

Malignant transformation of low-risk choroidal nevi: a case series

Emilia Zwolińska¹, Lazaros Konstantinidis², Iwona Rospond-Kubiak¹

¹Department of Ophthalmology, Poznan University of Medical Sciences, Poznan, Poland

²Faculty of Biology and Medicine of the University of Lausanne, Jules Gonin Hospital, Lausanne, Switzerland

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Key words: choroidal melanoma, choroidal nevus transformation, choroidal nevus growth rate, tumour doubling time.

Abstract

Introduction: A well documented transformation from a choroidal nevus to melanoma is uncommon.

Aim of the research: To report a series of choroidal melanocytic lesions diagnosed at the Ocular Oncology Service, Department of Ophthalmology, Poznan University of Medical Studies, Poland, presenting initially low-risk features for malignancy, which transformed into choroidal melanomas.

Material and methods: Retrospective data analysis of patients with choroidal nevi without major features for growth (thickness over 2 mm in ultrasound (US), subretinal fluid (SRF), orange pigment). Lesions were evaluated at all visits using multimodal imaging (colour and autofluorescence fundus photography, OCT, and US measurements) until the melanoma diagnosis. We measured alterations in thickness, growth rate (GR) and tumour doubling time (TDT) and across the consecutive visits.

Results: We identified 11 lesions with a median thickness of 0.95 mm at presentation (range: 0.3–1.9 mm). The median observation time until transformation was 47 months (range: 17–99 months). Ten (91%) lesions showed lipofuscin accumulation, 8 (73%) grew in thickness over 2 mm in US, 8 (73%) were diagnosed with SRF and 6 (54%) extended in their longitudinal diameter. The median overall GR was 0.67 mm/year (range: 0.0–3.4 mm/year) and the median overall TDT was 884 days (range: 167–3719 days). On follow-up, majority of lesions presented heterogeneous GR and TDT, and at the time of fastest growth, median GR was 1.88 mm/year (range: 0.0–5.6 mm/year) and median TDT was 201 days (range: 83–3044 days).

Conclusions: Choroidal nevus may transform into choroidal melanoma after years of stability and therefore should undergo a regular follow-up. Careful monitoring of GR and TDT may aid the diagnosis of malignant transformation.

Introduction

Choroidal nevus (CN) is a frequently observed melanocytic lesion during routine ophthalmic fundus examination. The prevalence of CN in the general population ranges from 0.3% to 6.5%, with no significant difference between men and women [1–6]. According to data from the National Health and Nutrition Examination Survey (NHANES) and the Multi-Ethnic Study of Atherosclerosis (MESA), CN is more prevalent among white Caucasians compared to other ethnic groups, such as Blacks, Hispanics, and others [2, 6].

Choroidal melanoma (CM) is a rare malignancy, with an incidence ranging from 1.3 to 8.6 cases per million annually among European countries. The prevalence of CM demonstrates a positive correlation with geographical latitude, exhibiting the highest rates in Scandinavian populations and the lowest in sub-Mediterranean regions [7]. Despite the progress of local ophthalmic treatment, the metastatic disease would affect almost 50% of patients with uveal melanoma within first 5 years after the diagnosis. It is estimated that approximately 1 in 8,845 choroidal nevi would progress to melanoma annually [8], un-

derscoring the importance of careful monitoring of all choroidal melanocytic lesions.

In daily clinical practice, the accurate differential diagnosis between CN and CM remains a challenge. In 1995, a hallmark paper in ocular oncology was published by Shields *et al.* identifying risk factors for growth of melanocytic lesions based on clinical findings: thickness over 2 mm (T), presence of the subretinal fluid (F), ocular symptoms (S), orange pigment (O) and location within 2 mm from the optic disk (M). The TFSOM (To Find Small Ocular Melanoma)-paradigm has recently been updated due to enhanced methods of ophthalmic imaging and now stands for TFSOM-DIM (T – thickness over 2 mm, F – presence of subretinal fluid, S – vision below 0.6, O – the presence of orange pigment (lipofuscin), M – melanoma ultrasound hollowness and DIM – diameter greater than 5 mm). It remains a useful tool for estimating the likelihood of growth and, consequently, an increased risk of malignant transformation of melanocytic lesions in the hands of an experienced ocular oncologist [9].

