STUDY

Rate of Growth in Melanomas

Characteristics and Associations of Rapidly Growing Melanomas

Wendy Liu, MBChB, PhD; John P. Dowling, MBBS; William K. Murray, MBBS; Grant A. McArthur, MBBS, PhD; John F. Thompson, MBBS, MD; Rory Wolfe, BSc, PhD; John W. Kelly, MBBS, MD

Objectives: To investigate the spectrum of growth rates in melanomas and to identify clinical associations of rapidly growing melanomas.

Design: Clinical interview, skin examination, and pathology review.

Setting: Three tertiary melanoma referral centers and 2 private dermatology practices.

Patients: A total of 404 consecutive patients with invasive primary cutaneous melanomas.

Main Outcome Measure: A surrogate for rate of growth in primary invasive melanoma was calculated as the ratio of Breslow thickness to time to melanoma development based on a previously reported assessment tool.

Results: One third of the melanomas grew 0.5 mm per month or more. The median monthly growth rate was 0.12 mm for superficial spreading melanomas, 0.13 mm for lentigo maligna melanomas, and 0.49 mm for nodular melanomas. Rapid tumor growth was associated with tumor thickness (≤1 mm, geometric mean ratio [GMR] = 1.0; 1.01-4 mm, GMR = 3.9; and >4 mm, GMR = 12.1) and mitotic rate (<1/mm^2, GMR = 1.0; 1-4/mm^2, GMR = 2.9; 5-10/mm^2, GMR = 6.1; and >10/mm^2, GMR = 9.7). Rapid tumor growth occurred more often in males (GMR = 1.7), elderly individuals (≥70 years old, GMR = 2.8), and patients with fewer melanocytic nevi (n<50, GMR = 2.0) and fewer freckles (GMR = 2.5). Rapidly growing melanomas were more often symmetrical (GMR = 2.5), elevated (GMR = 1.4), amelanotic (GMR = 1.7), regular in border (GMR = 2.5), and symptomatic (GMR = 1.7).

Conclusions: Rapid growth of primary cutaneous melanomas is associated with aggressive histologic features and atypical clinical features. It occurs more frequently in elderly men and individuals with fewer nevi and fewer freckles.

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Author Affiliations: Victorian Melanoma Service, The Alfred Hospital, Melbourne (Drs Liu, Dowling, and Kelly); Peter MacCallum Cancer Center, East Melbourne (Drs Liu, Murray, and McArthur); Department of Medicine, St Vincent's Hospital, The University of Melbourne, Melbourne (Drs Liu and McArthur); Sydney Melanoma Unit, Royal Prince Alfred Hospital and The University of Sydney, Sydney (Dr Thompson); and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne (Dr Wolfe), Australia.

RATE OF GROWTH (ROG) HAS been proposed as an important biological feature of malignant tumors. Clark et al,[1] who first described the differential ROG of various melanomas, suggested that ROG is greatest for nodular melanomas (NMs), followed by superficial spreading melanomas (SSMs), and least for lentigo maligna melanomas (LMMs). Since then, many attempts have been made to assess the rate of tumor proliferation using various biological markers, including mitotic rate,[2] ulceration,[3] Ki67,[4] cyclins,[5] and cyclin-dependent kinase inhibitors such as p16[6] and p27.[7]

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Despite these attempts, little information is available on the ROG of primary cutaneous melanomas. The major barrier to a study of primary melanoma ROG is the inability to prospectively measure the ROG. Grob et al[8] demonstrated that based on patient recall, melanoma ROG was an independent prognostic marker predicting relapse at 1 year and relapse-free survival. These researchers, in a related study,[9] concluded that aggressive tumor growth is responsible for the development of thick melanomas rather than delay in diagnosis.

There are currently few data to indicate the time available to detect and treat melanoma before it develops a significant likelihood of metastasis. Anecdotal experience suggests that there is a form of rapidly growing melanoma (**Figure 1**), but little is known about its frequency, ROG, or associations. An understanding of these factors would provide knowledge of the duration of the opportunity for early detection, the penalty in survival for delays in detection, and the groups more likely to develop rapidly growing melanomas. The aims of this study were to investigate the spectrum of ROGs in melanomas and to identify clinical associations of rapidly growing melanomas.

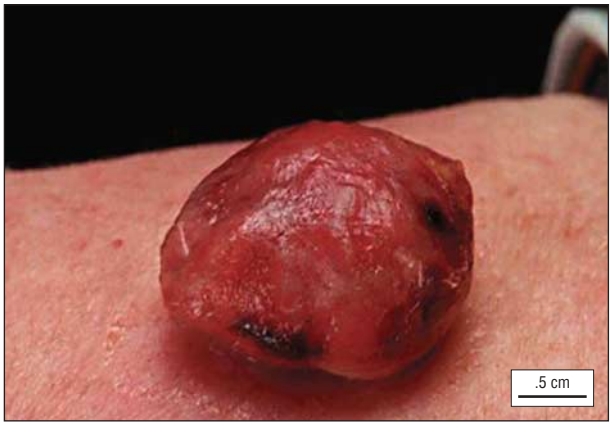

Figure 1. An example of a rapidly growing melanoma in a 57-year-old man that reached 15 mm in thickness in 8 weeks.

