were the first to describe differences in GR among various histological subtypes of melanoma. Grob et al[2] demonstrated that GR, calculated from the evolution time as provided by the patient, was an independent prognostic factor for disease-free survival (DFS). This observation has recently been corroborated in 2 other studies[3,4] that demonstrated the independent prognostic value of GR in overall survival (OS) among patients with melanoma. In addition, faster GR has been associated with a more aggressive melanoma phenotype, as well as with male sex and advanced age.[5,6]

At present, the most significant predictive prognostic factor for recurrence and OS in patients with melanoma is the presence of sentinel lymph node (SLN) metastasis.[7] Breslow thickness and ulceration are factors that have most consistently predicted SLN positivity in various studies.[8-11] Other predictive factors for the SLN positivity include mitotic index[12,13] and the absence of lymphocytic infiltrate.[12,13] Martorell-Calatayud et al[6] recently described a greater frequency of metastatic SLN involvement in melanomas with higher GR.

Because GR is a variable that seems to provide additional information about the aggressiveness of a melanoma relative to that afforded by classic histological features, such as Breslow thickness, ulceration, or mitotic index, it may be useful to predict SLN metastasis. Likewise, GR could provide extra prognostic information for patients with locoregional disease.

The main objective of this study was to determine whether GR of cutaneous mela-



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noma predicts the histological SLN positivity. A secondary aim was to determine whether GR influences recurrence and survival in these patients.

## METHODS

Study participants were selected from the databases of patients with melanoma from the following 2 participating hospitals: Hospital "Virgen de la Victoria" in Málaga, Spain, and Instituto Valenciano de Oncología in Valencia, Spain. The use of both databases is in compliance with applicable ethics regulations. The use of one of them, at Instituto Valenciano de Oncología, has been described in detail in previous publications.[14-16] These retrospective cohorts included all patients with a single primary melanoma and clinical stage I or II disease who underwent selective SLN biopsy between January 1, 2000, and June 30, 2010, at Instituto Valenciano de Oncología or between October 1, 2001, and January 30, 2010, at Hospital "Virgen de la Victoria." The study was approved by the ethics commissions of both institutions.

### CLINICAL AND HISTOLOGICAL FEATURES

The clinical factors evaluated were patient sex, age (≤65 vs >65 years), and tumor location. The anatomical location was identified as axial (head, neck, trunk, volar surfaces, or subungual) or extremities. We used the categorization by Kruper et al[12] to classify volar and subungual melanomas as axial because the other melanomas in this location present a worse prognosis[9] that could in part be related to genetic alterations differentiating them from the rest.[16]

Histological variables of melanomas included the following: Breslow thickness (grouped according to the American Joint Committee on Cancer staging system [≤1.00, 1.01-2.00, 2.01-4.00, or >4.00 mm]), ulceration (present vs absent), Clark level (II, III, IV, or V), regression (present vs absent), mitotic index (expressed as the number of mitoses per square millimeter [0, 1-5, 6-10, or >10]),[17] tumor-infiltrating lymphocytes (absent, nonbrisk, or brisk),[18] vascular invasion (present vs absent), microscopic satellitosis (defined as the presence of melanoma cell nests >0.05 mm separated from the tumor mass by a layer of collagen or subcutaneous fat ≥0.30 mm thick [present vs absent]), and perineural invasion (present vs absent).

### TUMOR GR

Three patient groups were defined in accord with the initial description by Grob et al.[2] In brief, this involves rates that measure volume increase per unit of time. Because no accepted method exists to measure tumor volume, Breslow thickness is used as a surrogate value. The variable time used in the calculation of GR is defined as the interval (in months) between the time that the patient or family first noticed the lesion in de novo cases or noticed changes to a previous lesion (time D1) and the time at which the lesion is removed, with its pathological report (time D2). Growth rate was calculated as the ratio of Breslow thickness to time (in months, defined as D2 minus D1) to melanoma development.

