Presumed incipient choroidal melanoma: proposed diagnostic criteria and management

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ABSTRACT

Aims To propose diagnostic criteria for a presumed incipient choroidal melanoma based on tumour growth rate and tumour doubling time (TDT) and to describe management of such tumours with transpupillary thermotherapy (TTT).

Methods Retrospective interventional case series of nine consecutive presumed incipient uveal melanomas diagnosed and treated with TTT in 2010–2017. Growth rate in mm/year and per cent/year in largest basal diameter (LBD) and TDT were compared with published data for uveal melanomas and growing naevi that did not transform to melanoma under long-term follow-up.

Results The median LBD and thickness were 1.6 mm (range 0.9–2.3) and 0.20 mm (range 0.15–0.29), respectively. The median age was 57 years (range 47–78). Seven tumours were classified as de novo melanomas and two as transformed naevi. The median time from first observation to diagnosis was 3.3 years (range 2.2–7.3), LBD growth rate 0.25 mm/year (range 0.11–0.72) and 34 per cent/year (range 10–1437), and TDT 609 days (range 97–1612). The estimates matched those reported for uveal melanoma (median TDT 521 days, 90th percentile 2192) and exceeded those for growing naevi (median growth rate 0.04 mm/year, 90th percentile 0.12; 1.1 per cent/year, 90th percentile 2.6). The predicted median age at de novo appearance was 51 years (range 32–63). No tumour grew after TTT during a median follow-up of 2.1 years (range 0.6–8.7).

Conclusions In this series, relative growth rate and TDT best qualified as diagnostic criteria for an incipient choroidal melanoma. Too small for brachytherapy, they could be managed with TTT.

Pathogenic variants in driver genes of choroidal melanomas appear to arise early during their evolution, an estimated 9.5 years or more before diagnosis of the primary tumour.[1–3] Five of 14 melanomas 2 mm or less in thickness had a gene expression profile (GEP) class higher than 1A, and 4 of 11 showed monosomy 3.[4] Metastatic dissemination also can occur early.[5] In the Small Fatal Choroidal Melanoma Study, the smallest melanoma that metastasised was 3.0 mm in largest basal diameter (LBD) and 1.0 mm in thickness at the time of treatment.[6] These findings support early treatment to minimise the risk of metastasis, but capability to disseminate cannot be predicted from clinical characteristics of small choroidal melanomas[6 7] and they also are challenging to biopsy early in their development.

We are unaware of diagnostic criteria for choroidal melanomas less than 3 mm in LBD and of reports describing treatment of such tumours. Descriptions of choroidal melanomas that emerged de novo are exceptional.[8 9] Here, we propose diagnostic criteria for a presumed incipient choroidal melanoma based on assessment of tumour growth, and report a consecutive series of nine such tumours treated with transpupillary thermotherapy (TTT).

METHODS

Inclusion criteria

Eligible were patients diagnosed with a presumed incipient choroidal melanoma and scheduled to have primary TTT between June 2010 and October 2017. We reviewed the database of the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, a national referral centre for uveal melanoma and identified nine eligible patients (for case reports, see online supplemental text 1). One of them had a history of a T2aN0M0, stage IIA, choroidal melanoma in the same eye, treated with a 15 mm ruthenium plaque 2.5 years earlier.

Clinical evaluation

We used digital fundus images, taken with a fundus camera in other hospitals at various times before referral and in our service (TRC-50DX, Topcon, Tokyo, Japan), to localise tumour margins, to measure its diameter and distance from the foveola and the optic disc, and to record orange pigment. We used enhanced depth imaging[10] spectral-domain optical coherence tomography (OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) to measure tumour thickness and to detect subretinal fluid. We measured best-corrected visual acuity (BCVA) using a test-type projector (Rodavist 2 and 524; Rodenstock GmbH, Ottobrunn, Germany, and TCP-2000A, Tomey, Nagoya, Japan).

Diagnosis at the time of treatment was based on calculated annual absolute tumour growth rate and tumour doubling time (TDT) and the age of the patient, relative to published data of growing choroidal naevi.[11] We collected age, gender, BCVA, tumour size and location, risk factors for growth,[12 13] and TTT parameters. Data collected after TTT included BCVA, tumour control, adverse outcomes and last survival status.

Calculation of tumour growth rate and doubling time

We calculated tumour growth rate both in mm/year and per cent/year from initial LBD. A theoretical LBD of 0.05 mm was used for two tumours that were not visible in the first available photograph.

We calculated TDT by using tumour volume estimated from cylindrical shape because all tumours were non-elevated relative to the adjacent choroid. We presumed that their thickness did not change, that is, the tumour replaced the full thickness of the choroid already when first photographed. Thus, tumour thickness was taken to equal choroidal thickness. LBD and surface area were measured with ImageJ (V.1.51, National Institute of Health, Bethesda, Maryland, USA).[14] Two investigators (SJ, RAJ) independently measured them both with manual drawing and with automatic recognition of tumour margins (for protocol, see online supplemental text 2). The estimate used in calculations was the mean of the four measurements (online supplemental table). The time of the first observation was the date when the tumour was first photographically documented. The time of diagnosis was the day when the photograph leading to the diagnosis of a presumed incipient melanoma was taken. Observation time was the difference between these dates.

