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Research Article

Is tumour thickness measurement required for MOLES scoring of melanocytic choroidal tumours?

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Short Title: Tumour thickness is not required for MOLES scoring of melanocytic choroidal tumours

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Abstract

Introduction: It can be challenging to distinguish between choroidal naevi and melanomas in the community setting, particularly without access to ultrasonography, required to measure the thickness of melanocytic choroidal tumours. We aimed to determine whether thickness measurement is required for MOLES scoring of melanocytic choroidal tumours.

Methods: The dataset of a recent MOLES evaluation was reviewed. Patients were selected for the present study if their MOLES tumour size category was determined by tumour thickness measured with ultrasonography (US). The largest basal tumour diameter and tumour thickness were then measured from ultra-widefield fundus images and optical coherence tomography (OCT) images, respectively.

Results: The tumour size category was determined by tumour diameter in 203/222 (91.4%) with no influence of tumour thickness. The tumour thickness influenced the MOLES score in 19/222 (8.6%) patients. In 11/19 patients with OCT measurements of tumour thickness, the US measurement exceeded the OCT by more than 25% in 5 patients, more than 50% in 2 patients and more than 75% in 1 patient. As a result, the revised tumour thickness based on OCT determined the size category in 4/216 (1.8%) patients. The Optos measurements increased the diameter score by 1 in 5 patients. As a result, the revised tumour thickness determined the size category in 4/216 (1.8%) patients. If both the revised diameter and thickness scores were considered, the MOLES score reduced in 4 patients. If both the diameter and thickness scores were considered, the MOLES score reduced in 5 and increased in 1. Only 0.94% (2/211) of melanocytic choroidal tumours assessed with MOLES when using Optos ultra-widefield fundus images diameter and OCT to measure tumour diameter and thickness, respectively, required a change in management from a reduction in MOLES score from 1 to 0.

Discussion/Conclusion: This study suggests that the MOLES category for size is influenced more by the tumour diameter, if it can be measured accurately, than by the thickness. This study suggests ignoring tumour thickness if this cannot be measured accurately with OCT, unless the tumour has a mushroom shape.

Introduction

It can be difficult to distinguish large choroidal naevi from melanomas, especially when expertise, imaging equipment, or both are lacking. This is a particular concern when patients are being assessed in the community where the facility to measure the thickness of melanocytic lesions is generally not available. As a result, patients with innocuous naevi may have to undergo unnecessary further investigations, possibly repeatedly and in some cases far from their home at one of the few Ocular Oncology Centres.[1] Conversely, some patients with melanoma may experience delays in diagnosis and treatment, so that any opportunities for preventing visual loss and potential metastasis are missed.[2]

The MOLES acronym and scoring system has recently been developed to help non-experts estimate the likelihood of malignancy according to mushroom shape, orange pigment, large size, enlargement, and subretinal fluid.[3-6] Each of these parameters is scored between 0 and 2, and tumours are categorised as 'common naevus', 'low-risk naevus', 'high-risk naevus' and 'probable melanoma' according to whether the total score is 0, 1, 2 or more than 2, respectively.[5] The large size component of the acronym uniquely includes two parameters, the diameter in millimetres (mm) and thickness in mm. Non-specialists or optometrists may not have access to ultra-widefield fundal imaging but generally have access to OCT imaging and may be able to estimate thickness of the lesion in question; however, for peripheral or large lesions, this may not be possible without the availability of a B-scan US machine and the necessary expertise to undertake the investigation and

measurements. The diameter of lesions that cannot be entirely imaged, can be estimated on fundus examination with a non-contact lens, using the number of disc diameters as an estimate.

The mnemonic TFSOM-DIM (To Find Small Ocular Melanoma Doing Imaging) is designed to estimate the risk of growth according to thickness, fluid under the retina, symptoms, orange pigment, tumour hollowness on ultrasonography, and diameter exceeding 5 mm.[7] Most community optometrists and many ophthalmologists, however, are unable to measure internal acoustic reflectivity, again, because they do not have the required equipment or expertise. MOLES has been developed to overcome this limitation by requiring only ophthalmoscopy, ideally with colour photography. Optical coherence tomography and fundus autofluorescence imaging make it easier to detect subretinal fluid and lipofuscin but are not essential.

There are concerns that without ultrasonography, it is not possible to measure tumour thickness, so reliance on tumour diameter alone may result in inaccurate MOLES scores and sub-optimal patient management.

The aim of this study was to determine whether tumour diameter alone is sufficient to give a score for the size of the tumour and hence how often thickness measurement is required for MOLES scoring of melanocytic choroidal tumours.