Finally, following the classification proposed by Liu et al,[5] melanomas were classified as slow-growth (SGMs [<0.10 mm/mo]), intermediate-growth (IGMs [0.10-0.50 mm/mo]), or fast-growth (FGMs [≥0.50 mm/mo]) melanomas. Although dichotomization of the variable at greater than 0.40 mm/mo has been reported to have prognostic implications for survival,[3] we chose to use the former classification because it considers SGMs independently, a subgroup comprising melanomas that largely follow an indolent course.[19]

### SLN STATUS

Pathological study of SLN biopsy results was performed similarly at both centers. At Instituto Valenciano de Oncología, the study begins with macroscopic identification of the SLN and, if necessary, cleaning of perinodal fat. Once identified, the adenopathy sample is placed in 10% formaldehyde for fixation and subsequent embedding in a paraffin block. Serial cross-sections are obtained from the entire paraffin-embedded lymph node every 250 μm. Three cross-sections are obtained at each section, one of which is stained with hematoxylin-eosin, and the others are reserved for immunohistochemical staining with S-100 and HMB-45, which is performed only after verifying that there is no metastasis in the hematoxylin-eosin sections. At Hospital "Virgen de la Victoria," 4 serial cross-sections are obtained, the first 3 for staining with hematoxylin-eosin and the fourth for immunohistochemical staining with HMB-45.

### STATISTICAL ANALYSIS

The variable "response" was SLN positivity. Factors were included as binary variables (age, sex, tumor location, ulceration, Clark level, regression, and tumor-infiltrating lymphocytes) or as categorical variables (Breslow thickness, mitotic index, and GR). Association of the SLN positivity with clinical and histopathological variables was performed using $\chi^2$ test or univariate logistic regression analysis. Based on the Wald method, odds ratios (95% CIs) were calculated for each variable. Forward and backward stepwise multiple logistic regression analysis was performed to identify independent predictors of SLN positivity. Using independent predictors of SLN positivity, a classification and regression tree analysis was performed with a recursive portioning algorithm. In the final tree, each group had at least 10 patients. Kaplan-Meier method was used for analysis of the distributions of DFS and OS. Log-rank test was used for univariate analysis. Multivariate analysis was performed using a forward stepwise Cox proportional hazards model. $P<.05$ was considered significant. The statistical analysis and the classification tree were performed using commercially available software (SPSS version 15.0; SPSS, Inc).

## RESULTS

Of 1315 patients seen for melanoma at both centers during the study periods, 720 had tumors fulfilling the accepted histopathological criteria, gave informed consent, and underwent selective SLN biopsy, among whom the SLN was identified in 698 (96.9%). Of these 698 patients included in the analysis, 355 (50.9%) were women, and 343 (49.1%) were men. Their median age was 53 years (interquartile range, 40-66 years). **Table 1** summarizes the clinical and pathological characteristics among these patients, stratified according to GR.

Fast-growth melanomas were more common in patients older than 65 years ($P=.001$) and in men ($P=.03$) (Table 1). They were more likely to be in an axial location. Fast-growth melanomas were associated with increased Breslow thickness (48.2% were >4.00 mm), ulceration, and mitotic index but with less regression. No association was found with the presence or absence of tumor-infiltrating lymphocytes or with the presence of vascular invasion, microscopic satellitosis, or perineu-



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**Table 1. Clinical and Pathological Characteristics of 698 Patients With Localized Cutaneous Melanoma**