We calculated TDT according to Schwartz[15]:

$$\mathrm{TDT} = \frac{T}{\left(\frac{\log_{10}\left(\frac{V_{dg}}{V_{ini}}\right)}{\log_{10}(2)}\right)} \quad (1)$$

where V_{ini}=initial tumour volume, V_{dg}=tumour vol at diagnosis and T=observation time.

We also calculated the predicted age at which the tumour likely would have been clinically invisible, using 0.05 mm as theoretical LBD and thickness, to assess whether it likely had originated during adult life and was, thus, consistent with a de novo melanoma:

$$\mathrm{Age}_{pred} = \mathrm{Age}_{ini} \frac{\mathrm{TDT} \times \frac{\log_{10}\left(\frac{Vini}{V_{orig}}\right)}{\log_{10}(2)}}{365.25} \quad (2)$$

where Age_{ini}=age when tumour was initially observed; V_{ini}=initial tumour volume; V_{orig}=theoretical vol 0.000125 mm^3 based on 0.05 mm dimension and TDT=tumour doubling time from (equation 1).

Our calculations are based on constant exponential growth,[16] which may differ from the actual growth rate of the tumour over time. We performed a sensitivity analysis for one patient with a previously documented stable naevus (table 1 and online supplemental text 1; patient 7) by calculating the observation time from two immediately preceding visits (without photograph), thus allowing for the possibility that minor growth might have been missed during the immediately preceding visit. A likely de novo melanoma was diagnosed when a tumour grew symmetrically in all directions and a previously normal fundus was either documented or predicted to have been present in adult life.

Reference data

As a reference for growth rate of choroidal naevi during long-term observation, we used a study that reported absolute overall growth for 89 naevi with photographic evidence of enlargement without clinical signs of malignant change developing over a median follow-up of 15 years.[11] Carol Shields (Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, USA) kindly provided us the data to calculate corresponding annualised growth rates, with a median of 0.04 mm/year (range 0.01–0.20; 90th percentile 0.12) and 1.1 per cent/year (range 0.2–11.6; 90th percentile, 2.6), excluding one fast growing tumour that soon had been diagnosed as a choroidal melanoma (unpublished observations).

As a reference for known choroidal melanomas, we collected the patient-level TDT of 196 uveal melanomas reported in four articles.[17–20] TDT was either reported in a published table or, for 145 patients, derived from published histograms.[20] Omitting two outliers with a very long TDT of more than 32 and 64 years,[20] the median was 521 days (range 10–8766; 90th percentile 2192).

Transpupillary thermotherapy

Three ocular oncologists (TK, MT, SE) treated all tumours with TTT using an 810 nm infrared diode laser (MedArt 426, MedArt, Hvidovre, Denmark) adapted to a slit lamp (Zeiss 30 SL-M, Zeiss, Munich, Germany). Depending on LBD, a spot 0.8, 1.2, 2.0 or 3.2 in diameter was applied under periocular anaesthesia through a contact lens (Area Centralis or Quadraspheric, Volk Optical, Mentor, Ohio, USA) after pupillary dilatation. The median power and duration to achieve a greyish white effect during the first treatment were 1500 mW (range 700–3500) and 120 s (range 60–285), respectively; the same parameters were used during any subsequent treatment. Up to four (median 1) slightly overlapping applications centred on the tumour were delivered to cover the tumour with a 0.5–1.0 mm margin. Treatment was repeated in six patients a median of two (range 2–4) times at 2 to 7-month intervals to achieve a white atrophic scar.

Table 1 Initial and final size, growth rate and predicted age when tumour was invisible for nine presumed incipient choroidal melanomas

Patient	Choroidal thickness (µm)	Initial size			Observation time (days)	Final size			Growth rate			Predicted		
		LBD (mm)	Area (mm^2)	Volume (mm^3)		LBD (mm)	Area (mm^2)	Volume (mm^3)	LBD (mm/year)	LBD (%/year)	TDT* (days)	NTD (X)	Interval (years)	Age when invisible (years)
1	158	0.47	0.15	0.023	1101	0.93	0.48	0.076	0.15	32	609	1.7	12.6	34
2	200	1.05	0.70	0.14	817	1.61	1.78	0.36	0.25	24	609	1.3	16.9	59
3†	191	1.09	0.63	0.12	1553	1.56	1.22	0.23	0.11	10	1612	0.95	N/A	N/A
4	290	0.52	0.12	0.035	1495	1.69	1.64	0.47	0.29	55	393	3.8	8.7	51
5	150	0.56	0.11	0.017	2664	1.97	2.31	0.35	0.19	34	601	4.4	11.7	32
6‡	179	0.05	0.0025	0.00045	1364	2.32	1.54	0.28	0.61	1214	147	9.3	34.6	63
7†	200	0.56	0.15	0.030	1192/773§	1.00	0.59	0.12	0.14/0.21§	24/38§	635/412§	2.0	N/A	N/A
8	227	0.46	0.17	0.039	804	1.30	0.89	0.20	0.39	85	337	2.4	7.6	47
9‡¶	265	0.05	0.0025	0.00066	931	1.88	1.89	0.50	0.72	1437	97	9.6	0.6	53

