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Choroidal melanoma growth patterns

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SUMMARY Thirty patients with choroidal melanoma in whom tumour thickness was found to increase on serial examination were retrospectively studied. Often when tumours started to increase in thickness, after a period of relative quiescence, the growth rate was relatively rapid. Increased tumour thickness was associated with increased tumour growth. During the phase of active tumour growth the height of the lesion tended to increase more than exponentially. Possible inadvertent biases in the selection of the patients studied prohibit wide-ranging conclusions from these data.

The detection and measurement of growth is important in the management of pigmented choroidal lesions. In most ocular oncology centres therapeutic intervention is not considered for patients with small choroidal melanomas (<10 mm in diameter and <3 mm in thickness) until growth is noted.[1,2] A change in tumour dimensions may be an important prognostic indicator.

Clinical and laboratory data on the growth rate of choroidal melanomas are sparse. We and others have studied a limited number of patients with small and medium sized choroidal melanomas in which growth occurred, but the rate of growth was not well delineated.[3–5] Most patients had therapeutic intervention once a change in tumour dimensions was detected. Ethical considerations have prohibited serial observation of enlarging tumours.

We have retrospectively recorded the changes in choroidal melanoma thickness in 30 patients. The growth rate for a given tumour and for tumours in different patients varied; some tumours had periods of no growth followed by rapid growth. Statistical analysis of the data suggests that tumour height tended to increase more than exponentially during active growth.

Material and methods

All patients with choroidal melanoma were examined in the Ocular Oncology Unit, University of California, San Francisco, where fundus photographs, fluorescein angiography, clinical examination, fundus drawing, immersion B-scan ultrasound, and quantitative echography were performed. Thirty patients with objective sequential data demonstrating tumour growth were included in this study. During the same period a total of approximately 200 patients with uveal melanoma who required therapy were examined in our Ocular Oncology Unit. Twenty-nine of 30 patients had posterior uveal melanomas. One patient had a ciliary body tumour. Fourteen patients were male and 16 female. Their mean age was 61·3 years.

Tumour dimensions of 10 patients were measured 4 or more times; 7 patients were examined on 3 occasions, 13 patients were observed twice. In all patients quantitative ultrasonography and indirect ophthalmoscopy were used to measure tumour thickness unless the lesion was flat. Patients initially examined when tumours were less than 1 mm in height were measured by indirect ophthalmoscopy alone. The variation between these 2 forms of measurement has previously been described.[6] The median observation interval was 13 months, with a mean of 25 months (range 4–81 months).

All patients were eventually treated after growth was observed. In 22 patients growth was noted during serial observation under ophthalmological care. In 8 other patients growth was noted after an interval in which they had been lost to medical follow-up prior to their referral to our unit. Eighteen patients were initially examined with small melanomas (<10 mm in

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diameter and <3 mm in thickness); 12 patients were initially examined with medium-sized tumours (10–15 mm in diameter and 3·5 mm in thickness).

Fourteen eyes were enucleated. The others have been successfully treated by other methods (photocoagulation or charged particle irradiation). Five patients had histologically confirmed spindle cell tumours, and 9 had either mixed or epithelioid lesions. There was close agreement between ultrasound and histological measurements of tumour thickness.[6]

All computations of growth were based on measurements of tumour thickness (height). We used this measure because it was more easily quantifiable than changes in diameter. Growth curves, based on tumour height, were plotted for all patients (Fig. 1). In a subgroup of 10 patients with posterior uveal melanomas some successive pairs of tumour height measurements were selected for further analysis on the basis of the following criteria: the interval between tumour height measurements was required to be less than 48 months, the tumour was elevated on the earlier examination, and the height increased between examinations. Periods in which there was no change in tumour height were deleted for statistical analysis, owing to our clinical impression that tumours are sometimes dormant for variable periods of time and then undergo a marked increase in activity and growth. Thus, rate of enlargement was assessed during periods of active growth. This selection produced 18 pairs of observations on 10 subjects. On each pair of observations the average height and straight-line slope of height were computed.[7] These may be viewed as estimates of the true height and growth rate at the midpoint of the given time interval.