| Variable | Melanoma Growth Rate, mm/mo, No. (%) | | | | *P* Value |
|---|---|---|---|---|---|
| | <0.10 | 0.10-0.50 | >0.50 | Total Patients | |
| Age, y | (n = 158) | (n = 231) | (n = 114) | (n = 503) | |
| ≤65 | 131 (82.9) | 190 (82.3) | 76 (66.7) | **397** (78.9) | .001 |
| >65 | 27 (17.1) | 41 (17.7) | 38 (33.3) | **106** (21.1) | |
| Sex | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Male | 76 (47.8) | 94 (40.5) | 63 (55.3) | **233** (46.1) | .03 |
| Female | 83 (52.2) | 138 (59.5) | 51 (44.7) | **272** (53.9) | |
| Tumor location | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Axial | 97 (61.0) | 143 (61.6) | 82 (71.9) | **322** (63.8) | .11 |
| Extremities | 62 (39.0) | 89 (38.4) | 32 (28.1) | **183** (36.2) | |
| Breslow thickness, mm | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| ≤1.00 | 73 (45.9) | 46 (19.8) | 2 (1.8) | **121** (24.0) | <.001 |
| 1.01-2.00 | 64 (40.3) | 106 (45.7) | 21 (18.4) | **191** (37.8) | |
| 2.01-4.00 | 19 (11.9) | 58 (25.0) | 36 (31.6) | **113** (22.4) | |
| >4.00 | 3 (1.9) | 22 (9.5) | 55 (48.2) | **80** (15.8) | |
| Ulceration | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Present | 135 (84.9) | 168 (72.4) | 60 (52.6) | **363** (71.9) | <.001 |
| Absent | 24 (15.1) | 64 (27.6) | 54 (47.4) | **142** (28.1) | |
| Clark level | (n = 154) | (n = 225) | (n = 109) | (n = 488) | |
| II | 29 (18.8) | 6 (2.7) | 2 (1.8) | **37** (7.6) | <.001 |
| III | 78 (50.6) | 87 (38.7) | 17 (15.6) | **182** (37.3) | |
| IV | 44 (28.6) | 121 (53.8) | 70 (64.2) | **235** (48.2) | |
| V | 3 (1.9) | 11 (4.9) | 20 (18.3) | **34** (7.0) | |
| Regression | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Present | 38 (23.9) | 21 (9.1) | 8 (7.0) | **67** (13.3) | <.001 |
| Absent | 121 (76.1) | 211 (90.9) | 106 (93.0) | **438** (86.7) | |
| Mitotic index[a] | (n = 95) | (n = 162) | (n = 73) | (n = 330) | |
| 0 | 17 (17.9) | 18 (11.1) | 6 (8.2) | **41** (12.4) | <.001 |
| 1-5 | 71 (74.7) | 107 (66.0) | 39 (53.4) | **217** (65.8) | |
| 6-10 | 4 (4.2) | 26 (16.0) | 20 (27.4) | **50** (15.2) | |
| >10 | 3 (3.2) | 11 (6.8) | 8 (11.0) | **22** (6.7) | |
| Tumor-infiltrating lymphocytes | (n = 74) | (n = 131) | (n = 64) | (n = 269) | |
| Absent | 11 (14.9) | 16 (12.2) | 4 (6.3) | **31** (11.5) | .22 |
| Nonbrisk | 22 (29.7) | 39 (29.8) | 28 (43.8) | **89** (33.1) | |
| Brisk | 41 (55.4) | 76 (58.0) | 32 (50.0) | **149** (55.4) | |
| Vascular invasion | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Present | 2 (1.3) | 9 (3.9) | 6 (5.3) | **17** (3.4) | .16 |
| Absent | 157 (98.7) | 223 (96.1) | 108 (94.7) | **488** (96.6) | |
| Microscopic satellitosis | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Present | 4 (2.5) | 8 (3.4) | 1 (0.9) | **13** (2.6) | .40 |
| Absent | 155 (97.5) | 224 (96.6) | 113 (99.1) | **492** (97.4) | |
| Perineural invasion | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Present | 0 | 6 (2.6) | 3 (2.6) | **9** (1.8) | .10 |
| Absent | 159 (100.0) | 226 (97.4) | 111 (97.4) | **496** (98.3) | |
| SLN positivity | (n = 159) | (n = 232) | (n = 114) | (n = 505) | |
| Positive | 13 (8.2) | 46 (19.8) | 43 (37.7) | **102** (20.2) | <.001 |
| Negative | 146 (91.8) | 186 (80.2) | 71 (62.3) | **403** (79.8) | |

Abbreviation: SLN, sentinel lymph node.
[a] Expressed as the number of mitoses per square millimeter.

ral invasion. Results of SLN biopsy revealed the presence of metastasis in more patients having FGMs (37.7%) compared with patients having IGMs (19.8%) or SGMs (8.2%) ($P < .001$).

## SLN STATUS

Univariate analysis showed that the following were associated with SLN metastasis: mitotic index, Breslow thickness, Clark level, the presence of ulceration, the absence of regression, the presence of vascular invasion, the presence of microscopic satellitosis, and GR (**Table 2**). After including these variables in a multivariate logistic regression analysis, only GR, Breslow thickness, and the presence of microscopic satellitosis were independently associated with SLN positivity.