*Equation of Schwartz.[15]
†Likely a transformed naevus.
‡Tumour initially invisible, modelled using presuming an initial tumour diameter of 0.05 mm.
§Sensitivity analysis, presuming minor growth present/absent at the visit immediately preceding the one at which growth was noticed.
¶In an eye with a previously irradiated choroidal melanoma.
LBD, largest basal diameter; N/A, not available; NTD, number of tumour doublings; TDT, tumour doubling time.

Statistical methods

We prospectively collected follow-up data up to 30 June 2019, into a database (MS Access; Microsoft, Seattle, Washington, USA) and analysed them with Stata (Release V.15; Stata Corp). The BCVA was transformed to logarithmic scale. We summarised the data as median and range for continuous variables. All tests were two-sided and p value <0.05 was considered statistically significant.

RESULTS

The mean age of the nine patients (male:female (4:5)), all white Caucasians, was 55 years (range 41–77) when the pigmented choroidal tumour in a fundus photograph taken for various reasons was still absent in two eyes and first detected in seven eyes, in two eyes retrospectively (figure 1 and online supplemental text 1). Four were documented as presumed naevi. The median LBD was 0.52 mm (range 0.05–1.09; table 1). None of

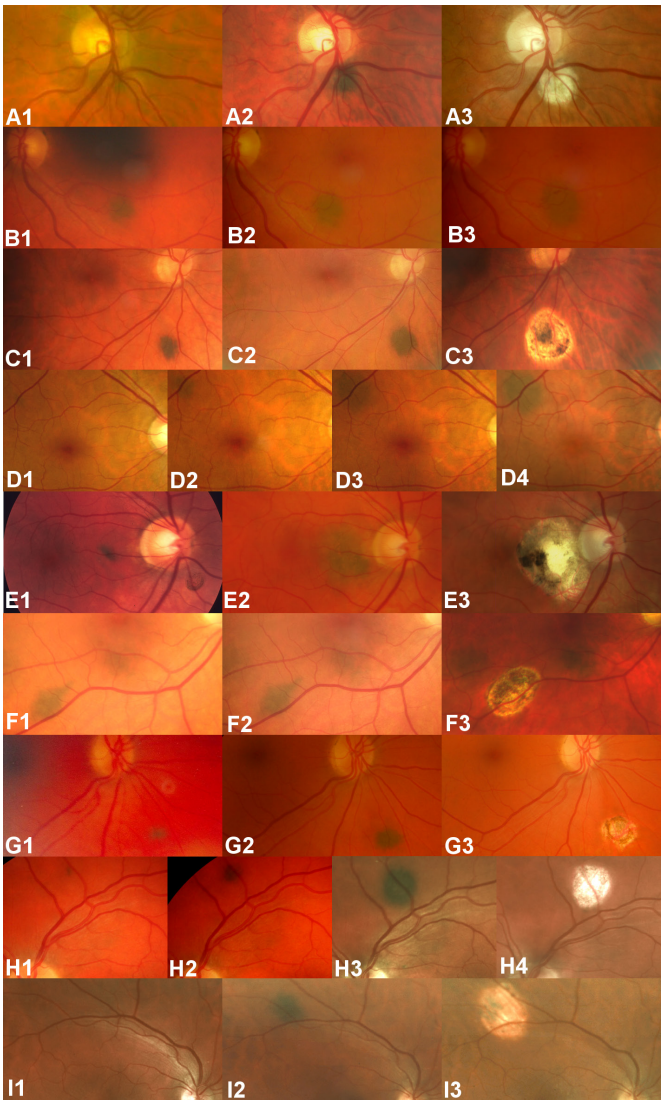

Figure 1 Clinical features of nine presumed incipient choroidal melanomas. (A1) Patient 1. A documented juxtapapillary fleck, (A2) grew within 2 years and (A3) became a white scar after two sessions of transpupillary thermotherapy (TTT). (B1) Patient 2. A presumed naevus documented during screening for diabetic retinopathy, (B2) was larger in the next screening photograph (B3) and showed further growth 3.5 months later. (C1) Patient 3. A documented presumed naevus, (C2) grew asymmetrically within 4 years and (C3) became a stable scar with a nodule of reactive proliferation of the retinal pigment epithelium (RPE) 15 months after one session of TTT. (D1–D3) Patient 4. A pigmented lesion was overlooked in fundus photographs taken as part of glaucoma screening. It was later observed to have grown, (D4) and further growth was noticed within the next 6 months. (E1) Patient 5. A documented peripapillary pigmented lesion was, (E2) subsequently noted to have grown with four new risk factors and, (E3) was a flat scar with some RPE hypertrophy 5 years after two sessions of TTT. Patient 6: in a previously normal location, (F1) a small pigmented tumour was identified in the next photographs taken as part of diabetic retinopathy screening, (F2) it grew further during the next 5 months and, (F3) became a scar with RPE pigment stippling 13 months after three sessions of TTT. (G1) Patient 7. A tiny presumed naevus was documented, (G2) grew within the next 7 years and (G3) became a white scar 2 years after one session of TTT. (H1) Patient 8. A tiny pigmented lesion was overlooked in a screening fundus photograph to identify diabetic retinopathy and (H2) in the next one taken a year later. (H3) It was diagnosed as an incipient choroidal melanoma 2 years later after further growth, (H4) and became a white scar with a few granules of RPE-related pigment 1.5 years after two sessions of TTT. (I1) Patient 9. A new small pigmented choroidal lesion, not visible in a previous photograph 2 years earlier, (I2) was diagnosed as an incipient choroidal melanoma in an eye previously treated for a T2a, stage IIA choroidal melanoma. (I3) The outcome was a white scar with a small nodule of reactive RPE proliferation 1.5 years after two sessions of TTT.

