An observational study regarding the rate of growth in vertical and radial growth phase superficial spreading melanomas

ROBERTO BETTI[1], ELENA AGAPE[1], RAFFAELLA VERGANI[1], LAURA MONEGHINI[2] and AMILCARE CERRI[1]

[1]Dermatology Clinic; [2]Division of Pathology, Department of Health Sciences, University of Milan, Hospital San Paolo, 20142 Milan, Italy

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Abstract. The natural history of superficial spreading melanomas (SSMs) involves the progression from a radial growth phase (RGP) to a vertical growth phase (VGP). Currently, a patient's history represents the only method to estimate the rate of tumor growth. The present study aimed to verify whether the estimated rate of growth (ROG) of SSMs with a RGP or VGP exhibited any differences, and to evaluate the possible implications for the most important prognostic determinants. ROG was quantified as the ratio between Breslow's thickness in millimeters (mm) and the time of tumor growth in months, defined as the time between the date that the patient had first noticed the lesion in which melanoma subsequently developed and the date on which the patient first felt this lesion changed. A total of 105 patients (58 male and 47 female) were studied. Of these, 66 had VGP-SSMs, whilst 39 had RGP-only SSMs (RGP-SSMs). No significant differences in age and gender were observed between these groups. The mean Breslow's thickness in patients with VGP-SSMs was significantly greater than in patients with RGP-SSMs (0.78±0.68 vs. 0.48±0.22 mm, P=0.0096). Similarly, the ROG was observed to be higher in VGP-SSM vs. RGP-SSM patients (0.13±0.16 vs. 0.065±0.09 mm/month, P=0.0244). In patients with VGP-SSMs, Breslow's thickness and ROG were significantly higher for tumors with a mitotic rate of ≥1 mitosis/mm^2 compared with those with <1 mitosis/mm^2 (1.15±0.96 vs. 0.56±0.30 mm, P=0.0005; and 0.188±0.20 vs. 0.09±0.12 mm/month, P=0.0228, respectively). According to these results, two subsets of SSMs exist: The first is characterized by the presence of mitosis and a higher ROG, while the second exhibits a more indolent behavior and is characterized by an RGP only. Given the differences in the Breslow's thickness and ROG, clinicians must be aware of the possible diagnostic delay in these subsets of melanoma that, differently from true nodular melanomas, generally fulfill the classical ABCD clinical criteria.

Correspondence to: Dr Roberto Betti, Dermatology Clinic, Department of Health Sciences, University of Milan, Hospital San Paolo, 8 Via di Rudinì, 20142 Milan, Italy
E-mail: berbet@alice.it

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Introduction

Superficial spreading melanoma (SSM) and nodular melanoma (NM) exhibit different growth patterns, being characterized by slower and faster growth, respectively. The radial growth phase (RGP), which is present in SSM and absent in NM, is of paramount importance in the classification of melanoma (1-3). The rapid growth of primary melanomas is associated with aggressive features and a negative effect on prognosis (4). According to the linear model of progression, malignant melanocytes in SSM spread radially prior to invading vertically. Clark *et al* (1) designated this invasion pattern the vertical growth phase (VGP), and defined it as the focal formation of a dermal nodule within the RGP. Melanomas with a VGP do not necessarily indicate NM.

Patient interviews are a useful source of information about the growth phase of the tumor (5). The rate of growth (ROG), which is defined as the ratio between Breslow's thickness in millimetres and the duration of tumor growth in months, currently represents the only method to measure the growth of a tumor over time, and has been used as an index of aggressiveness and even as a prognostic marker in cases of melanoma (4-6). The aim of the present study was to evaluate the ROG of RGP- and VGP-SSMs in order to assess their differences and their impact on the most important prognostic determinants (7).

Patients and methods

Patients. Consecutive patients with cutaneous primary melanomas treated at the Department of Dermatology of San Paolo Hospital (Milan, Italy) between 1st January 2011 and 30th September 2014 were included in the present study. The demographic and clinical characteristics of each patient were recorded, including age, gender and site of presentation of the tumor. Each patient was asked to recall two dates: T1, the date when they had first noticed a lesion at the location where melanoma subsequently developed; and T2, the date when they first felt that the lesion changed and/or became suspicious. All

Table I. Breslow's thickness and ROG in patients with VGP-SSM and RGP-SSM.