METHODS

PARTICIPATING CENTERS AND PATIENTS

Three tertiary melanoma referral centers participated: the Victorian Melanoma Service, the Peter MacCallum Cancer Center, and the Sydney Melanoma Unit. Two private dermatology practices in Melbourne with expertise in melanoma also contributed patients. Ethics approvals were obtained from the ethics committees of The Alfred Hospital, the Peter MacCallum Cancer Center, and the Royal Prince Alfred Hospital. Consecutive patients who attended the participating centers and fulfilled the following criteria were enrolled: (1) newly diagnosed primary cutaneous melanoma, (2) histologic slides available for review, (3) age at least 16 years, and (4) provision of informed consent.

PHYSICAL AND PATHOLOGIC EXAMINATIONS

Examination of the skin was performed by 1 of the 2 consultant dermatologists (J.W.K. and Martin Haskett, FACD) only on patients attending the Victorian Melanoma Service. Skin phenotypic features examined were total number of melanocytic nevi (<50 or ≥ 50), number of clinically dysplastic nevi (0, 1-4, or ≥ 5), presence of solar keratoses (yes or no), and number of freckles and solar lentigines (few or many). A clinically dysplastic nevus was defined as a melanocytic nevus that fulfilled 3 of the following 5 criteria: (1) ill-defined border, (2) irregularly distributed pigmentation, (3) diameter larger than or equal to 5 mm, (4) irregular border, and (5) background erythema.[10]

The melanoma histologic findings were reviewed by 1 of the dermatopathologists based at each participating tertiary referral center, and the following features were assessed: Breslow thickness, Clark level, ulceration, mitoses per square millimeter, and tumor subtype. Tumor subtypes were defined according to the classification system of Clark et al.[1]

PATIENT INTERVIEW

Patients were interviewed by a medically trained investigator (W.L.) either face to face or via telephone. The information sought included (1) demographic factors, such as age, sex, educational background, living arrangement, place of residence, previous attendance for skin examination, a history of skin lesion removal, and frequency of visiting a physician; (2) risk factors for skin cancer, such as a history of melanoma (yes or no), a history of nonmelanoma skin cancer (yes or no), a family history of melanoma (yes or no), a history of solar keratoses (yes or no), skin phototype (type I-VI[11]), eye color (light or dark), a history of blistering sunburns (yes or no), estimated occupational sun exposure (low or high), estimated recreational sun exposure (low or high), and estimated childhood sun exposure (low or high); (3) presenting tumor characteristics, such as pigmentation, shape, symmetry, border, texture, and symptoms (bleeding, itching, and change in sensation); (4) mode of detection (physician vs patient or family); and (5) visibility of the melanoma to the patient.

Tumor pigmentation was assessed by means of (1) patient-determined amelanosis, defined as a predominantly pink, red, or white color in a melanoma as reported by the patient, and (2) pathologically determined amelanosis, defined as the lack of pigment in a melanoma based on macroscopic examination of the excised tissue by a laboratory scientist; such information was extracted from the pathology report. This assessment was performed as part of routine specimen processing without the knowledge that the specimen was study material.

A series of questions addressed the validity and accuracy of the answers provided by patients on a scale of 1 to 10. Patients were asked to assess the level of accuracy in their answers regarding melanoma ROG (the patient's self-reported accuracy score). The interviewing investigator (W.L.) also rated her perception of the patient's accuracy in his or her answers related to ROG (the investigator-reported accuracy score). Patients were also asked to rate their general level of anxiety about health issues.

Patients and their family members were interviewed as soon as possible after diagnosis. Whenever possible, interviews were conducted with both the patient and his or her family present. Answers for each question were based on the consensus from both parties involved in the process of melanoma detection.

INDEX TO ESTIMATE TRUE TUMOR ROG

The melanoma ROG index was calculated based on information provided by the patients and their family using a previously described assessment tool.[8] All the patients and their families were asked to recall 2 dates: the time they first noticed a lesion on the skin surface from which the melanoma later developed (D1) and the time they first noticed that the lesion had changed or became suspicious (D2). The time of excision (D3) was extracted from the pathology report. We attempted to distinguish most of the melanomas arising from a preexisting nevus from most of those beginning de novo by using different times to indicate the onset of melanoma growth. A lesion was considered to be malignant from the onset (a de novo melanoma) if the interval between D1 and D3 was 5 years or less. When the interval between D1 and D3 was more than 5 years, D2 was then considered to be an indicator of the onset of malignancy within a preexisting benign lesion. The time that a melanoma had been developing was estimated as the interval between D1 and D3 in the case of a de novo melanoma. In the case of a melanoma arising from a preexisting benign lesion, the time for a melanoma to develop was estimated as the interval between D2 and D3. The ROG of a 3-dimensional tumor can be defined as an increase in tumor volume per unit of time. Because there is no accepted method for assessing tumor volume, Breslow thickness was used as a surrogate. The ratio between Breslow thickness and the time for a melanoma to develop was used as the index that is an estimate of true ROG, based on a previously used method.[8]