the tumours showed risk features for growth, nor had a halo or drusen as a sign of having been long standing.

Tumour characteristics at diagnosis

By the time of diagnosis as a presumed incipient choroidal melanoma, one of the nine patients (median age 57 years; range 47–78) had developed symptoms (online supplemental text 1, patient 5). Her tumour had developed three other risk factors: subretinal fluid, orange pigment and tumour margin touching the optic disc (figure 1). The BCVA was 6/7.5 or better, except 6/12 in one patient with a cataract. Seven tumours were consistent with a de novo melanoma, including two with a previously normal fundus (patients 6 and 9). In one eye the tumour developed from a previously stable presumed naevus, suggesting malignant change close to its centre (patient 7). In one eye, growth occurred at two tumour margins only, suggesting eccentric malignant change of another previous naevus (patient 3). By the time of diagnosis, the LBD had grown to a median of 1.6 mm (range 0.9–2.3). The median thickness, when first measured by OCT, was 0.20 mm (range 0.15–0.29), the same as the thickness of the adjacent choroid. The median distance of the tumour margin to the foveola and optic disc was 3.7 mm (range 0.5–5.3) and 2.3 mm (range 0–6.8), respectively.

Tumour growth rate and doubling time

The median observed time before diagnosis was 3.3 years (range 2.2–7.3; table 1). The median observed growth in LBD was 0.8 mm (range 0.4–2.3), and the median growth rate 0.25 mm/year (range 0.11–0.72), corresponding to 34 per cent/year (range 10–1437; table 1). The latter rate, which takes into account the LBD, was faster than that for 88 growing naevi in the published reference data, except for the asymmetrically growing likely transformed naevus (figure 2A,B; $p<0.001$ for both, Kruskal-Wallis test). Restricted to the seven likely de novo melanomas, these rates were 0.29 mm/year (range 0.15–0.72) and 55 per cent/year (range 24–1437), respectively. The latter rates always exceeded the reference data (figure 2B).

The median TDT of 609 days (range 97–1612; table 1) for all nine tumours and 393 days (range 97–609) for the seven likely de novo melanomas were comparable with the median of 521 days (range 10–8766) for 194 melanomas in the published data ($p=0.74$), as was their range (figure 2C).

Excluding the two likely transformed naevi (patients 3 and 7; table 1), the predicted interval from the time when the tumour would have been clinically invisible, including the observed interval for the two eyes in which this was photographically documented, was a median of 11.7 years (range 0.6–34.6; table 1). The corresponding predicted median age was 51 years (range 32–63; table 1), consistent with a likely de novo melanoma developing in adult life.

Transpupillary thermotherapy

A white scar with minor retinal pigment epithelium (RPE) remnants was obtained in five patients (figure 3A,E,F), a white scar with focal reactive proliferation of RPE in three patients (figure 3B,D,G), and a scar with prominent reactive RPE proliferation, following an RPE tear, in one patient (figure 3C), according to OCT. Choroidal thickness in the treated volume was minimally reduced, regardless of follow-up (figure 3). One patient who needed five sessions of TTT had a senile cataract and underwent phacoemulsification with intraocular lens implantation after the fourth session because of inadequate beam transmission.