In contrast, the more recently developed MOLES system is recommended for routine clinical evaluation

Table 1. Demographic data of our series

Feature	N (%)
Gender (<i>n</i> = 11)	
Female	6 (55)
Male	5 (45)
Age [years] mean (median, range), <i>n</i> = 11	57 (65, 17–76)
Race (<i>n</i> = 11)	
Caucasian	11 (100)
African	0
Hispanic	0
Asian	0
Other	0
Eye (<i>n</i> = 11)	
Right	4 (36%)
Left	7 (64%)

of choroidal melanocytic lesions without the need for ultrasound, as it aids in identifying lesions that require prompt referral to an ocular oncology unit for further evaluation [10–12]. Of note, it has been proved in various studies that the risk of metastatic disease positively correlates with the primary lesion's basal diameter and thickness [13] making the timely diagnosis of malignant transformation crucial for the patient's survival.

Aim of the research

The aim of this study is to report a case series of small choroidal melanocytic lesions presenting initially as low-risk for growth, which subsequently transformed into choroidal melanomas during the observation period.

Material and methods

This study involves retrospective data from patients of the Ocular Oncology Service, Department of Ophthalmology, Poznan University of Medical Studies, Poland, who were diagnosed with benign choroidal melanocytic lesions and screened between 2005 and 2023. Given the evolving criteria for the assessment of choroidal melanocytic lesions over time (TF-SOM, TFSOM-DIM, MOLES), we focused on three key features most closely linked to the progression of choroidal nevi into melanoma, namely lesion thickness (Th), presence of orange pigment (O), and subretinal fluid (F). All lesions according to the MOLES scale were 0–2 (common to low-risk nevi). Therefore, we included choroidal melanocytic lesions in the posterior pole that lacked lipofuscin (O) visible on fundus autofluorescence (FAF), with thickness less than 2 mm

on ultrasound (US) and no SRF visible at their initial visit. Patients with no documented follow-up or a lack of good-quality fundus photographs at presentation were excluded from the study.

At each visit, all lesions were evaluated using colour fundus photography (2005–2021: Topcon TRC-50DX, Topcon Co.; 2021–2024: Clarus 500, Carl Zeiss), FAF imaging (2005–2021: Topcon TRC-50DX, Topcon Co.; 2021–2024: Clarus 500, Carl Zeiss), optical coherence tomography (OCT) (2005–2018: Cirrus HD, Carl Zeiss; 2018–2024: Topcon DriOCT, Topcon Co.), and B-scan US (2005–2020: EyeCubed, Ellex; 2020–2024: ABSolu, V1.03, Quantel Medical). The ultrasound software was utilized to measure the longitudinal basal diameter (LBD) and tumour thickness (Th) of each lesion. Radial OCT scans from the following visits were analysed for any sign of new subretinal fluid.

The observation time was recorded from the initial visit until the moment of melanoma diagnosis, which was made based on documented lesion growth in ultrasound and/or fundus photographs along with the appearance of subretinal fluid and/or orange pigment (lipofuscin). The height of flat lesions not visible in US examination was arbitrarily assumed to be 0.3 mm according to previous literature findings [14–16].

We determined the growth rate (GR) for each lesion as the gain of mm in LBD per year. Tumour volume and doubling time (TDT) were calculated using the mathematical formula suggested by Stålhammar [17]. We performed calculations for every follow-up visit and then determined the overall results for every lesion during their whole observation time.