STATISTICAL ANALYSES

Variables that followed approximately symmetric distributions are summarized as mean (SD). Variables that followed

skewed distributions are summarized as median (range or interquartile range [25th-75th percentile]). The ROG followed a heavily skewed distribution but was normalized after a log transformation. Geometric means (GMs), similar in value to the medians, are used to summarize ROG on the original scale of measurement (millimeters per month) and to provide a link with statistical analyses on the log scale. Linear regression models were used to analyze log ROG, and the model coefficients could be interpreted as ratios of GMs between groups of melanoma defined by characteristics such as patient sex. All the variables that had a significant (defined as $P<.05$) univariate association with ROG were entered into a stepwise selection procedure based on likelihood ratio tests with terms removed if $P>.10$ and terms included again if $P<.05$ to construct a multivariate linear regression for log (ROG).

Owing to the different kinds of variables analyzed and the close interrelationships between some of these variables, 3 multivariate linear regression models were constructed relating to tumor characteristics, host characteristics, and clinical features to elucidate the independent relationships between each of these and ROG.

RESULTS

Of the 569 patients contacted by the investigators, 22 (4%) refused to participate. The median tumor thickness of those who refused to participate was 1.00 mm, similar to the median tumor thickness of those who agreed to participate (1.14 mm). Between May 1, 2003, and September 30, 2004, 547 patients enrolled in the study. Excluded from analyses were 94 patients with in situ melanoma, for which ROG cannot be calculated; 2 patients with poor-quality melanoma specimens, in which tumor thickness could not be accurately assessed; and 47 patients who could not recall D1 or D2. Of 404 patients included in the final analyses, 222 were male (55%) and 182 patients were female (45%). The mean (SD) age of the patients was 54.2 (17) years (range, 16-91 years). The overall median tumor thickness was 1.3 mm.

Most patients (75.4%) were interviewed within 90 days of diagnosis. The median interval between melanoma excision and interview was 52 days (mean, 64.5 days; range, 0-336 days). There was no correlation between the interview delay and ROG ($P=.75$). Overall, 30% of the study patients were interviewed together with a family member or a friend.

VALIDATION OF ROG

To explore the validity of the method of assessing ROG, we analyzed the correlation of ROG (a subjective measure of tumor growth) with tumor mitotic rate (an objective measure of tumor proliferation). The ROG correlated moderately to strongly with mitotic rate (Spearman rank correlation coefficient = 0.46; $P<.001$) (**Figure 2**).

To analyze whether inaccuracies in patients' answers could have contributed to variations in ROG, we analyzed the correlation of accuracy scores with ROG. No correlation was found between patients' self-reported accuracy scores and ROG (Spearman rank correlation coefficient = –0.008; $P=.88$), nor was any correlation found between investigator-reported accuracy scores and ROG (Spearman rank correlation coefficient = –0.03; $P=.59$).

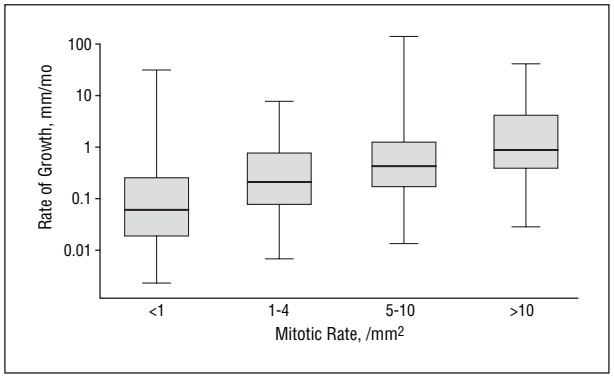

Figure 2. Box plots of the relationship between mitotic rate (an objective measure of tumor proliferation) and clinical rate of growth (a subjective measure of tumor growth). Error bars represent the minimum and maximum values; horizontal lines within boxes, the 25th percentile, median, and 75th percentile values.

Table 1. Growth Rates in Melanoma

Rate of Growth, mm/mo	Melanomas, No. (%) (n = 404)
<0.10	141 (35)
0.10-0.19	53 (13)
0.20-0.49	83 (21)
0.50-0.99	54 (13)
1.00-2.00	33 (8)
>2.00	40 (10)

DESCRIPTION OF ROG

Approximately a third of all melanomas (n = 141) grew less than 0.10 mm per month, a third (n = 136) grew 0.10 to 0.49 mm per month, and a third (n = 127) grew 0.50 mm per month or more (**Table 1**). The spectrum of melanoma ROGs, as reflected by the interquartile range, ranges from 0.03 mm per month in a slowly growing LMM to 1.48 mm per month in a rapidly growing NM (**Table 2**). The NM grew faster than melanomas with an associated radial growth phase, such as SSMs and LMMs. The median monthly ROG was 0.12 mm in SSMs, 0.13 mm in LMMs, and 0.49 mm in NMs. The ROGs in acral lentiginous melanomas and desmoplastic melanomas were higher still, but the sample sizes were small.