## CLASSIFICATION TREE

The independent variables (GR, Breslow thickness, and the presence of microscopic satellitosis) were used to create a prognostic tree for regional lymph node involvement (**Figure 1**). Breslow thickness was the first factor used to dichotomize the tumors greater than 2.00 mm.



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**Table 2. Univariate and Multivariate Analyses of Predictive Factors for Sentinel Lymph Node Positivity in 693 Patients With Localized Cutaneous Melanoma**

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Independent Variable** | ***P* Value** | **Odds Ratio (95% CI)** | ***P* Value** | **Odds Ratio (95% CI)** |
| Age, y | | | | |
| ≤65 | .60 | 1 [Reference] | . . . | . . . |
| >65 | | 1.1 (0.7-1.7) | | . . . |
| Sex | | | . . . | |
| Female | .60 | 0.9 (0.6-1.3) | . . . | . . . |
| Male | | 1 [Reference] | . . . | . . . |
| Tumor location | | | | |
| Axial | .10 | 1 [Reference] | . . . | . . . |
| Extremities | | 0.7 (0.4-1.5) | . . . | . . . |
| Mitotic index[a] | | | | |
| 0 | . . . | 1 [Reference] | . . . | . . . |
| 1-5 | .30 | 1.6 (0.7-4.8) | . . . | . . . |
| 6-10 | .001 | 5.2 (1.9-13.8) | . . . | . . . |
| >10 | .001 | 6.5 (2.0-20.5) | . . . | . . . |
| Breslow thickness, mm | | | | |
| ≤1.00 | . . . | 1 [Reference] | . . . | 1 [Reference] |
| 1.01-2.00 | .05 | 2.1 (0.9-4.4) | .50 | 1.5 (0.4-6.0) |
| 2.01-4.00 | <.001 | 8.8 (4.3-18.1) | .005 | 6.7 (1.8-25.1) |
| >4.00 | <.001 | 11.1 (5.3-23.5) | .001 | 11.6 (2.9-46.5) |
| Clark level | | | | |
| II or III | <.001 | 1 [Reference] | . . . | . . . |
| IV or V | | 2.7 (1.8-4.0) | . . . | . . . |
| Tumor-infiltrating lymphocytes | | | | |
| Present | .80 | 1 [Reference] | . . . | . . . |
| Absent | | 0.9 (0.6-1.6) | . . . | . . . |
| Ulceration | | | | |
| Present | <.001 | 2.7 (1.8-4.0) | . . . | . . . |
| Absent | | 1 [Reference] | . . . | . . . |
| Regression | | | | |
| Present | .049 | 0.5 (0.3-1.0) | . . . | . . . |
| Absent | | 1 [Reference] | . . . | . . . |
| Vascular invasion | | | | |
| Present | .003 | 3.6 (1.5-8.8) | . . . | . . . |
| Absent | | 1 [Reference] | . . . | . . . |
| Microscopic satellitosis | | | | |
| Present | <.001 | 5.0 (1.9-13.1) | .06 | 4.5 (0.9-21.8) |
| Absent | | 1 [Reference] | | 1 [Reference] |
| Perineural invasion | | | | |
| Present | .22 | 1.9 (0.7-5.7) | . . . | . . . |
| Absent | | 1 [Reference] | . . . | . . . |
| Growth rate, mm/mo | | | | |
| <0.10 | . . . | 1 [Reference] | . . . | 1 [Reference] |
| 0.10-0.50 | .002 | 2.8 (1.5-5.3) | .04 | 3.2 (1.0-10.3) |
| >0.50 | <.001 | 6.8 (3.4-13.5) | .008 | 5.5 (1.6-19.3) |

Abbreviation: Ellipses, not applicable.
[a]Expressed as the number of mitoses per square millimeter.

The thin tumors (≤2.00 mm) were then categorized as those without and with microscopic satellitosis, with rates of regional node involvement of 7.3% and 50.0%, respectively. The thick tumors (>2.00 mm) were categorized according to their GR, with one group of SGMs (regional node involvement rate, 18.2%) and another group of IGMs and FGMs (regional node involvement rates of 35.1% and 41.0%, respectively).