Materials and Methods

This retrospective study was approved by the Clinical Audit Department of Moorfields Eye Hospital and adhered to the tenets of the Declaration of Helsinki. The dataset of a recent MOLES evaluation was reviewed.[4] Patients were selected for the present study if their MOLES tumour size category was determined by tumour thickness measured by US. This included patients with a measured largest basal diameter score of 0 or 1, and the corresponding US measured thickness achieved a greater score of 1 or 2, respectively. Patients with largest basal diameter and US thickness scores of both 0 or 2 were not included. These patients were subcategorised into choroidal naevi and choroidal melanoma according to how they were subsequently diagnosed. The largest basal tumour diameter was estimated by using the calliper function on the baseline ultra-widefield fundal images (Optos California [Optos PLC, Dunfermline, Scotland]). Where lesions were round, multiple measurements were taken, and the largest recorded (Fig. 1). The “blend” function was used to examine the red channel, which is known to penetrate retinal tissue deeper than the green channel from the retinal pigment epithelium to the choroid, to ensure accurate estimation of basal diameter.[8]

In addition to B mode US scan, tumour thickness was measured using OCT images (Heidelberg Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) acquired with the enhanced depth imaging (EDI) settings. It should be noted that all patients in the entire dataset had B scan and EDI OCT at every visit, allowing us to perform the analysis retrospectively. For the EDI OCT, manual segmentation of the choroidal-scleral interface was performed where this was not well defined (Fig. 2). The calliper function was then used to place a line from the base of the retinal pigment epithelium (RPE) at the apex of the thickest part of the tumour at an angle orthogonal to the underlying choroidal-scleral interface or manually segmented line.

These measurements were carried out independently by the senior author (B.D.) and the first author (J.C.). Interobserver differences were analysed. The final measurements were used to determine whether there were any changes in tumour thickness size category based on the original measurements documented previously[4] using data from Topcon (Topcon Fundus Camera, Topcon Corporation, Tokyo, Japan) and Optos (Optos PLC, Dunfermline, Scotland) fundal images, and B-scan US (ACUSON S2000, Siemens Healthcare Ltd, UK) thickness measurements.

Results

Patient demographics

The tumour size category was determined by tumour thickness in 19/222 (8.6%) patients (Table 1). There were 8 (72.7%) males and 11 (57.9%) females in this group, with an average age of 61.7 (SD 15.4) years old. Of these patients, 7 (36.8%) were diagnosed with choroidal naevi and 12 (63.1%) with choroidal malignant melanoma. The average MOLES score was 3.1 (range 1-6). None of the lesions had a mushroom shape. Orange pigment was present in trace amounts in 4 (21%), confluent orange pigment was detected in 4 (21%), and 11 (57.9%) had no orange pigment present. The average tumour diameter was 2.5 disc diameters (SD 0.9), and the average tumour thickness measured by US was 1.8 (SD 0.6). Subretinal fluid was detected in trace quantities in 7 (36.8%), in significant quantities in 7 (36.8%) and absent in 5 (26.3%). No tumour enlargement was documented in any of the patients. Measurement of tumour thickness with OCT was possible in 11/19 patients.

Tumour diameter

Since the tumour diameters were assessed by a number of different physicians on different fundus imaging cameras (Topcon and Optos), these measurements were repeated independently by B.D and J.C. on baseline Optos ultra-widefield fundal images (Table 2). The interobserver diameter measurements were compared and found to differ only in a single patient (Table 3.). This patient's melanocytic choroidal tumour diameter was measured as 2.973 and 3.060 disc diameters by Observer 1 and 2, respectively. This small difference of 0.087 makes this a borderline patient that may be ascribed an additional MOLES size point if greater than 3.0 disc diameters. As such, the average of the two Observer's measurements was taken and found to be 3.017, resulting in no difference between the original MOLES size score. The Optos measurements increased the diameter score by 1 in 5 patients. The remaining 6 patients had no change in the MOLES diameter scores.

Tumour thickness

Thickness measurements using OCTs were undertaken by Observer 1 and 2 and compared (Table 4). No interobserver difference was found using this modality. When comparing the MOLES thickness score to the original MOLES thickness score, there was a reduction by 1 point in 5 patients and a reduction by 2 points in 2 patients (Table 5). The remaining 4 patients had no change in MOLES thickness score using the OCT measurements.

In these, the US measurement exceeded the OCT by more than 25% in 5 patients, more than 50% in 2 patients and more than 75% in 1 patient. The OCT measurement reduced the thickness score in 7 patients. As a result, the revised tumour thickness determined the size category in 4/216 (1.8%) patients.

If the diameter score was left unchanged, the revised thickness score reduced the MOLES size score by 1 in 8 patients (Table 6). Of these patients, 2 patients had a reduction in MOLES score from 1 to 0 and would have been monitored in the community. Two patients had a reduction in MOLES score from 2 to 1 and would have been referred non-urgently to an Ocular Oncology Centre for further evaluation and/or monitoring. Two patients had a reduction in MOLES score from 3 to 2, which would have resulted in a non-urgent referral instead of an urgent referral to an Ocular Oncology Centre. Two patients had a reduction in MOLES score from 4 to 3, which would not have changed management. Three patients had no change in MOLES score. This translates to a change in clinical management in 1.9% (4/211) of melanocytic choroidal tumours assessed with MOLES when using OCT instead of US to measure tumour thickness.