Results

Among the 1,315 patients with choroidal melanocytic lesions registered in our database, 11 (0.8%) patients met all the inclusion criteria: 6 women and 5 men, with a median age of 65 years (range: 17–76 years). Detailed demographic data of the patients are outlined in Table 1 and initial photographs of all the lesions are presented in Figure 1.

During the initial assessment, the median lesion thickness measured by US was 0.83 mm (range: 0.3–1.91 mm), with no presence of subretinal fluid or lipofuscin deposits. The median follow-up until the diagnosis of choroidal melanoma was 47 months (range: 17–99 months). The treatment was initiated before 24 months for 3 (27%) patients, after 24 months for 8 (73%) patients.

Throughout this period, 91% of the lesions (*n* = 10) developed orange pigment, while 73% (*n* = 8) exhibited an increase in thickness beyond 2 mm as measured by US. Subretinal fluid was detected in 73% of patients (*n* = 8), and a distinct enlargement in the LBD (> 50%) was noted in 54% of lesions (*n* = 6) as demonstrated in Figure 2. 45% of lesions (*n* = 5) presented all



Figure 1. Eleven lesions that met the inclusion criteria – colour fundus photography at the initial visit

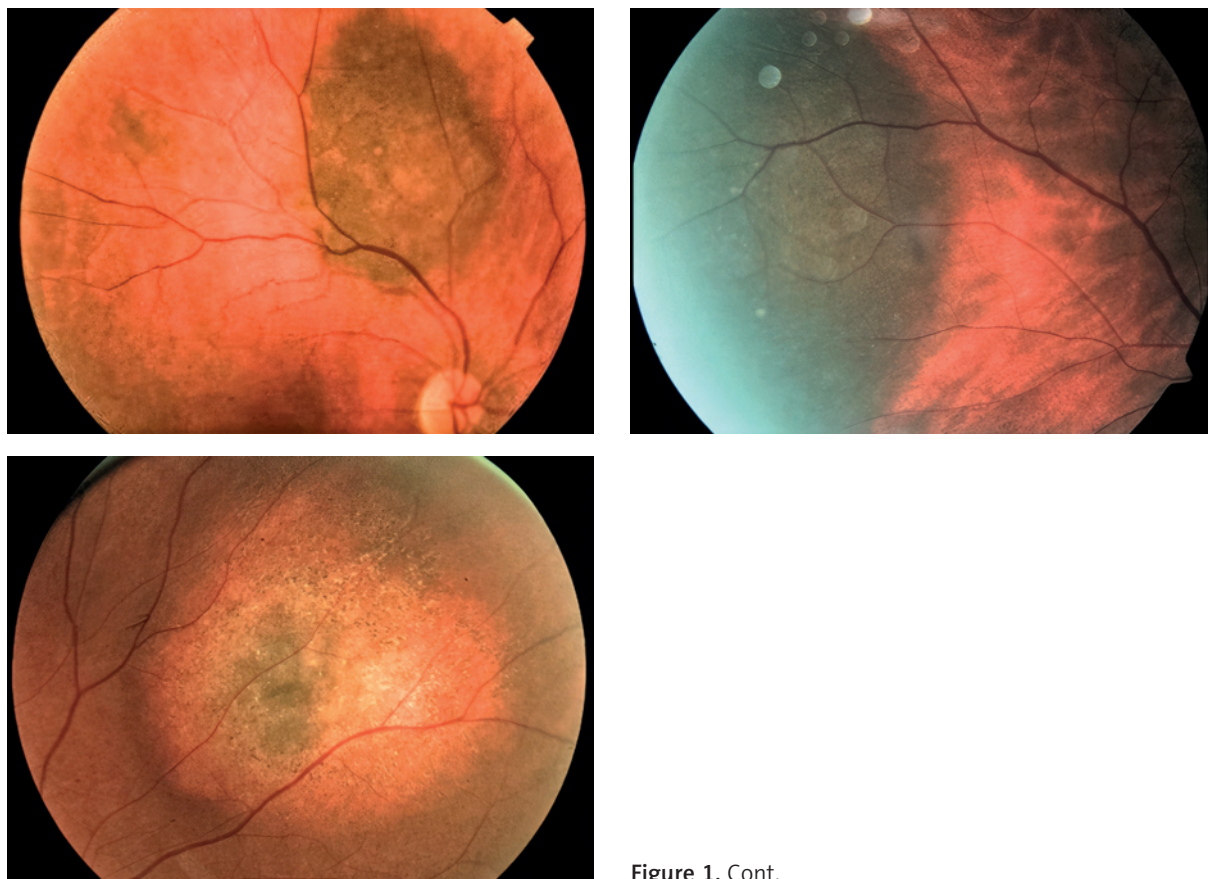


Figure 1. Cont.

the features at the same time. The median US thickness at transformation was 2.40 mm (range: 0.3–7.9 mm). When the subretinal fluid was present, it was predominantly located along the slope of the lesion in 55% of patients ($n = 6$), with only 21% ($n = 2$) showing fluid at the apex of the lesion.

In 5 (45%) patients, the lipofuscin appeared in the centre of the lesion and in 6 (55%) patients – at the lesion's border (Figure 3).

The median increase in Th was 89% (range: 0–2533%), with a trend of acceleration over time, as illustrated in Figure 4. Two lesions remained unchanged in thickness despite the passage of time.