Results

Fig. 1 plots tumour height versus time. The growth curves were not homogeneous. In 8 of 30 patients intervals of no growth were documented. There did not appear to be a difference in the growth rate between patients with histologically proved spindle cell tumours (5) and those with mixed or epithelioid lesions (9).

We used regression analysis to examine various possible forms for the relationship between slope and average height, using the 18 pairs of average height and slope values which were derived as described above.[7] The most satisfactory model appeared to be one which expressed the logarithm of the slope as linearly related to the logarithm of average height. The fitted equation for this model was $\log_e$ (slope)= $-4{\cdot}69+2{\cdot}16 \log_e$ (average height), and this is plotted in Fig. 2. This equation predicts the slope as 0·000919 (average height $^{2{\cdot}16}$), which suggests that height tended to increase more than exponentially in this data. The coefficient value of 2·16 is significantly different from 1, with a computed 2-tailed p value <0·01.

Discussion

We have studied the patterns of enlargement of tumour thickness in 30 patients with choroidal melanoma in whom growth was noted on serial examinations. Only a small minority of patients with

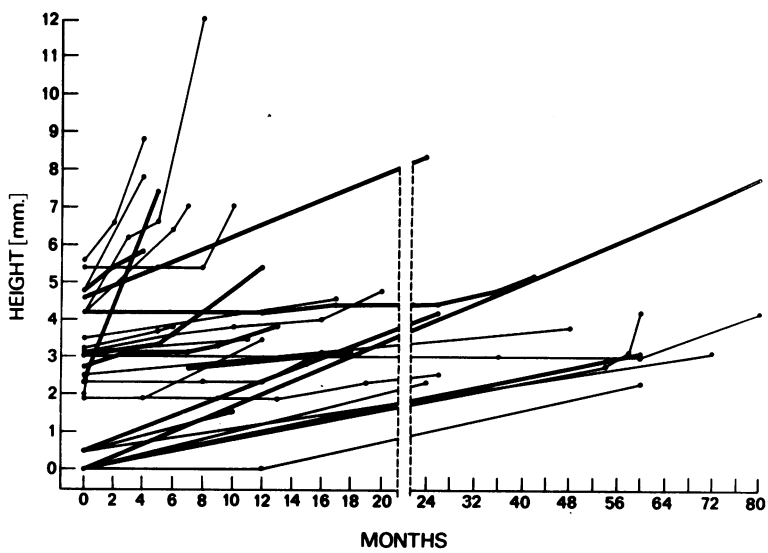

Fig. 1 *Choroidal melanoma growth patterns. The time scale is contracted after 22 months and this artefactually alters the shape of those curves over 22 months. Single and double lines are used only to differentiate different patients.*

choroidal melanoma show a change in tumour dimensions during the course of their ophthalmologic examinations.[2] This finding was also substantiated in our series, in which approximately 30 of 200 patients with uveal melanoma showed enlargement of tumour.

In those patients in whom frequent serial observations were available the majority had periods of tumour inactivity followed by rapid growth. Some patients had slow, progressively enlarging tumours. Unfortunately many patients in this study were examined only on 2 occasions, which made it impossible to determine the actual shape of the growth curve between these 2 time points.

In a few patients whose tumour developed a collar-button appearance during the observation interval, the tumour height appeared to increase rapidly. However, this was not always so. In some patients with collar-button lesions the tumour remained stable in height.

Our analysis of a selected part of these data suggests that tumour thickness increased in a greater than exponential manner during the active phase of growth in patients with posterior uveal melanomas. This pattern of growth has also been observed in other human and animal primary and metastatic tumours.[8-11] The analysis supporting this proposal is not definitive. As noted under 'Methods', the average height and slope values analysed were estimates of mid-interval tumour heights and growth rates, and all the observations are not statistically independent. While previous studies from our institution have demonstrated an excellent correlation between clinical, ultrasound, and histological determinants of tumour thickness, some variation can occur.[6] It is possible that a change in tumour dimensions not associated with an increased number of cells could occur at the time of a break in Bruch's membrane and this might affect the conclusions drawn from these data.