Analysis of whether GR and the presence of microscopic satellitosis remained independent predictive factors for lymph node involvement relative to each category of Breslow thickness (≤1.00, 1.01-2.00, 2.01-4.00, or >4.00 mm) showed no significant differences for any of the variables (data not shown). However, when Breslow thickness was dichotomized at greater than 2.00 mm, the presence of microscopic satellitosis remained an independent predictor for lymph node involvement in melanomas of 2.00 mm or less (**Table 3**). Growth rate remained an independent predictor for melanomas thicker than 2.00 mm.

## DFS AND OS

The median follow-up time was 47 months (range, 1-128 months). Sixty-five patients died, and 122 patients had relapses (uncensored in the Cox proportional hazards



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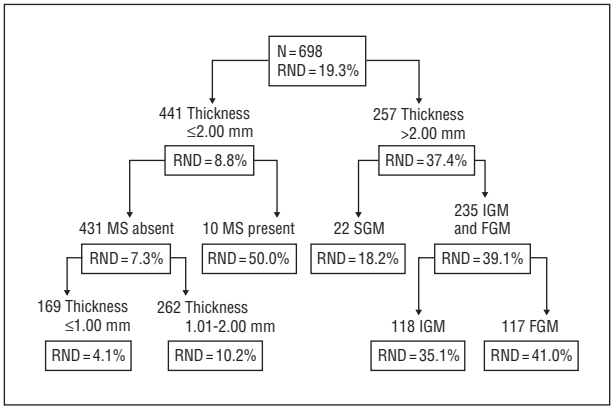


**Figure 1.** Classification tree for the risk of sentinel lymph node involvement in patients with localized cutaneous melanoma. FGM indicates fast-growth melanoma; IGM, intermediate-growth melanoma; MS, microscopic satellitosis; RND, regional node disease; and SGM, slow-growth melanoma.

**Table 3. Predictive Value of Growth Rate and Microscopic Satellitosis for Regional Metastatic Involvement by Breslow Thickness**

| Predictive Factor | Odds Ratio (95% Confidence Interval) | *P* Value |
|---|---|---|
| **Breslow Thickness ≤2.00 mm (26 Events)** | | |
| Growth rate | . . . | . . . |
| Microscopic satellitosis | | |
| Absent | 1 [Reference] | <.001 |
| Present | 17.1 (3.6-81.5) | |
| **Breslow Thickness >2.00 mm (96 Events)** | | |
| Growth rate, mm/mo | | |
| <0.10 | 1 [Reference] | . . . |
| 0.10-0.50 | 2.6 (1.2-5.7) | .01 |
| >0.50 | 5.3 (2.4-11.7) | <.001 |
| Microscopic satellitosis | . . . | . . . |

models for DFS and OS). The most important prognostic factor for DFS and OS was SLN positivity (**Figure 2** and **Figure 3**). Five-year DFS was 84.4% for patients with SLN negativity compared with 50.0% for patients with SLN positivity ($P<.001$). Five-year OS was 92.1% for patients with SLN negativity compared with 73.0% for patients with SLN positivity.

The multivariate Cox proportional hazards model was adjusted for the significant variables in univariate analysis (age, Breslow thickness, ulceration, Clark level, mitotic index, vascular invasion, microscopic satellitosis, and perineural invasion). Sentinel lymph node positivity was the most important prognostic factor for DFS (hazard ratio, 2.13; 95% CI, 1.20-3.76) and for OS (hazard ratio, 3.99; 95% CI, 1.67-9.53).

When the stage of the SLN was not considered, DFS at 5 years was better for SGMs (89.5%) than for IGMs (80.7%) or FGMs (58.3%) ($P<.001$). Similarly, when GR was not considered, OS at 5 years was better for SGMs (98.2%) than for IGMs (92.1%) or FGMs (81.5%) ($P=.001$). These data could not be confirmed in multivariate analysis because they did not reach statistical significance.