A, Melanoma growth subtypes

Variable	Patients (n)	Breslow's thickness (mm)	ROG (mm/month)
VGP-SSM	66	0.78±0.68	0.13±0.16
RGP-SSM	39	0.48±022	0.065±0.09
P-value		0.0096	0.0244

B, VGP-SSMs with mitoses

Variable	Patients (n)	Breslow's thickness (mm)	ROG (mm/month)
VGP-SSM, ≥1 mitosis/mm^2	24	1.15±0.96	0.188±0.20
VGP-SSM, <1 mitosis/mm^2	42	0.56±0.30	0.09±0.12
P-value		0.0005	0.0228

ROG, rate of growth (millimeters of Breslow/number of months); VGP-SSM, superficial spreading melanoma with a vertical growth phase; RGP-SSM, superficial spreading melanoma with a radial growth phase only.

suspected cases were treated by surgical excision within one week from the physician's observation. The inclusion criteria for analysis were complete surgical excision and a histologically confirmed diagnosis of primary SSM melanoma. The following exclusion criteria were also applied: Histological diagnosis of NM, lentigo maligna, lentigo maligna melanoma or *in situ* melanoma; or inability to provide precise information regarding ROG.

Evaluation of specimens. A dermatopathologist evaluated all specimens and reported the histological subtype, Breslow's thickness (categorized as <1 or ≥1 mm), ulceration (present or absent) and mitotic rate (<1 or ≥1 mitosis/mm^2) based on the hot-spot technique (7). The VGP was defined as the presence of a cell nest in the dermis larger than the junctional nests and composed of tumor cells cytologically different from those in the junctional component. SSMs were thus divided into groups: Those that exhibited a VGP (VGP-SSMs) and those that did not (RGP-SSMs).

Quantification of the kinetics of the visible growth was performed using a previously described method (5). According to this method, the ROG is defined as the ratio between Breslow's thickness in millimetres (mm) and the duration of tumor growth in months (T2-T1); this may be used as a surrogate value for melanoma kinetics. Patients with *de novo* melanomas and those with melanomas from a pre-existing nevus were distinguished according to previously suggested criteria: melanomas were considered to be *de novo* if the T1-T2 interval was ≤5 years, and from a pre-existing nevus when this interval was >5 years (5).

Statistical analysis. The VGP-SSM and RGP-SSM groups were compared with regard to differences in ROG and Breslow's thickness using the Student's *t*-test. Statistical analyses were performed using SPSS software for Windows (version 15.0; SPSS, Inc., Chicago, IL, USA) and P<0.05 was considered to indicate a statistically significant difference.

Results

Of the 169 patients contacted by the investigators, 64 (37.8%) declined to participate or provided answers that were judged to be poorly reliable. The remaining 105 patients (58 male and 47 female) were hence enrolled in the study. Of these, 66 had VGP-SSM [mean age (± SD), 59.61±16.89 years] and 39 had RGP-SSM (mean age, 62.62±16.38 years; P=0.17 vs. VGP-SSM group). No significant differences in gender or age between the two groups were identified. Table IA reports the results obtained from the two groups of patients with melanomas with regard to Breslow's thickness and ROG (mm/month), including P-values. Table IB shows the results for the same parameters in patients with VGP-SSM only, comparing cases with mitotic rates of <1 or ≥1 mitosis/mm^2.

Ulceration was observed in only one patient with VGP-SSM. The mean Breslow's thickness in patients with VGP-SSMs was significantly greater compared with patients with RGP-SSMs (0.78±0.68 vs. 0.48±022 mm, respectively; P=0.0096). Similarly, the ROG differed significantly between VGP- and RGP-SSM patients (0.13±0.16 vs. 0.065±0.09 mm/month, respectively; P=0.0244). Of the cases of VGP-SSM, 24 had a mitotic rate of ≥1/mm^2, whilst only one RGP-SSM case had a mitotic rate ≥1/mm^2. In patients with VGP-SSMs, Breslow's thickness was significantly greater when the mitotic rate was high (≥1/mm^2) compared to the low group (1.15±0.96 vs. 0.56±0.30 mm, respectively; P=0.0005). The ROG differences were also more evident between VGP-SSMs with a high mitotic rate and VGP-SSMs with a low mitotic rate (0.188±0.20 vs. 0.09±0.12 mm/month, respectively; P=0.0228).

Discussion

A previously published study emphasized the importance of the presence of two populations of cells in melanoma, which were termed slow-growing and fast-growing cells (8). These

different populations of cells reflect the common observation in clinical practice that different types of melanomas grow at different rates.