McLean *et al.* have retrospectively studied a large group of choroidal melanomas and observed that the mean age of patients with small-diameter tumours was approximately 7 years less than those with large-diameter melanomas.[12] They suggested that the rate of horizontal enlargement of a choroidal melanoma is relatively slow. In that study, based on patients' ages, spindle-cell tumours appeared to have a slightly faster growth rate than mixed-cell melanomas; however, they could not explain this apparently contradictory observation.

Our data appear to conflict with those of McLean and his colleagues.[12] McLean and colleagues measured the maximum tumour diameter; we measured tumour thickness. This difference may have accounted for some or all of the discrepancies. We chose to measure alterations in tumour thickness because it has been our clinical impression that tumours undergo greater changes in thickness than in diameter. Many of our patients had relatively rapid tumour enlargement. In some patients the tumour increased in thickness by as much as 6 mm over a period of less than 6 months; in others the tumour growth appeared to be relatively slow. Unfortunately many patients were observed only at 2 widely separated times. Some of these patients probably had periods in which the tumour remained static and other periods when it grew rapidly. In our study we were unable to demonstrate a significant difference between enlargement in patients with spindle-cell versus mixed or epithelioid-cell melanomas; however, the numbers studied were too few to show a significant difference.

There were insufficient data to determine tumour doubling times in this study. While tumour doubling times have been measured for pulmonary metastases

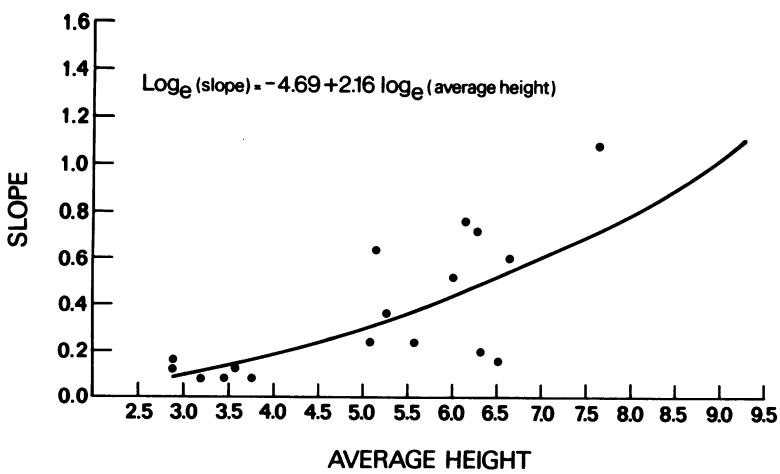

Fig. 2 *Predicted slope versus average height of choroidal melanomas during the phase of active growth.*

and some other human and animal tumours, there are almost no data on them for choroidal melanomas. On the basis of cases shown in Fig. 1 it would appear that the doubling times have marked variation in choroidal melanomas. Some lesions double in less than 4 months, while others remain dormant for long periods.

The results of our study must be interpreted cautiously. In most patients with choroidal melanoma it is impossible to obtain serial measurements of tumour growth, because most choroidal melanomas are treated at the time that growth is detected. The 30 patients studied here represent a very small subgroup of patients with choroidal melanoma managed at the Ocular Oncology Unit, University of California, San Francisco, and therefore may not be representative of all melanoma patients. Most of these patients were initially examined with small choroidal melanomas. It is conceivable that the growth pattern in large or medium sized choroidal melanomas could be significantly different from the pattern observed. We could not detect such a difference. However, the very small number of patients followed up with initially medium or large tumours precludes definitive conclusions. In addition there may have been inadvertent biases in the selection process which we were unable to detect, or measurement artefacts with increased thickness not related to an increase in the number of tumour cells.

The retrospective nature of this study, and the ethical considerations which we believe prohibit a prospective study, further limit the applicability of the observations we have made. Many patients were examined on only 2 occasions, and the absence of data collected at regular intervals prevents us from determining the precise nature of events which occur when a melanoma changes from inactivity to active enlargement.

This study does suggest that during the period of active tumour enlargement, the lesion appears to increase in height at a greater than an exponential rate. It also tends to support our clinical impressions that, when small tumours start to grow, they generally grow rapidly, and, as tumour thickness increases, the growth rate accelerates.

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