## COMMENT

The most relevant finding in this study is that GR of primary cutaneous melanoma, together with Breslow thickness and the presence of microscopic satellitosis, predicts the SLN positivity. The concept of SLN biopsy is based on the assumption that the tumor spreads from the primary tumor first to the SLN and subsequently to the rest of the regional lymph nodes.[20] Although there is insufficient evidence to assert that complete regional lymphadenectomy after determination of SLN positivity is superior in terms of survival compared with lymph node dissection after the appearance of clinically palpable nodules,[21] the SLN positivity is considered the principal prognostic factor for DFS and OS.[7]

Therefore, it is useful to search for new factors that might help predict the SLN positivity. Breslow thickness has been the most important independent predictive factor for SLN positivity in the most important studies[11-13,22-30] to date (**Table 4**). Mitotic index, the presence of ulceration, and the absence of tumor-infiltrating lymphocytes are other factors that are frequently related to SLN positivity.

In our study, the presence of microscopic satellitosis proved to be an independent predictive factor for SLN positivity, as it was in a study by Mocellin et al.[25] The term *microscopic satellites* was first used by Day et al,[31] and its predictive value has been demonstrated in various studies. The presence of microscopic satellitosis is classified as N2c (stage III) in the American Joint Committee on Cancer classification.[7] Its inclusion in this category is in part because it has been associated with survival rates similar to those in patients with macroscopic satellitosis.[32-34] Microsatellitosis is considered an early stage of lymphatic metastasis; therefore, its presence is related to SLN positivity.

Growth rate has been shown to be an independent predictive factor for SLN positivity. Despite that GR is a recent concept, Clark et al[1] in 1969 associated different GRs of melanoma with the various histological types. More recently, differing conclusions based on epidemiological trends led Lipsker et al[35] to suggest a new classification of melanoma predicated primarily on its association with sun exposure, *BRAF* expression, and GR. Liu et al[5] grouped these different types of melanoma according to their GRs. Therefore, type 1 consists of melanomas with a stable incidence over time and a random distribution on the body, suggesting no association with sun exposure; their GRs exceed 0.50 mm/mo. In contrast, type 2 and type 3 refer to melanomas associated with sun exposure, which have shown an epidemiological increase in recent years. Type 2 is associated more with intermittent sun exposure and *BRAF* expression,[36] having GRs between 0.10 and 0.50 mm/mo. Type 3, consisting of melanomas associated with continuous sun exposure and without *BRAF* expression, have GRs of less than 0.10 mm/mo. Investigators have observed increased incidences even for thick melanomas, which shows the biological complexity of this type of tumor.[37]

Martorell-Calatayud et al[6] recently showed that FGMs seem to demonstrate 2 different clinical profiles relative