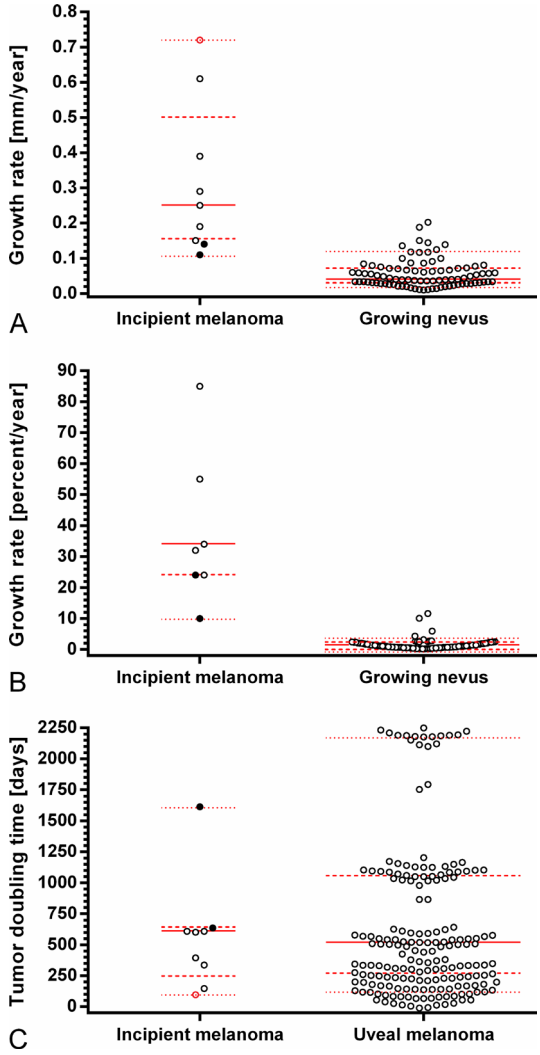

Figure 2 Tumour growth of nine presumed incipient choroidal melanomas as compared with reference data. For the incipient melanomas, hollow symbols indicate likely de novo melanomas, solid symbols melanomas likely developing from a previous naevus, and the red symbol a melanoma that developed in an eye with a previously treated choroidal melanoma. Annual absolute growth rate of tumour largest basal diameter (A) and its annual relative growth rate (B) compared with growth rates of 87 reference patients with a growing choroidal naevus without malignant change during a long-term follow-up.[11] The latter plot omits two fastest growing incipient choroidal melanomas with an off-scale relative growth rate of 1214 (patient 6) and 1437 (patient 9) per cent/year. Calculated tumour doubling time compared with 194 reference patients diagnosed with a choroidal melanoma (C).[17–20] The plot omits 13 reference tumours with doubling times exceeding 4000 days. The red lines indicate median, the dashed lines the 25th and 75th percentiles (ie, IQR), and the dotted lines the 10th and 90th percentiles. Jitter was applied to display overlapping observations.

The median follow-up after completing TTT was 2.1 years (range 7.5 months–8.7 years). None of the patients had developed a local recurrence, or metastases. The BCVA remained unchanged in seven eyes. It decreased from 6/6 to 6/12 in an eye with a tumour under the papillomacular bundle (patient 5). She later developed a macular epiretinal membrane, removed 8 years after TTT (figure 3D and online supplemental text 1). BCVA

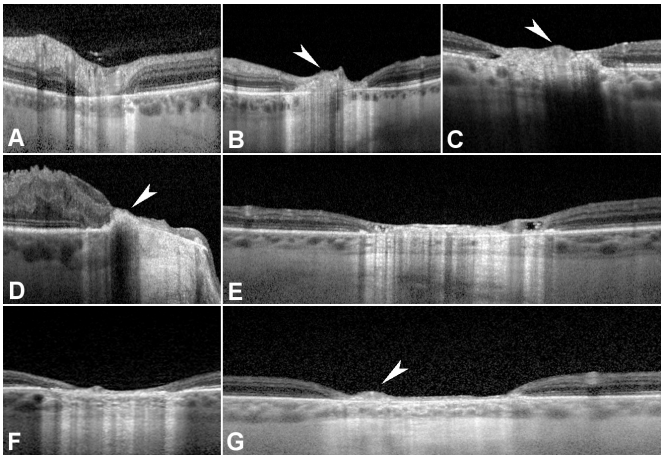

Figure 3 Postoperative optical coherence tomography (OCT) horizontal scans through the centre of the scar in seven patients with a small incipient choroidal melanoma treated with transpupillary thermotherapy (TTT); two patients did not have a postoperative OCT image available. (A) 1 year after the second TTT (patient 1, compare with figure 1A3). (B) 1 year and 3 months after a single TTT (patient 3, compare with figure 1C3). (C) 3 years after a single TTT (patient 4). (D) 8 years and 3 months after the second TTT (patient 5, compare with figure 1E3). (E) 6 months after the third TTT (patient 6, compare with figure 1F4). (F) 1 year and 6 months after the second TTT (patient 8, compare with figure 1H4). (G) 6 months after the second TTT (patient 9, compare with figure 1I3 taken 1 year later). A retinal scar with proliferation of the retinal pigment epithelium (arrowhead in B–D) and (G), a simple outer (A) to full thickness retinal atrophy (E,G), both with minimal change in choroidal thickness, and wrinkling of the adjacent retina after epiretinal membrane formation (D). Scale, 1:1 pixel (A–D); 1:1 µm (E–G).

was 6/40 in one patient despite cataract surgery because of non-exudative macular degeneration (patient 2).