High ROG was associated with indicators of poor prognosis, such as high tumor thickness, high mitotic rate, and ulceration. The median monthly ROG was higher in elderly patients (≥70 years, 0.52 mm; <70 years, 0.17 mm) and in males (males, 0.28 mm; females, 0.13 mm).

TUMOR CHARACTERISTICS ASSOCIATED WITH ROG

Univariate analyses of the tumor characteristic associations with ROG showed that the GM of the melanoma ROG was higher in NMs than in SSMs (**Table 3**). The GM of the ROG increased with increasing tumor thickness and mitotic rate. A higher GM of the ROG was also associated with the presence of ulceration and amelanosis as determined by a laboratory scientist based on the

Table 2. Spectrum of ROGs in Melanoma

Group	Melanomas, No. (n = 404)*	ROG, Median (IQR), mm/mo
Tumor subtype		
SSM	250	0.12 (0.04-0.48)
NM	84	0.49 (0.17-1.48)
LMM	41	0.13 (0.03-0.44)
ALM	11	0.40 (0.20-1.00)
DM	10	1.19 (0.35-1.86)
Other	7	0.25 (0.12-0.36)
Tumor thickness, mm		
≤1	170	0.06 (0.02-0.22)
1.01-4	168	0.27 (0.09-0.75)
>4	66	0.73 (0.38-2.00)
Ulceration		
Yes	80	0.52 (0.22-1.36)
No	321	0.16 (0.04-0.50)
Mitotic rate, /mm^2		
<1	145	0.06 (0.02-0.25)
1-4	148	0.20 (0.07-0.73)
5-10	55	0.42 (0.17-1.08)
>10	52	0.67 (0.29-1.66)
Age, y		
<70	322	0.17 (0.04-0.50)
≥70	82	0.52 (0.16-1.65)
Sex		
M	222	0.28 (0.07-0.75)
F	182	0.13 (0.04-0.48)

Abbreviations: ALM, acral lentiginous melanoma; DM, desmoplastic melanoma; IQR, interquartile range (25th-75th percentile); LMM, lentigo maligna melanoma; NM, nodular melanoma; ROG, rate of growth; SSM, superficial spreading melanoma.

*Variation in total numbers of patients in each category is due to some data being unobtainable.

macroscopic appearance. Multivariate analyses showed that greater tumor thickness and higher mitotic rate were independently associated with high ROG ($P<.001$ for both). Tumor subtype, ulceration, and amelanosis did not reach statistical significance after adjustment for tumor thickness and mitotic rate.

HOST CHARACTERISTICS ASSOCIATED WITH ROG

Univariate analyses revealed that older people (≥70 years) and males had tumors with faster growth rates. Conversely, those with more melanocytic nevi and freckles had melanomas with slower growth rates (**Table 4**). Factors that were not associated with ROG were number of dysplastic nevi, number of solar lentigines, a history of solar keratoses, a history of blistering sunburns, skin phototype, eye color, a history of melanoma, a family history of melanoma, recreational sun exposure, occupational sun exposure, and childhood sun exposure.

Given that only a subset of patients (those at the Victorian Melanoma Service) had skin examination data available, the characteristics of the examined and nonexamined patients were compared. The examined patients (n=200) comprised approximately half of the total patients included in the analyses (n=404). Age, sex, and tumor thickness distributions were similar between the examined and nonexamined patients (**Table 5**).

We next considered whether the higher ROGs seen in males and elderly individuals were possibly due to bias in ROG measurement. The age- and sex-associated features are given in **Table 6** and **Table 7**, respectively. The data suggest that patients 70 years and older were less accurate in their reporting of melanoma growth (investigator-reported accuracy score, $P<.001$), more frequently have incidentally diagnosed melanomas ($P=.002$), were less likely to have received tertiary education ($P<.001$), and more often lived alone ($P=.048$). On the other hand, people 70 years and older more often had melanomas located on easily visible sites ($P=.05$), visited physicians more often ($P<.001$), and were likely to have been more aware of skin malignancy through previous experience with skin lesion excision ($P=.01$) and melanomas ($P=.07$). Males seemed to be less accurate in their description of the history of melanoma growth (investigator-reported accuracy score, $P=.04$), less likely to have self-detected their melanomas ($P=.04$), and less anxious about health issues in general ($P<.001$). Males more often had experience with previous skin lesion excision ($P=.02$) and more often had melanomas located on easily visible sites ($P=.004$). Multivariate analyses revealed that male sex, older age, fewer total body melanocytic nevi, and fewer freckles remained as significant associations with high ROG ($P<.05$).

CLINICAL FEATURES AS REPORTED BY PATIENTS AND THEIR ASSOCIATION WITH ROG

Rapid tumor growth was associated with atypical clinical features, including amelanosis ($P=.004$), border regularity ($P<.001$), symmetry ($P=.001$), elevation ($P<.001$), and symptoms ($P=.01$) (**Table 8**). When we combined the features of irregular border, irregular color, and asymmetry as features of "bad-looking" melanomas, the bad-looking melanomas were associated with slower ROGs compared with those that were not bad looking (GM ratio=0.41; $P<.001$). Variables that were not associated with ROG were educational background, place of residence, living arrangement, frequency of physician visits, level of anxiety, a history of attending skin examination, and detection pattern. Multivariate analyses showed that symmetry and elevation were independently associated with higher ROG ($P<.001$ for both).