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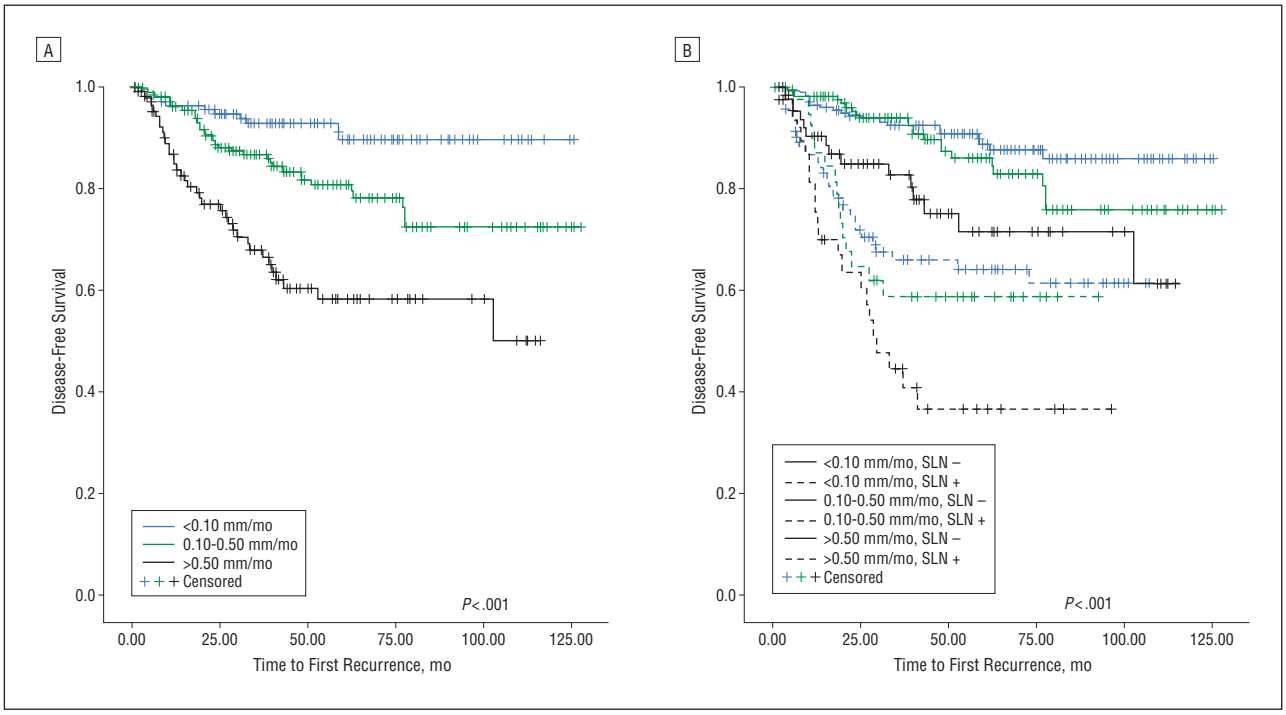


**Figure 2.** Kaplan-Meier disease-free survival. A, Among patients with slow-growth melanomas (<0.10 mm/mo), intermediate-growth melanomas (0.10-0.50 mm/mo), and fast-growth melanomas (>0.50 mm/mo). B, By sentinel lymph node (SLN) positivity or negativity. Disease-free survival was better in patients with slow-growth melanomas. When patients are categorized by SLN status, disease-free survival benefit is associated with growth rate. RND indicates regional node disease. *P* values indicate the differences in disease-free survival between the different growth rates by survival analysis.