Median overall GR for all lesions was 0.67 mm/year (range: 0.0–3.04 mm/year). Median GR during periods of the fastest growth of each lesion was 1.88 mm/year. Patient-specific fluctuations of the following GR calculations between follow-up visits are shown in Figure 5. Median overall TDT was 884 days (range: 167–3719 days). Variations of TDT for each lesion throughout the observation period from visit to visit were highly variable, with each lesion showing distinct changes over time, as presented in Figure 6. The median of the lowest TDTs observed during the most rapid growth phase of each lesion was 201 days.

The general results of the US measurements and GR and TDT calculations for each lesion are presented in Table 2.

Discussion

This is a rare case series of patients with documented growth of the initially low-risk choroidal nevi that turned out to be melanomas. The strength of the study is a well-documented follow-up; the major shortcoming would be different equipment used for the measurement of transforming lesions as the observation period covers nearly 20 years. Moreover, small number of follow-up visits and prolonged intervals in some cases may have impacted the accuracy of our calculations.

The documented transformation of choroidal lesion is exceedingly rare with very limited data published [18–20] although there are some historical cohorts of patients that were observed for lesion growth [21]. All our patients at the initial visit presented no major risk for lesion growth.

The question of whether choroidal melanoma always arises *de novo* or can develop from a preexisting choroidal nevus, has been a topic of ongoing debate. It is well established that both scenarios are possible [22,