OVERALL MULTIVARIATE ANALYSIS

The independent associations of ROG from the 3 multivariate models were entered into a final multivariate linear regression model including tumor thickness, mitotic rate, age, sex, number of nevi, number of freckles, symmetry, and elevation. Tumor thickness, older age, fewer freckles, and symmetry remained as independent associations of ROG (**Table 9**).

COMMENT

In this study, rapid tumor growth was shown to be closely associated with Breslow thickness and mitotic rate. Rapid tumor growth was also associated with male sex, older age, and fewer melanocytic nevi and freckles. Furthermore, rap-

Table 3. Tumor Characteristics and Rate of Growth in Melanoma

Characteristic	Melanomas, No.*	GM, mm/mo	Univariate Analyses		Multivariate Analyses†	
			GM Ratio (95% CI)	*P* Value	GM Ratio (95% CI)	*P* Value
Thickness, mm						
≤1	170	0.08	1.0		1.0	
1.01-4	168	0.30	3.9 (2.8-5.5)	<.001	2.5 (1.6-3.9)	<.001
>4	66	0.91	12.1 (7.7-19.1)	<.001	6.3 (3.5-11.5)	<.001
Tumor subtype						
SSM	250	0.14	1.0		NA	NA
NM	84	0.54	3.8 (2.5-5.8)	<.001	NA	NA
LM	41	0.13	0.9 (0.5-1.6)	.71	NA	NA
ALM	11	0.29	2.0 (0.7-5.8)	.20	NA	NA
DM	10	0.83	5.8 (1.9-17.6)	.002	NA	NA
Other	7	0.20	1.4 (0.4-5.2)	.62	NA	NA
Ulceration						
Yes	80	0.53	1.0		NA	NA
No	321	0.16	0.3 (0.2-0.5)	<.001	NA	NA
Mitotic rate, /mm^2						
<1	145	0.08	1.0		1.0	
1-4	148	0.23	2.9 (2.0-4.2)	<.001	1.6 (1.0-2.4)	.048
5-10	55	0.48	6.1 (3.6-10.2)	<.001	2.3 (1.2-4.2)	.01
>10	52	0.76	9.7 (5.7-16.5)	<.001	3.0 (1.6-5.7)	.001
Amelanosis‡						
Yes	77	0.36	1.0		NA	NA
No	290	0.18	0.5 (0.3-0.8)	.003	NA	NA

Abbreviations: ALM, acral lentiginous melanoma; CI, confidence interval; DM, desmoplastic melanoma; GM, geometric mean of log-transformed ROG; IQR, interquartile range (25th-75th percentile); LMM, lentigo maligna melanoma; NA, not applicable; NM, nodular melanoma; ROG, rate of growth; SSM, superficial spreading melanoma.

*Variation in total numbers of patients in each category is due to some data being unobtainable.

†Variables noted as NA were considered for inclusion in the final multivariate model but were omitted during the stepwise selection process.

‡Pathologically determined amelanosis.

Table 4. Host Characteristics and Rate of Growth in Melanoma

Characteristic	Melanomas, No.*	GM, mm/mo	Univariate Analyses		Multivariate Analyses†	
			GM Ratio (95% CI)	*P* Value	GM Ratio (95% CI)	*P* Value
Age, y						
<70	322	0.16	1.0		1.0	
≥70	82	0.45	2.8 (1.8-4.3)	<.001	3.4 (1.6-7.2)	.001
Sex						
M	222	0.26	1.0		1.0	
F	182	0.15	0.6 (0.4-0.8)	.003	0.5 (0.3-0.9)	.02
Total nevi, No.†						
<50	77	0.31	1.0		1.0	
≥50	116	0.15	0.5 (0.3-0.8)	.01	0.5 (0.3-0.9)	.03
Freckling†						
Few	149	0.24	1.0		1.0	
Many	36	0.09	0.4 (0.2-0.8)	.01	0.5 (0.2-0.9)	.02

Abbreviations: CI, confidence interval; GM, geometric mean of the log-transformed rate of growth.

*Variation in total numbers of patients in each category is due to some data being unobtainable.

†Examined patients only.

idly growing melanomas were shown to display atypical clinical features, including symmetry, elevation, amelanosis, border regularity, and the presence of symptoms.

