An objective measure of growth rate using partial biopsy specimens of melanomas that were initially misdiagnosed

Matthew J. Lin, MBBS,[a] Victoria Mar, MBBS,[a,b] Catriona McLean, MD,[a,c] and John W. Kelly, MBBS, MD[a]
Melbourne, Australia

Background: To calculate melanoma rate of growth (ROG), previous studies have relied on subjective patient recall to estimate time delay to diagnosis.

Objective: To objectively calculate ROG by measuring the rate of increase in melanoma thickness between 2 sequential biopsy specimens over time.

Methods: This was a retrospective review of 51 melanomas in which pathologic misdiagnosis of a partial biopsy specimen caused a delay before referral and excisional biopsy between January 1998 and January 2013. ROG was calculated as rate of increase in tumor thickness between biopsy specimens.

Results: The median delay between the 2 biopsy specimens was 27 months (range, 3-89 months). Biopsy specimens of melanomas that were obtained initially in their in situ phase were thinner at excision compared to those that were first obtained as invasive tumors (median, 0.7 vs. 3.2 mm; $P < .01$) and had a lower ROG (median, 0.04 vs. 0.11 mm/month; $P = .05$). Faster growth was associated with increased tumor thickness, higher mitotic rate, symptoms, elevation, and amelanosis.

Limitations: Partial biopsy specimens may not be representative of deepest tumor thickness.

Conclusion: We have demonstrated an objective measure of melanoma growth rate using sequential biopsy specimens. The correlation between faster growth and aggressive tumor features supports what others have found and validates the historical measure of growth rate as a reliable clinical marker. (J Am Acad Dermatol 2014;71:691-7.)

Key words: melanoma; misdiagnosis; rate of growth; tumor kinetics.

Melanomas grow at different rates, and several studies have attempted to clinically assess tumor kinetics.[1-9] However, to calculate rate of growth (ROG), previous investigators have used a historical estimate, relying on patient recall of time delay leading up to melanoma diagnosis. Although this is readily available and useful information, it is subjective data and is associated with many potential sources of error. Accuracy of patient recall may be influenced by numerous factors, including age, sex, memory, psychosocial circumstances, and visibility of the lesion. It has been suggested that the historical measure of growth rate

Abbreviations used:

DM:	desmoplastic melanoma
LM:	lentigo maligna
LMM:	lentigo maligna melanoma
ROG:	rate of growth
SSM:	superficial spreading melanoma
VMS:	Victorian Melanoma Service

From the Victorian Melanoma Service[a] and the Department of Anatomical Pathology,[c] Alfred Hospital, and the Department of Epidemiology and Preventive Medicine,[b] Monash University, Melbourne.
Funding sources: None.
Conflicts of interest: None declared.
Presented in part at the 8th World Congress of Melanoma, Hamburg, Germany, July 17-20, 2013.
Accepted for publication April 29, 2014.

Reprints not available from the authors.
Correspondence to: Matthew J. Lin, MBBS, Victorian Melanoma Service, Alfred Hospital Commercial Rd, Prahran, Victoria, Australia, 3181. E-mail: drmatthewlin@gmail.com.
Published online June 26, 2014.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.04.068

might overestimate ROG in thin tumors with an early invasive phase that may not have been changing enough to be noticed by the patient.

Despite these difficulties in measurement, ROG is an important biologic feature of melanoma. Unlike other pathologic features, such as mitotic rate and thickness, which are assessed at a single point in time, growth rate is unique in its ability to provide information on tumor evolution. It should be considered a distinct tumor feature. Previous investigators have shown that ROG may provide useful prognostic information about predicting nodal diesase,[1,2] the temporal appearance of metastatic disease,[3] and disease-free and overall survival.[4-7] In addition, faster growth has been associated with aggressive pathologic factors, including nodular morphology, advanced thickness, high mitotic rate, and ulceration.[6-9] Rapidly growing melanomas are more likely to occur in the elderly and have a distinct clinical presentation with symmetry, regular borders, and amelanosis.[9]

CAPSULE SUMMARY

- To calculate melanoma rate of growth, previous studies have relied on a subjective patient recall–based method.
- We objectively calculated rate of growth by measuring the rate of increase in melanoma thickness between 2 biopsy specimens.
- Correlations between faster rate of growth and aggressive features support what others have found using the historical rate of growth measure.

The aim of this study was to more objectively calculate ROG by measuring the increase in melanoma thickness between 2 sequential biopsy specimens that were obtained over time. Using this measure of growth rate, we aimed to reassess previously established relationships between ROG and the clinicopathologic characteristics of melanoma.

METHODS

Institutional ethics board approval was obtained, and all patients involved provided written informed consent.

The Victorian Melanoma Service (VMS) is an Australian tertiary referral, multidisciplinary treatment center for melanoma. A retrospective review of the VMS database from January 1998 to January 2013 was performed to identify all primary melanomas in which pathologic misdiagnosis on the initial partial biopsy specimen caused a delay before excisional biopsy. All cases of initial histologic misdiagnosis occurred in community care before the delayed diagnostic excision and subsequent referral to the VMS. For inclusion, partial biopsy specimens (ie, punch, shave, and incisional specimens) were required to extend beyond the depth of the melanoma. Delay was defined as >3 months between biopsies.

For the purposes of analysis, we divided our cohort into 2 groups: (1) melanomas from which the first biopsy specimen was obtained while the melanoma was still in its in situ phase and (2) melanomas from which the first biopsy specimen was obtained while the melanoma was considered an invasive tumor. To calculate ROG, Breslow thickness was used as a surrogate of tumor volume, based on a previously used method.[4] ROG was calculated as the rate of increase in tumor thickness between the partial and excisional biopsy specimens, given in millimetres per month (Fig 1).

Clinicopathologic characteristics were recorded at the time of the patient's initial diagnosis and entered to the database. These data were confirmed and supplemented from the individual clinical records. Clinical information included age, sex, and tumor site (recorded as head and neck, trunk, upper limb, or lower limb). All previous pathology results obtained before referral were reassessed by an expert dermatopathologist at the VMS, and pathologic features reviewed included melanoma subtype according to current World Health Organization classification,[10] Breslow thickness, mitotic rate, and ulceration. For the purposes of analysis, age was dichotomized as <70 or ≥ 70 years, thickness was categorized as thin (<1.0 mm), intermediate (1.0-4.0 mm), or thick (>4.0 mm), and mitotic rate on excisional biopsy was categorized as <1, 1-4, or >4 mitoses per square millimeter. Symptoms such as itch, altered sensation, or bleeding at any point in time were noted, as was elevation and amelanosis. Amelanosis was assessed by the patient, immediately after diagnosis, as a lesion that lacked apparent pigmentation.

To identify factors with univariate associations with rate of growth, the Wilcoxon rank sum or Kruskal–Wallis tests were used where appropriate. ROG was considered as a continuous variable. Two-tailed tests with a significance level of 5% were used throughout. Statistical analysis was performed using Stata 12 software (State Corporation, College Station, TX).

RESULTS

Fifty-one melanomas satisfied the inclusion criteria. This represented 1.06% of the total number