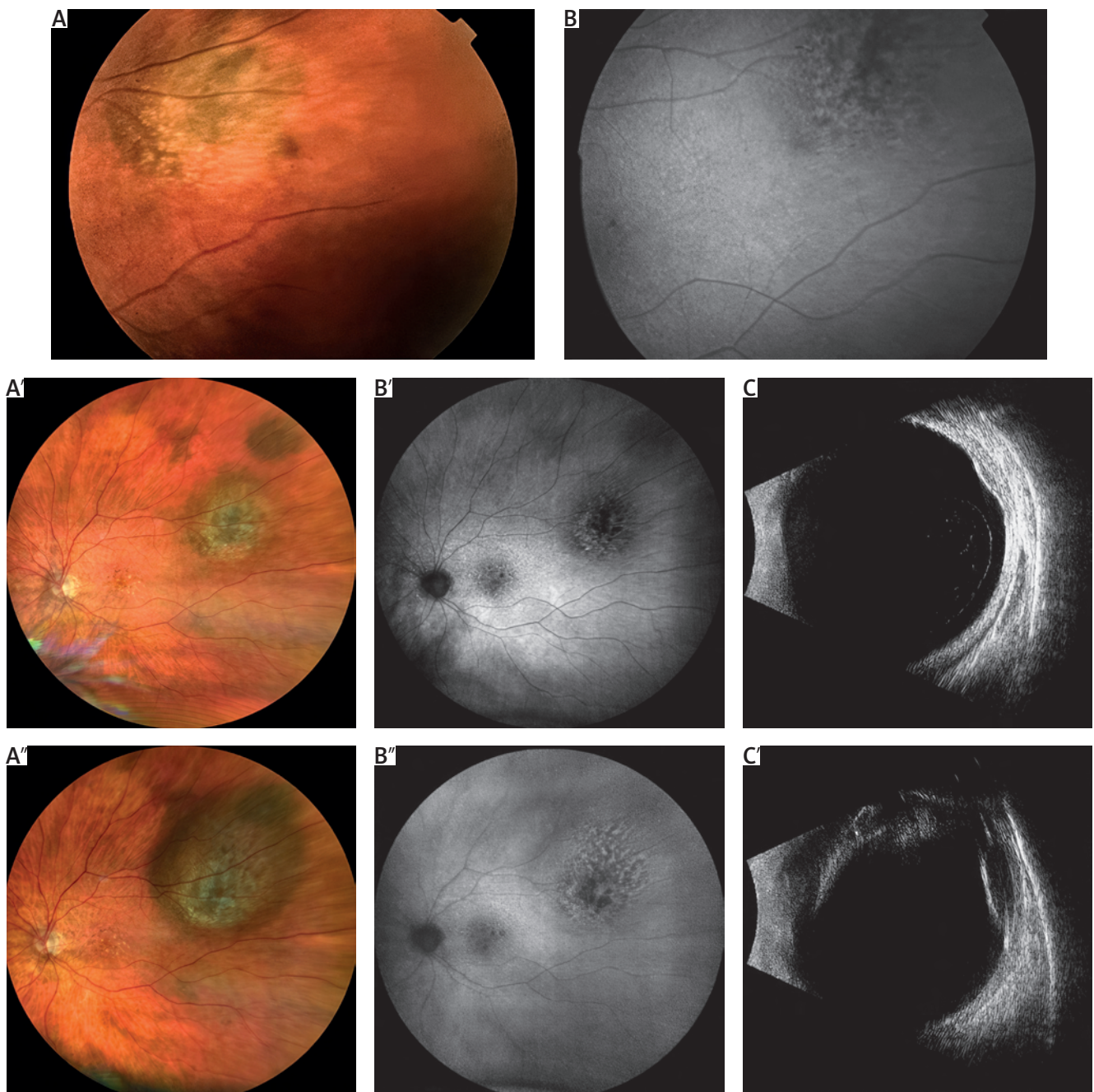


Figure 2. Patient 3 – 73-year-old woman; **A, B** – colour and autofluorescence (FAF) photography at presentation; **A', B', C** – colour and FAF photography and US after 54 months of observation; **A'', B'', C'** – colour and FAF photography and US at the transformation diagnosis after 64 months

23]. In a large retrospective study involving over 2,500 choroidal nevi, features indicative of lesion growth (and therefore transformation) were identified in 180 (7%) cases, demonstrating that, although rare, benign melanocytic lesions can evolve into malignancy [18]. However, some researchers argue that inconsistencies in classification and diagnostic criteria may lead to certain choroidal melanocytic lesions being initially

misclassified as nevi. Over time, as these lesions grow and exhibit additional features, they may eventually meet the clinical criteria for melanoma diagnosis [24].