A major weakness of this study is that it was based on patient recall to assess ROG and, therefore, depended on the varying reliability of patients in identifying the event of tumor appearance (D1) and the event of change (D2). Ideally, tumor ROG would be studied in prospective longitudinal cohort studies, but practical and ethical issues prohibit such studies. Factors that may affect the time to detection include the visibility of the lesion and the appearance of the lesion. For example, acral lentiginous melanomas, which are located on acral skin, and desmoplastic melanomas, which are often skin-colored

Table 5. Characteristics of the Examined and the Nonexamined Patients

Characteristic	Examined Patients (n = 200)	Nonexamined Patients (n = 204)
Age, mean, y	52.4	56.0
Sex, % male	51.7	58.1
Breslow thickness, median, mm	1.25	1.30
Rate of growth, mm/mo	0.18	0.22

Table 6. Clinical Characteristics Associated With Age*

Characteristic	Age <70 y	Age ≥70 y	*P* Value
Investigator-reported accuracy score	9.0	8.3	<.001
Self-reported accuracy score	8.5	8.1	.02
Interviewed with family, %	28	43	.01
Self-detected melanoma, %	91	78	.002
Frequency of physician visit (>1/y), %	63	98	<.001
Tertiary education, %	36	15	<.001
Live alone, %	11	20	.048
Previous skin lesion removal, %	56	73	.01
Skin lesion removal in family members, %	56	40	.02
Previous melanoma, %	7	13	.07
Location of melanoma (easily visible), %	26	38	.05

*No differences were observed between the age groups in place of residence, level of anxiety, a history of attending skin examination, a family history of melanoma, and the ability to visualize the lesion.

Table 7. Clinical Characteristics Associated With Sex*

Characteristic	Males	Females	*P* Value
Investigator-reported accuracy score	8.8	9.0	.04
Self-reported accuracy score	8.3	8.5	.05
Interviewed with family, %	42	18	<.001
Self-detected melanoma, %	85	91	.04
Self-reported anxiety score	5.8	6.7	<.001
Previous skin lesion removal, %	65	53	.02
Skin lesion removal in family members, %	43	64	<.001
Patient-reported family history of melanoma, %	16	25	.04
Location of melanoma (easily visible), %	30	25	.004

*No differences were observed between males and females in a history of attendance for skin examination, a history of melanoma, level of education, living arrangement, place of residence, and frequency of physician visits.

lumps, may remain undetected for a long time, leading to overestimation of the ROG. Furthermore, recall error due to poor memory may also contribute to inaccuracies in the data. To minimize such error, we used a variety of measures. First, we used a previously reported method to facilitate recall.[8,9] Second, we minimized the time delay to interview after the diagnosis. Third, we interviewed the patients with their family whenever possible (30% of interviews). Patient-reported tumor ROG correlated with tumor mitotic rate (Figure 2), supporting the validity of this method of assessing ROG.

Three other limitations of the ROG index used were the assumption that the ROG of any given melanoma is constant, the assumption that melanomas are invasive from the onset, and the use of Breslow thickness as a surrogate for tumor volume. It is likely that many tumors begin with slow radial growth until certain clones of malignant cells with aggressive growth potential appear. Our ROG index represents average growth during the growth period rather than describing the actual ROG at any point in evolution. This method of ROG calculation is based on the assumption that melanomas are invasive from the onset, although many have a significant in situ phase prior to invasion. The thickness-based model used to calculate ROG in this study (ie, Breslow thickness/time) has been used in a previous study[8] of 362 patients and conferred independent prognostic information. An earlier study[12] based on 35 patients suggested that tumor volume may be superior to tumor thickness as a prognostic indicator. Melanomas are highly variable in morphologic features, adding to the difficulty of assessing volume. No validated model has been described to assess tumor volume, and it is likely that any method will be, at best, a loose approximation of tumor volume.

Almost a third of the melanomas in this patient population grew 0.5 mm per month or more. Even short delays in diagnosis and treatment of these tumors will be associated with a significant increase in risk. The patients studied herein were derived mainly from tertiary referral centers, which treat a greater proportion of thick melanomas, NMs, and amelanotic melanomas. Retrospective assessment of ROG based on patient recall is often biased, with a tendency to overestimate ROG. This overestimation may also contribute to the high incidence of rapidly growing melanomas observed in this study.

This study confirms the suggestion that thicker melanomas grow faster.[9] Although ROG is calculated as Breslow thickness divided by time, it is independent of thickness and time. An analogy to this is the body mass index, calculated as weight in kilograms divided by height in meters squared and yet independent of both weight and height. Earlier, Richard et al[9] observed that delay in diagnosis is inversely related to tumor thickness, implying that in a population that is well informed about melanoma, tumor thickness may correlate more strongly with ROG than with delay in detection. The present study supports this viewpoint by demonstrating that rapid melanoma ROG is responsible, at least in part, for the finding of thick melanomas. Together, these observations may explain why the incidence of thick melanomas and melanoma-related mortality have remained stable in the past 2 decades[13] despite improvements in early detection and a decline in median tumor thickness.[14,15]

Older age and male sex were also strongly associated with rapidly growing tumors. These associations may be affected by factors that lead to errors in the reporting of ROG. For example, failing eyesight, lack of a partner, and poor memory in the case of elderly individuals[16] and a higher

Table 8. Clinical Features as Reported by Patients and Rate of Growth in Melanoma