The method described by Grob *et al* (5), which uses the thickness of the lesion and its period of evolution as provided by the patient, is the only possible tool to estimate the speed of grow of a melanoma. Applying this method, Liu *et al* (4) observed that fast growing melanomas often conform to the category of thick melanomas, predominantly observed in the elderly. From a clinical perspective, these melanomas are symmetrical, not fulfilling the classical 'Asymmetry, Border, Color, Diameter' (ABCD) rule (9), with atypical clinical presentation (i.e., amelanotic and nodular). However, many types of melanoma do not fit in these categories (10,11). According to the progression model provided for many types of melanoma, following a phase of radial growth, the loss of cell cycle regulation causes the ability to spread into the dermis and the formation of a dermal nodule. These melanomas were termed VGP melanomas by Clark *et al* (1). Many of these melanomas belong to the superficial spreading type. The scheme of melanoma progression suggested by Clark *et al* in 1989 (2), was externally validated (12,13), and it was demonstrated that growth phase and dermal mitosis are independent prognostic factors. Evidence suggests that ~45% of melanoma cases are entirely in an RGP, 10% have a VGP alone (thus classified as nodular or d'emblèe types, which are often amelanotic) (14), and the remaining 45% of cases present with a VGP tumor nodule surrounded by an RGP, in which they presumably arose (15).

The present study was conducted with the aim of defining the ROG of these melanoma subsets. The results obtained indicated that in the current sample of SSMs classically fulfilling the clinical ABCD diagnostic criteria, two tumor subtypes were present: A faster growth group with a higher ROG, and a more indolent type group (Table I). This result may have relevance with regard to the consequences of diagnostic delay and prognosis. Previously, the calculated ROG values of SSMs as a whole were found to vary from 0.05 to 0.12 mm/month (16-18); however, the heterogeneity of these lesions (RGP-SSMs and VGP-SSMs) was not considered.

If patients do receive a correct diagnosis, this will delay surgical excision and result in a worse prognosis; in our experience, the rate of growth of RGP-SSM is approximately double that of a VGP-SSM (0.065 vs. 0.13 mm/month). In a screening project for suspected nevi, there is a short time in which to suspect, determine or correct a diagnosis, even for SSMs if they escape from their RGP into a tumorigenic phase. Liu *et al* (4) observed that the ROG increases with increasing tumor thickness and mitotic rate, and that a correlation was present between ROG and mitotic rate; however, the assessment of clinical features of these melanomas fulfilled the clinical criteria for a nodular subtype (4); by contrast, a slow ROG was associated with melanomas appearing to be of an SSM subtype. Although the ROG of the SSMs reported in the present study is not as high as that observed by Liu *et al* (4) for nodular melanomas (0.4-0.5 mm/month), it is equally relevant due to the implications of a possible invasive melanoma on prognosis.

The presence of mitosis has been demonstrated to be an independent factor associated with prognosis, and mitosis may be present in SSMs with a VGP (2,11). In the present study, SSMs with mitotic frequency of $\geq 1/mm^2$ were observed to have a higher Breslow's thickness and ROG compared with their counterparts without mitosis (Table IB). Thus, these results indicate that two subsets of SSM exist; the first characterized by the presence of mitosis and higher ROG, the second with a more indolent behavior and characterized by an RGP only.

Gimotty *et al* (19), in a study of Ki-67 expression (a marker of cellular proliferation), revealed that the proliferation of melanoma increases with the onset of tumorigenic VGP, even in thin invasive cutaneous melanomas, and not only in true nodular melanomas. The present results on the heterogeneity of VGP-SSMs indicate that attention must be paid to the subgroup with a high ROG and mitosis. The diagnostic delay of RGP-SSM versus VGP-SSM melanoma, with the higher rate of growth of the latter, may dramatically change the prognosis.

The predominant limitation of the current study was the anamnestic criteria used for the evaluation of the ROG, which remains the only method currently available to assess the growth speed of a melanoma. The ROG also assumes that tumor growth is constant and linear, and ROG cannot describe changing growth rate over time. Another limitation regards the number of patients and the high percentage of data that were lost (37.8%). In summary, the current study provides descriptive data on the spectrum of SSMs with different ROGs and mitotic frequencies. Certain of these subgroups are associated with a relatively fast growth rate, which is lower than that of true nodular melanomas, but greater than that of SSMs with an RGP only and without the presence of mitosis. Given the differences in Breslow's thickness, clinicians must be aware of the possible diagnostic delay in the subset of melanomas that generally fulfill the classical ABCD clinical criteria.

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