DISCUSSION

Our primary criterion for managing the nine patients was a TDT compatible with those reported for known uveal melanoma[17–20] and relative growth rates exceeding those of choroidal naevi.[11] Supporting criteria were older age when naevi rarely grow[11] and new naevi do not develop, appearance of a new tumour in a previously normal fundus, predicted appearance in adult age, or asymmetric growth.

The distribution of our calculated TDT matched that of published reference data for uveal melanomas.[17–20] The median observed growth rate of 0.25–0.29 mm/year was 6–7 times faster than 0.04 mm/year reported for growing choroidal naevi.[11] The median relative growth rate of 34–55 per cent/year was 30–50 times faster than the calculated reference of 1.1 per cent/year. This rate in all seven eyes with a likely de novo melanoma arising in adult life was at least two times the upper range of the published values. We now consider such an annual relative growth rate, which takes the LBD into account, a clearer criterion to diagnose a presumed incipient choroidal melanoma than the annual absolute growth rate.

It seems reasonable to say that tumours of this size can presently only be diagnosed clinically based on growth characteristics. None of them increased the thickness of the choroid and were thus less than 0.3 mm thick and, with one exception, they were less than 2.0 mm in LBD. Until now, the smallest choroidal melanomas that have undergone a successful biopsy in experienced hands have been 2–3 mm in LBD[4 7 21–24] and 0.7–1.0 mm in thickness[24–26] and thus, approximately 3–30 times larger in volume than our presumed incipient choroidal melanomas.

The only risk feature associated with class 2 GEP among 217 patients with a choroidal melanoma less than 3.5 mm thickness was thickness exceeding 2.25 mm,[7] as compared with 0.3 mm or less in our study. The risk features in the Small Fatal Choroidal Melanoma Study that focused on 45 melanomas 3.0 mm or less in thickness that metastasised were similar to those for all choroidal melanomas of similar size.[6] Twenty-one (47%) of the 45 fatal melanomas were less than 2.25 mm in thickness. None was less than 3.0 mm in LBD when treated, and because the nine presumed incipient choroidal melanomas were less than 2.5 mm in diameter they were very unlikely to have developed the capacity to metastasise, whether or not such capacity was to emerge in them during later tumour progression.

The study of 217 small choroidal melanomas identified one new risk feature associated with GEP class 2, namely age over 60 years.[7] This corresponds with the rarity of growing naevi in this age group.[11] The authors speculated that older age is associated with a higher risk of a small choroidal melanoma to harbour a *BAP1* pathogenic variant. However, 28 (62%) patients in the Small Fatal Choroidal Melanoma Study were younger than 60 years. One of the two incipient melanomas with the fastest TDT arose de novo in an eye with a previously irradiated, non-adjacent choroidal melanoma, and perhaps had a *BAP1* mutation.[27] Though we cannot exclude the possibility that it was an implantation growth seeded subretinally, it was non-adjacent and developed in the choroid rather than the subretinal space in an area that had previously been normal.

The authors of the study of 217 small choroidal melanomas speculated that benefit from treating a small GEP class 1 choroidal melanoma, which likely harbours an *EIF1AX* or an *SF3B1* mutation, might be negligible compared with one that has a *BAP1* mutation or no mutation yet, unless growth is documented.[7] Their main argument for deferring treatment of small class 1 melanomas was that many more patients need to be treated to prevent one metastasis, yet everyone is exposed to risk of visual deterioration. All tumours that we treated were documented to grow faster than choroidal naevi. The risk of delayed visual loss after TTT is smaller than after brachytherapy. A limitation of TTT as a primary treatment is the higher rate of local recurrences as compared with irradiation.[28] For this reason, and because we observed relatively little choroidal atrophy despite disappearance of the pigmented tumour, we recommended long-term follow-up for our patients,[29] including B-scan ultrasonography because of the risk for extraocular recurrence after TTT.[30 31] A larger number of risk features is associated with a higher rate of local recurrence after primary TTT.[29] However, our patient with four risk features has not developed any recurrence during 7 years of follow-up.

One incipient melanoma had a substantially longer TDT than the median and appeared to be a previous naevus that underwent an eccentric transformation into a melanoma, based on asymmetric growth. The corresponding calculated growth rate and TDT for this tumour are underestimates, because an unknown proportion of it was growing. The rates for the patient who had a previously stable naevus before symmetric growth appeared may be underestimated as well, depending on how long growth had occurred undetected within the borders of the prior naevus.

A limitation of our retrospective study is the small number of patients. Our reference data share the same limitation. Measurements from photographs are subjective. We aimed to minimise

bias by using the mean of four different measurements. None of the tumours underwent histopathological or genetic verification, which has not yet been reported for any choroidal tumour this small. Though 51 uveal melanomas in the published reference dataset had a histopathological diagnosis,[17–19] none had undergone a genetic analysis. Longer follow-up is needed to confirm local tumour control and vision outcome after TTT in this group of patients.