In 5 of our patients (45%), growth observed in colour fundus photography during follow-up visits occurred at the site of the lesion's margin, often accompanied by new lipofuscin deposits at the same location when present. Among six lesions exhibiting



Figure 3. Two patterns of lesion growth: **A** – patient 5: colour fundus photography at the first visit; **B** – same lesion with temporal growth and lipofuscin accumulation at the margin (white arrowheads); **C** – patient 8: colour fundus photography at the first visit; **D** – same lesion with uniform growth and central distribution of orange pigment (yellow arrowheads)

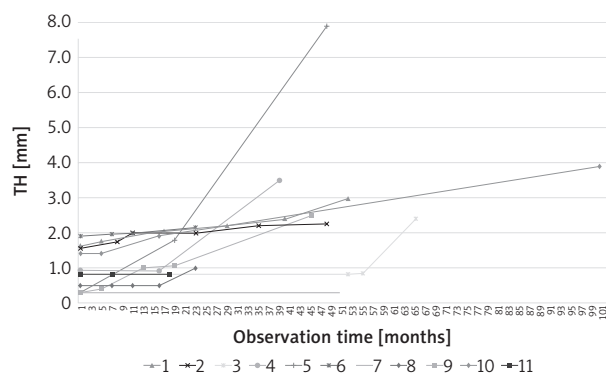


Figure 4. Patient-specific tumour height (TH) growth across follow-up visits

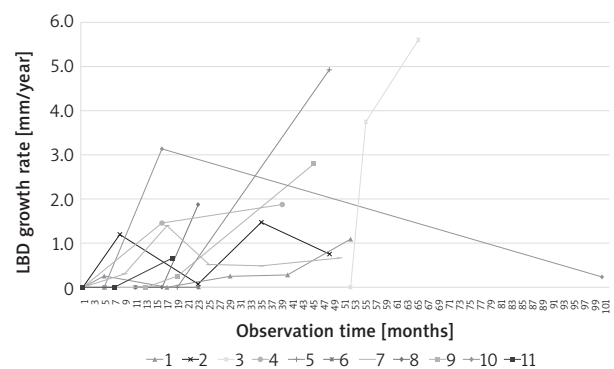


Figure 5. Patient-specific fluctuations in longitudinal basal diameter (LBD) growth rate during the observation period

even growth (55%), lipofuscin, if present, was located in the centre of the lesion or was distributed evenly on the lesion's surface. Examples of both growth patterns are shown in Figure 6. It remains unclear whether these differences in growth patterns are associated with distinct lesion types. Further investigation is warranted, as understanding these patterns may

help differentiate between a transforming nevus and a small but growing melanoma *de novo*.

The concept of TDT in relation to choroidal melanoma was first introduced by Augsburger *et al.* in 1984, employing a formula designed for cubic tumour shapes [25]. Since then, a limited number of studies have explored similar approaches, using alternative

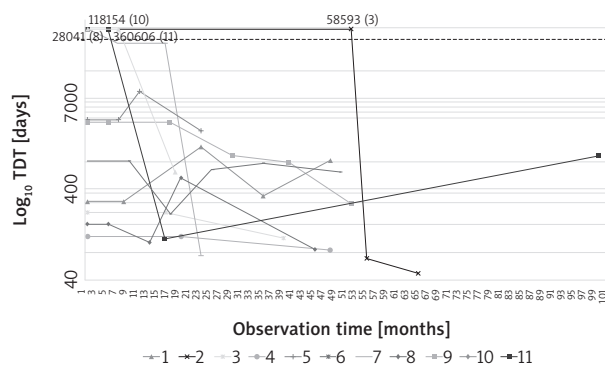


Figure 6. Patient-specific fluctuations in tumour doubling time (TDT) during the observation period; dashed line represents the threshold for values exceeding 40,000; over-the-dashed-line TDT values shown are original measurements (patient number)

formulas tailored to different tumour geometries [26–28]. Among these, the semi-ellipsoidal shape has been the most adopted, as in our study, however, one research group chose a cylindrical model to estimate TDT in small choroidal melanocytic lesions [28]. To our knowledge, only a single study has applied such calculations specifically to choroidal nevi [20]. A meta-analysis of TDT estimations in choroidal melanoma found that the choice of formula based on tumour shape did not significantly impact the overall comparability of results [29].