Feature	Melanomas, No.*	GM, mm/mo	Univariate Analyses		Multivariate Analyses†	
			GM Ratio (95% CI)	*P* Value	GM Ratio (95% CI)	*P* Value
Amelanosis‡						
Yes	94	0.31	1.0		NA	NA
No	304	0.17	0.6 (0.4-0.8)	.004	NA	NA
Regular border						
Yes	152	0.28	1.0		NA	NA
No	227	0.11	0.4 (0.3-0.6)	<.001	NA	NA
Regular color						
Yes	177	0.22	1.0		NA	NA
No	211	0.17	0.7 (0.5-1.1)	.11	NA	NA
Symmetry						
Yes	209	0.32	1.0		1.0	
No	177	0.12	0.4 (0.3-0.5)	<.001	0.5 (0.3-0.7)	<.001
Diameter						
Continuous	393	NA	1.04 (1.01-1.06)	.01	NA	NA
Elevation						
Continuous	397	NA	1.4 (1.3-1.5)	<.001	1.3 (1.2-1.4)	<.001
Symptoms						
Yes	191	0.26	1.0		NA	NA
No	213	0.16	0.6 (0.4-0.9)	.01	NA	NA
Location					NA	NA
Easily visible	113	0.17	1.0		NA	NA
Visible sometimes	162	0.18	1.1 (0.7-1.7)	.74	NA	NA
Visible in private	127	0.27	1.6 (1.0-2.6)	.04	NA	NA

Abbreviations: CI, confidence interval; GM, geometric mean of the log-transformed rate of growth; NA, not applicable.
*Variation in total numbers of patients in each category is due to some data being unobtainable.
†Variables noted as NA were considered for inclusion in the final multivariate model but were omitted during the stepwise selection process.
‡Patient-reported amelanosis.

incidence of melanoma on the back in the case of males[17] may delay the observation of D1 (or D2) and, hence, overestimate ROG. However, such delays are unlikely to fully explain the occurrence of rapidly growing melanomas in elderly men. Our assessment of age- and sex-associated features (Tables 6 and 7) suggests that older people and males more frequently have melanomas located on easily visible sites and have more experience with previous melanomas and skin lesion removals. Hanrahan et al[18] found that older people (>50 years) were as able as younger people to identify changes of early melanoma in computer-generated images of pigmented lesions. Studies[3,19] of survival have suggested that melanoma tends to be more aggressive in men. One study[20] reported that melanoma is histologically associated with less inflammation with increasing age. During the past 20 years in Australia, elderly men have been the only group for which the rise in mortality has been greater than the rise in incidence,[21] suggesting that the biological features of melanoma may be different in the elderly male population.

Melanomas in individuals with fewer melanocytic nevi and freckles were associated with higher ROGs. This contrasts with the knowledge that higher melanocytic nevi and freckle numbers are strong and independent markers of melanoma risk. However, it has been reported that thicker melanomas[22] and NMs[20,23,24] are associated with lower nevus numbers. Because thicker melanomas and NMs were associated with rapid tumor growth in the present study, we may be able to explain why rapidly growing melanomas were not associated with large numbers of nevi.

Another important finding of this study is that rapid tumor growth is associated with atypical clinical features, including amelanosis, symmetry, border regularity, elevation, and the presence of symptoms. These features have already been described for NMs[25] but are likely to be shared by any area of rapid expansile proliferation, whether it occurs de novo, as in an NM, or supervenes on a preexisting radial growth phase.

In summary, this study provides descriptive data on the spectrum of melanoma ROGs and insights into subgroups of patients with melanoma that are associated with rapid growth. We propose that this information on melanoma ROG be incorporated into education programs for patients and health professionals. Special attention should be given to the promotion of awareness of the clinical characteristics of rapidly growing melanomas, such as symmetry, elevation, amelanosis, border regularity, and symptoms. Lack of awareness of the features associated with rapidly growing melanomas among health care practitioners frequently leads them to inappropriately reassure patients about their lesions. The penalty associated with diagnostic delay is particularly severe with a rapidly growing melanoma. Awareness of these lesions among health care practitioners should lead to expedited treatment rather than potentially catastrophic delay. Patients who develop aggressive tumors seem to lack the most important risk factors for melanoma, particularly the presence of a large number of nevi and freckles. The lack of these risk factors makes it more difficult for the physician to identify a lesion with atypical clinical features as a

Table 9. Overall Multivariate Analysis

Characteristic	GM Ratio (95% CI)	*P* Value
Thickness, mm		
≤1	1.0	
1.01-4	3.9 (2.0-7.8)	<.001
>4	5.8 (1.8-18.2)	.003
Mitotic rate, /mm^2		
<1	1.0	
1-4	1.0 (0.5-1.9)	.90
5-10	1.3 (0.5-3.6)	.56
>10	2.4 (0.9-6.6)	.09
Age, y		
<70	1.0	
≥70	2.1 (1.1-4.3)	.03
Sex		
M	1.0	
F	0.6 (0.4-1.0)	.07
Total nevi, No.		
<50	1.0	
≥50	0.8 (0.5-1.4)	.42
Freckles		
Few	1.0	
Many	0.5 (0.3-1.0)	.05
Symmetry		
Yes	1.0	
No	0.4 (0.2-0.7)	.001
Elevation		
Continuous	0.9 (0.2-3.5)	.87

Abbreviations: CI, confidence interval; GM, geometric mean.

melanoma. We propose that further education programs target early detection and accelerated management of the most aggressive melanomas. Further research is required to investigate the clinical, histologic, epidemiologic, and molecular associations of rapidly growing melanomas.