The prognosis of metastatic choroidal melanoma has not improved.[32] Early detection and treatment of the primary tumour are crucial, because small tumours have a better prognosis.[33 34] This is likely attributable to their lower probability of having acquired cytogenetic abnormalities that provide metastatic capability.[34 35] When an incipient choroidal melanoma is diagnosed, the risk for metastases is minimal and the risk for treatment-related complications low. We propose annual relative growth rate and TDT as criteria to identify incipient choroidal melanomas so that they can be treated as early as possible. Because fundus imaging is becoming more common, we expect that incipient choroidal melanomas will be diagnosed much more often than until now.

Contributors SJ and RAJ conducted the work and TK was the supervisor. All authors, SJ, RAJ, MT, SE and TK contributed to the planning and reporting of the work, the design and implementation of the research, the analysis of the results and the writing of the manuscript.

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Ethics approval Our study was approved by the institutional review board of the Helsinki University Hospital. It followed the tenets of the Declaration of Helsinki.

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METHODS

Protocol for ImageJ

Calculate area manually by using a mask:

• Open the original photograph
• Use the straight-line selection tool to make a line selection that corresponds to known distance
  Analyze > Measure (the dimeter of the optic disc)
  Analyze > Set scale (enter known distance, unit: 1.5 mm)
• Create mask
  Use Polygon tool to outline the tumour
  Edit > Selection > Fit spline (to smooth the margins)
  Edit > Selection > Create mask
• Open a Mask image
  Image > Adjust > Threshold (125-255 works well)
• Make area measurements
  Analyze; select ”Area” and ”Fit ellipse”
• Analyze > Analyze particles; select ”Display results” and ”Add to manager”
• Save, and close mask

Calculate area by automatic recognition:

• Open the original photograph
• Use the straight-line selection tool to make a line selection that corresponds to known distance
  Analyze > Measure (the dimeter of the optic disc)
  Analyze > Set scale (enter known distance, unit: 1.5 mm)
• Image > Type > 8-bit
• Image > Adjust > Threshold

The threshold dialog window allows you to highlight pixels in an image that have values within a range you define. Adjust the sliders so that the dark, low-value pixels turn red (including tumor) but those that represent other parts do not change. Close the threshold window without clicking any of the buttons.

• Analyze > Set measurements; select “Area” and “Limit to threshold”)
• Analyze > Analyze particles; select ”Display results” and ”Add to manager”
• Save

RESULTS

Case Reports

Patient 1. A tiny juxtapapillary pigmentary anomaly was documented in a fundus photograph of a 49-year-old man by an optician in February 2015 (figure 1A1). In October 2017 (figure 1A2) it had grown, and they referred him. Based on rapid documented growth the tumour was diagnosed as a presumed incipient choroidal melanoma and managed with two sessions of TTT at 8-month interval. The outcome was a flat white scar (figure 1A3), stable at 1.5 years.

Patient 2. A small presumed naevus close to the foveola was first noted in October 2014 during screening with fundus photography to identify diabetic retinopathy in a 77-year-old woman (figure 1B1). It had grown in a subsequent screening photograph taken in October 2016 (figure 1B2) and she was referred to a retinal specialist. He observed it for 3.5 months, noted further growth (figure 1B3), and referred her. Because of documented progressive growth and apparent origin in her 50's, based on calculated tumour doubling time, the tumour was diagnosed as a presumed incipient choroidal melanoma and managed with five sessions of TTT. The first 4 sessions did not produce an adequate response because of cataract, necessitating its extraction before the last TTT session. Dry macular degeneration was noted. One year 2 months after the last session, the referring specialist reported a flat white scar.

Patient 3. A private ophthalmologist documented a small presumed pigmented naevus close to the optic disc (figure 1C1) in a 67-year-old woman in December 2005. During a later appointment in March 2010 it was noted to have grown (figure 1C2). Based on documented, asymmetric growth we diagnosed a presumed incipient choroidal melanoma which likely originated from her small prior naevus and managed it with one session of TTT. The outcome was a pigmented flat stable scar (figure 1C3). No regrowth has occurred within 10 years of follow-up.

Patient 4. A 64-year-old man was suspected of having glaucoma. A tiny pigmented lesion was overlooked in fundus photographs taken as part of glaucoma screening in August 2012 (figure 1D1). It had grown in September 2016, and the patient was referred. In retrospect, we noticed that the lesion had progressively grown in November 2013 (figure 1D2), in February 2016 (figure 1D3), and in September 2016 (figure 1D4). We diagnosed this tumour as a presumed incipient choroidal melanoma and managed it with one session of TTT that caused a retinal pigment epithelium (RPE) tear. It healed with reactive proliferation of the RPE, and further sessions were not administered. No relapse has occurred within three years and 5 months from the TTT treatment

Patient 5. A private ophthalmologist had taken a fundus photograph of a small peripapillary pigmented lesion in a 50-years-old woman in February 2003 (figure 1E1). In June 2010, she noticed decreased vision. The lesion had grown notably (figure 1E2) and it had 4 risk factors for malignancy (subretinal fluid, symptoms, orange pigment, and margin touching optic disc). Together with fast growth the tumour was diagnosed as a presumed incipient choroidal melanoma. The tumour was not well suited for brachytherapy because of its small size and location next to the optic disc, coinciding with the optic nerve sheath behind. Despite its location in the papillomacular bundle and thus predicted marked reduction of vision, she elected TTT. We treated it with two sessions of TTT two months apart, resulting in a partly pigmented flat scar. A tiny bleeding was noted after the second session. Two years after treatment her best corrected visual acuity (BCVA) was 20/40 with eccentric fixation (figure 1E3). Five years later, she had a symptomatic vitreous detachment that left her with a macular epiretinal membrane and a drop in BCVA to 20/100. She has recently undergone vitrectomy.