According to Jouhi *et al.*, tumour growth rate and TDT may be used as a diagnostic criteria for recognition of choroidal melanoma at the early stage [28]. All of our lesions demonstrated a GR exceeding 0.04 mm per year at some point, a threshold previously associated with distinction between benign and malignant lesions [30]. Median overall TDT in our group was 884 days, which is higher than in previously published results [20, 25, 26, 29, 31]. However, taking into consideration the lowest calculated TDT for each lesion (during the periods of the fastest growth), the median TDT was 201 days which was even slightly lower than in the aforementioned studies. Looking closer at the dynamics of TDT changes in time, we noted that all lesions displayed periods of accelerated TDT, with nine of these (82%) alternating between phases of acceleration and deceleration in TDT over the course of observation. The reason of such variations is not yet clear; it could be attributed to measurement bias or to the periods of accelerated growth associated with genetic alterations in growing melanoma [32]. Furthermore, it is important to consider the potential bias introduced by estimating Th in lesions undetectable on US. The value of 0.3 mm may be either underestimated or overestimated, resulting in discrepancies in the actual TDT measurements.

In a recently published review [21], on the basis of the analysis of the published series of patients,

Table 2. Lesions' measurements at the initial and final visit with overall growth rate (GR) and tumour doubling time (TDT)

No.	Age at presentation [years]	Observation time [months]	Initial US thickness [mm]	Final US thickness [mm]	Initial LBD [mm]	Final LBD [mm]	Overall GR [mm/year]	Overall TDT [days]
1	76	51	1.63	2.98	6.45	7.90	0.38	1051
2	65	47	1.57	2.26	7.60	10.69	0.79	933
3	73	64	0.83	2.40	3.30	8.94	1.06	435
4	54	38	0.95	3.50	3.47	8.90	1.71	248
5	17	47	0.30	7.90	4.50	16.40	3.04	167
6	65	22	1.91	2.16	9.31	9.31	0.00	3719
7	44	50	0.30	0.30	3.50	6.23	0.67	884
8	39	23	0.50	1.00	4.49	5.60	0.61	403
9	73	45	0.30	2.49	3.85	10.04	1.69	187
10	52	99	1.42	3.89	5.39	9.95	0.55	922
11	65	17	0.82	0.83	5.78	6.39	0.43	1661

the authors observed that a majority of the recorded transformations happened within 5 years of observation, among including 67% within first 2 years. Some authors of the analysed series also noticed sudden acceleration in lesion growth before the diagnosis. Owing to that observation, the authors suggested that the lesions exhibiting early growth (before 24 months) should rather be called 'melanoma in evolution' and perhaps were just small tumours from the beginning. The actual transformation of choroidal nevi most probably happens later; also the growth of a lesion at the level of 0.04 mm/year is practically undetectable given the resolution of currently used equipment before 24 months [21].

Conclusions

Choroidal nevi, even after long periods of stability, may transform into choroidal melanoma. Therefore, all choroidal melanocytic lesions should undergo thorough follow up, reasonably once/twice a year, as the lesion's GR may quickly accelerate. The findings indicate that newly diagnosed melanocytic lesions without growth features should undergo reassessment at 6-month intervals during the initial two years of observation, and at least once per year thereafter. Careful monitoring of GR and TDT may aid in the diagnosis of malignant transformation.

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Ethical approval

The research was conducted following the Declaration of Helsinki and the ethical approval for this study was obtained from the Institutional Review Board (Poznan University of Medical Sciences Bioethics Committee, approval no. 939/21; the informed consent was obtained from the patients for the publication of their clinical images).

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence

Iwona Rospond-Kubiak
Department of Ophthalmology
Poznan University of Medical Sciences
Poznan, Poland
E-mail: irospondkubiak@ump.edu.pl

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