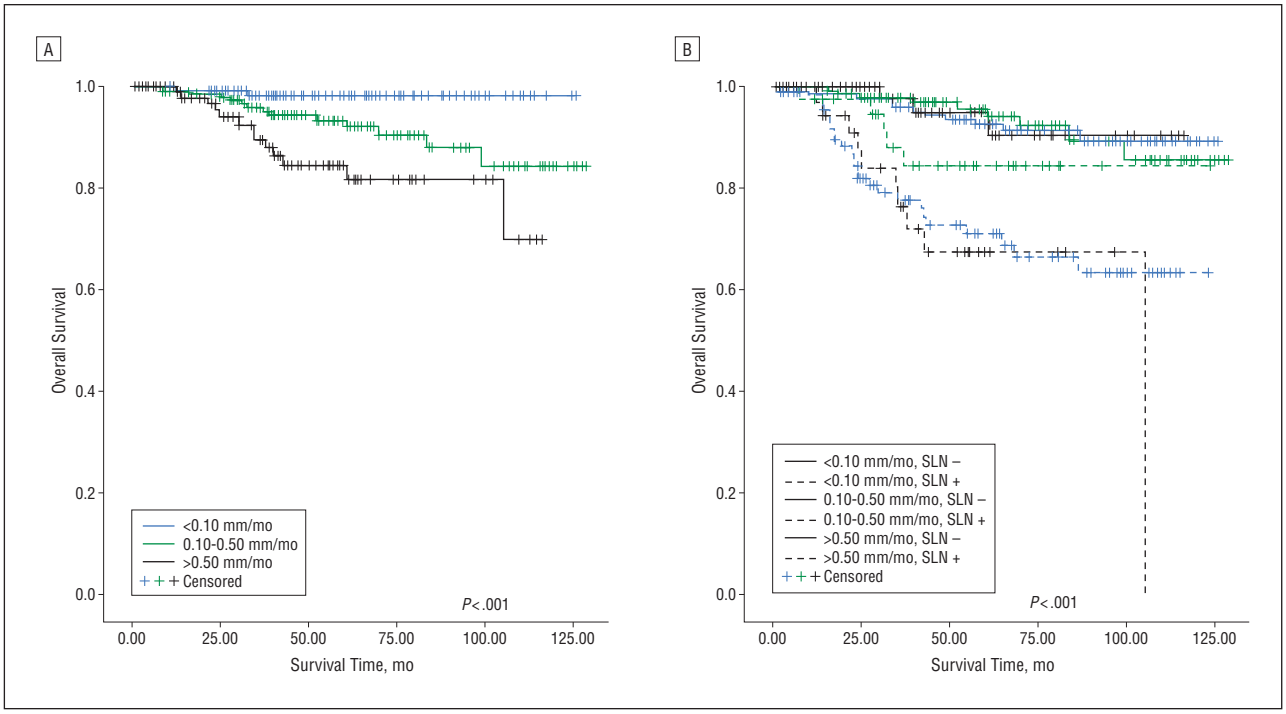


**Figure 3.** Kaplan-Meier overall survival. A, Among patients with slow-growth melanomas (<0.10 mm/mo), intermediate-growth melanomas (0.10-0.50 mm/mo), and fast-growth melanomas (>0.50 mm/mo). B, By sentinel lymph node (SLN) positivity or negativity. Overall survival was better in patients with slow-growth melanomas. When patients are categorized by SLN status, overall survival benefit is not associated with growth rate. *P* values indicate the differences in disease-free survival between the different growth rates by survival analysis.

to sun exposure. These include those observed at sites that receive chronic sun exposure and those observed in areas that rarely receive sun exposure.

Notably, our classification tree showed that GR is a prognostic factor only for lesions thicker than 2.00 mm and demonstrated that important differences exist, par-



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**Table 4. Most Relevant Studies Assessing Predictive Factors for Sentinel Lymph Node (SLN) Positivity**

| Source | No. of Patients | Variables Associated With SLN Positivity |
|---|---|---|
| Sondak et al,[22] 2004 | 419 | Breslow thickness, age, mitotic index |
| Wong et al,[23] 2005 | 4087 | Breslow thickness, ulceration, age, tumor location, Clark level |
| Kruper et al,[12] 2006 | 682 | Breslow thickness, mitotic index, tumor-infiltrating lymphocytes |
| Karakousis et al,[24] 2006[a] | 882 | Mitotic index, ulceration, sex, growth phase |
| Mocellin et al,[25] 2006 | 234 | Breslow thickness, mitotic index, microscopic satellitosis |
| Taylor et al,[11] 2007 | 875 | Breslow thickness, ulceration, sex, tumor-infiltrating lymphocytes |
| Paek et al,[13] 2007 | 910 | Breslow thickness, mitotic index, age, vascular invasion, tumor location |
| Mandalà et al,[26] 2009 | 394 | Breslow thickness, tumor location, tumor-infiltrating lymphocytes |
| Kunte et al,[27] 2010 | 854 | Breslow thickness, histological type |
| Mays et al,[28] 2010[b] | 1110 | Breslow thickness, tumor-infiltrating lymphocytes, age |
| Mitra et al,[29] 2010 | 561 | Breslow thickness, mitotic index, tumor-infiltrating lymphocytes, tumor location |
| Roach et al,[30] 2010 | 551 | Breslow thickness, ulceration |
| Present study | 698 | Breslow thickness, growth rate, microscopic satellitosis |

[a] The study included only melanomas with Breslow thickness of less than 1.00 mm.
[b] The study included only melanomas with Breslow thickness between 1.00 and 2.00 mm.

ticularly in SGMs compared with IGMs and FGMs. This may be explained by the greater number of events in thick melanomas, highlighting the biological differences of melanomas with different GRs.

The primary limitation of GR is that it is based on information provided by the patient and is subject to determinants such as tumor location and age, sex, and psychological state of the patient.[2] Nevertheless, bias relative to evolution time as reported by patients seemed minimal in a small study[38] that reevaluated the responses of patients a few months later. Furthermore, from a histopathological point of view, GR correlated significantly with mitotic index and with markers of cell cycle progression (Ki-67) and mitosis (phosphorylated histone H3).[39]

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