Patient 6. A small presumed naevus, in a location where it was not detectable upon reviewing her first fundus images, taken at a screening for diabetic retinopathy in January 2014 (figure 1F1), was noticed in May 2017 (figure 1F2) in a 67-year-old woman. Her father had a history of renal cell cancer, and a second cousin had died of conjunctival melanoma. She did not carry *BAP1* pathogenic variants. Because it was a *de novo* tumour and showed growth during a 5-month interval before she was referred, we diagnosed a presumed incipient choroidal melanoma (figure 1F3) and treated it with three sessions of TTT. Two years from the last TTT treatment, the outcome is a flat white scar with a few pigment granules.

Patient 7. A 47-year-old woman had regularly been seen by her ophthalmologist because of ocular hypertension, and a tiny presumed choroidal naevus was first documented in April 2002 (figure 1G1). In February 2006 and April 2007, it was stable. In May 2009, it was first noticed to have grown (figure 1G2) and she was referred. Because of recent growth we diagnosed a presumed incipient choroidal melanoma and managed it with one session of TTT. The outcome at one year was a flat white scar with some pigment (figure 1G3) that is stable at 11 years.

Patient 8. A tiny pigmented lesion was overlooked in April 2010 (figure 1H1) and in March 2011 (figure 1H2) when it was first noted during screening with fundus photography to identify diabetic retinopathy. It had further grown in May 2013 (figure 1H3). The 56-year-old man was referred, and we diagnosed a presumed incipient choroidal melanoma and managed with two sessions of TTT with a 3 month interval. The outcome at 11 months was a flat white scar with a few granules of pigment (figure 1H4) stable 5 years later.

Patient 9. We diagnosed a 54-year-old man with a T2a, stage IIA, medium-sized choroidal melanoma that was 5.0 mm in height and 10.8 mm in LDB, located inferotemporally with an exudative retinal detachment extending to the fovea, and managed it successfully with ruthenium brachytherapy in March 2014. In June 2016, just above the superotemporal vascular arcade in a previously normal area (figure 1I1), we noticed a new small pigmented choroidal lesion (figure 1I2) and diagnosed a presumed incipient choroidal melanoma, a putative second primary given no evidence of breached RPE. We managed it with two sessions of TTT 6 months apart. The outcome at 1.5 years was a flat white scar and eccentric small patches of pigment (figure 1I3). The scar is unchanged at 3.5 years after TTT.

Supplementary Table Initial and final largest basal diameter and area of 9 presumed incipient choroidal melanomas that were independently measured by two investigators (SJ, RTA) both by manual drawing and by automatic recognition of tumour margins when measuring the area and only manual drawing when measuring the diameter, presuming the optic disc diameter to be 1.5 mm.

	Initial						Final					
	LBD (mm)		Area (mm²) Manual		Automatic		LBD (mm)		Area (mm²) Manual		Automatic	
Patient	SJ	RTA	SJ	RTA	SJ	RTA	SJ	RTA	SJ	RTA	SJ	RTA
1	0.572	0.376	0.174	0.116	0.198	0.101	0.875	0.991	0.477	0.537	0.470	0.429
2	1.112	0.979	0.709	0.704	N/A	0.690	1.614	1.613	1.794	1.810	N/A	1.730
3*	1.135	1.052	0.682	0.585	0.761	0.494	1.670	1.451	1.305	1.154	1.412	1.017
4	0.591	0.451	0.134	0.109	N/A	0.103	1.648	1.736	1.731	1.663	1.631	1.522
5	0.590	0.534	0.141	0.094	N/A	0.077	1.980	1.963	2.366	2.541	N/A	1.980
6†	0.05	0.05	0.0025	0.0025	0.0025	0.0025	2.449	2.186	1.993‡	0.993‡	2.345‡	0.847‡
7*	0.571	0.539	0.165	0.142	N/A	0.131	0.941	1.053	0.576	0.560	0.733	0.492
8	0.446	0.465	0.167	0.148	0.227	0.144	1.351	1.256	1.044	0.796	1.043	0.674
9†	0.05	0.05	0.0025	0.0025	0.0025	0.0025	1.974	1.789	2.513	1.826	1.623	1.611

LBD = Largest basal diameter; N/A = Not available because failure to measure with automatic recognition

* Likely a transformed naevus

† Tumour initially invisible, modeled using presuming an initial tumour diameter of 0.05 mm

‡ Tumour margins diffuse and difficult to define