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Correspondence: Wendy Liu, MBChB, PhD, Research, Level 2, Peter MacCallum Cancer Center, East Melbourne, Victoria 3002, Australia (wendy.liu@petermac.org).
Author Contributions: *Study concept and design:* Liu, McArthur, and Kelly. *Acquisition of data:* Liu, Dowling, Murray, Thompson, and Kelly. *Analysis and interpretation of data:* Liu, McArthur, Wolfe, and Kelly. *Drafting of the manuscript:* Liu, McArthur, and Kelly. *Critical revision of the manuscript for important intellectual content*: Liu, Dowling, Murray, McArthur, Thompson, Wolfe, and Kelly. *Statistical analysis:* Wolfe. *Obtained funding:* Liu and Kelly. *Administrative, technical, and material support:* Liu, Dowling, Murray, Thompson, and Kelly. *Study supervision:* McArthur and Kelly.
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REFERENCES

1. Clark WH, From L, Bernardino EA, et al. The histogenesis and biologic behaviour of primary human malignant melanomas of the skin. *Cancer Res*. 1969; 29:705-726.
2. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. *Cancer*. 2003;97:1488-1498.
3. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622-3634.
4. Talve LA, Collan YU, Ekfors TO. Nuclear morphometry, immunohistochemical staining with Ki-67 antibody and mitotic index in the assessment of proliferative activity and prognosis of primary malignant melanomas of the skin. *J Cutan Pathol*. 1996;23:335-343.
5. Florenes VA, Faye RS, Maelandsmo GM, et al. Levels of cyclin D1 and D3 in malignant melanoma: deregulated cyclin D3 expression is associated with poor clinical outcome in superficial melanoma. *Clin Cancer Res*. 2000;6:3614-3620.
6. Straume O, Sviland L, Akslen LA. Loss of nuclear p16 protein expression correlates with increased tumor cell proliferation (Ki-67) and poor prognosis in patients with vertical growth phase melanoma. *Clin Cancer Res*. 2000;6:1845-1853.
7. Florenes VA, Maelandsmo GM, Kerbel RS, et al. Protein expression of the cell-cycle inhibitor p27Kip1 in malignant melanoma: inverse correlation with disease-free survival. *Am J Pathol*. 1998;153:305-312.
8. Grob JJ, Richard MA, Gouvernet J, et al. The kinetics of the visible growth of a primary melanoma reflects the tumor aggressiveness and is an independent prognostic marker: a prospective study. *Int J Cancer*. 2002;102:34-38.
9. Richard MA, Grob JJ, Avril MF, et al. Melanoma and tumor thickness: challenges of early diagnosis. *Arch Dermatol*. 1999;135:269-274.
10. Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi: a clinicopathologic correlation. *J Am Acad Dermatol*. 1986;14:1044-1052.
11. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol*. 1988;124:869-871.
12. Friedman RJ, Rigel DS, Kopf AW, et al. Volume of malignant melanoma is superior to thickness as a prognostic indicator: preliminary observation. *Dermatol Clin*. 1991;9:643-648.
13. Lipsker DM, Hedelin G, Heid E, et al. Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. *Arch Dermatol*. 1999;135: 1451-1456.
14. Armstrong BK, Kricker A. Cutaneous melanoma. *Cancer Surv*. 1994;19:219-239.
15. Buettner PG, Leiter U, Eigentler TK, et al. Development of prognostic factors and survival in cutaneous melanoma over 25 years: an analysis of the Central Malignant Melanoma Registry of the German Dermatological Society. *Cancer*. 2005; 103:616-624.
16. Kelly JW. Melanoma in the elderly: a neglected public health challenge. *Med J Aust*. 1998;169:403-404.
17. Green A, MacLennan R, Youl P, et al. Site distribution of cutaneous melanoma in Queensland. *Int J Cancer*. 1993;53:232-236.
18. Hanrahan PF, Hersey P, Menzies SW, et al. Examination of the ability of people to identify early changes of melanoma in computer-altered pigmented skin lesions. *Arch Dermatol*. 1997;133:301-311.
19. Clark WH Jr, Elder DE, Guerry D, et al. Model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst*. 1989;81:1893-1904.
20. English DR, Heenan PJ, Holman CD, et al. Melanoma in Western Australia in 1980-81: incidence and characteristics of histological types. *Pathology*. 1987;19: 383-392.
21. Australian Institute of Health and Welfare Web site http://www.aihw.gov.au. Accessed October 17, 2006.
22. Chamberlain AJ, Fritschi L, Giles GG, et al. Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. *Arch Dermatol*. 2002;138:609-614.
23. Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. *J Natl Cancer Inst*. 1984;72:257-266.
24. Marks R, Dorevitch AP, Mason G. Do all melanomas come from "moles"? a study of the histological association between melanocytic naevi and melanoma. *Australas J Dermatol*. 1990;31:77-80.
25. Chamberlain AJ, Fritschi L, Kelly JW. Nodular melanoma: patients' perceptions of presenting features and implications for earlier detection. *J Am Acad Dermatol*. 2003;48:694-701.