Tumour size and thickness combined

If both the revised diameter and thickness scores were considered, the MOLES score reduced in 4 patients, if taking the average of Observer 1 and 2 diameter score in patient 7, where a small interobserver difference was detected as discussed earlier (Table 7). Two of these patients would

have been managed in the community with a MOLES score of 0 instead of 1, and the remaining two patients' management would not have been changed as they would still have been referred urgently to an Ocular Oncology Centre with a MOLES score of 3 or more (Table 8). In the 7 patients, whose size score was unchanged, there was 1 patient with the same diameter and thickness scores in both analyses, 3 in whom these scores balanced each other, and 3 in whom the discrepancy did not occur in the determining indicator. This translates to a change in clinical management in 0.94% (2/211) of melanocytic choroidal tumours assessed with MOLES when using Optos ultra-widefield fundal images to measure tumour diameter and OCT instead of US to measure tumour thickness.

Discussion

The main finding of this study is that tumour thickness influenced the MOLES score in 8.6% (19/222) of patients, this percentage reducing to 1.9% (4/211) if this indicator was measured with OCT and to only 0.94% (2/211) if basal diameter was also measured, with callipers of the Optos camera. This has implications for decision making in general ophthalmic clinics, that in the majority of cases, an accurate basal diameter is sufficient to provide a score in the MOLES size category, and that thickness on OCT or US can be used to confirm the score.

It is well known that tumour thickness measurements obtained with OCT are less than those obtained with US. Previous studies by Shields et al. and Shah et al. demonstrated that EDI-OCT measurements are 55% and 54%, respectively, less than US measurements of thickness.[9, 10] This is thought to be partly due to the exclusion of retina and sclera from OCT measurements that can be inadvertently included in US based measurements due to the difference in axial resolution of the two modalities resulting in differences in the error range; 5 – 10 μm for EDI-OCT and 50-200 μm for US.

Swept source OCT (SS-OCT) provides greater tissue depth resolution using a 1050 nm wavelength laser source and has been shown to enhance imaging of the choroido-scleral interface.[11] Morphological features of choroidal melanocytic lesions can be evaluated in more detail with SS-OCT than EDI-OCT; however, thickness measurements compared to US measurements have not been robustly studied.[12, 13] In the future, SS-OCT may become more wide-spread, warranting further study of this modality in evaluating choroidal melanocytic tumours in relation to the MOLES thickness score.

Although this study focusses on thickness measurements, basal tumour dimension data are considered in this study because they influence the impact of MOLES thickness score and hence on size score. The discrepancy between the Optos ultra-widefield fundus image measurements in the present study and those reported in the previous study may be due to greater interobserver differences between a larger number of clinicians inputting size measurements, which may also be further confounded by fundus images from two different imaging systems (Optos and Topcon).

The green channel of the Optos ultra-widefield images was not used to take diameter measurements because not all non-experts will have access to this and it has yet to be shown to differentiate between choroidal naevi and melanomas.[8, 14] Further, non-experts may need to estimate tumour diameter based on clinical examination alone if the lesion is too peripheral to image, for example.

Higher MOLES scores resulting from overestimation by US thickness measurements compared to OCT would result in a small number of patients being referred unnecessarily to an ophthalmologist and a few being referred urgently instead of non-urgently. These numbers are likely to be small because MOLES estimates are based not only on thickness but also diameter, orange pigment, etc. This suggests that tumour thickness should be ignored if it cannot be measured accurately by OCT. This proposal is supported by the rarity with which thickness influences the MOLES score if basal tumour diameter is measured accurately. It is rare for uveal melanomas to be thick if they are not also wide at their base. Problems arising from inaccurate measurements of tumour dimensions are, to some

extent, mitigated by the inclusion of other indicators of malignancy in the MOLES scoring system (i.e., mushroom shape, orange pigment, enlargement and subretinal fluid).

Although it is tempting to remove thickness measurement from the MOLES scoring system, this is not possible because mushroom shape is given a score of only 2, despite being almost pathognomonic of melanoma. This is intended to simplify the scoring system by giving each of the five indicators a range of three potential scores, which is possible only because mushroom-shaped tumours inevitably have a thickness score of at least 1 so that a total MOLES score of 3 results, indicating malignancy and a need for urgent referral to an ophthalmologist.

To our knowledge, this study has not been performed previously. The findings are relevant to other methods of distinguishing choroidal naevi from melanomas, such as TFSOM-DIM, which includes thickness and diameter greater than 2 mm and 5 mm, respectively, as indicators.[7] A strength of this study is the large number of patients in the original cohort. The main weakness is that the original thickness measurements were obtained by ultrasonography in a routine clinic and not a research setting, although some may consider this to be a strength and not a limitation.

In conclusion, this study suggests ignoring tumour thickness if this cannot be measured accurately with OCT, unless the tumour has a mushroom shape. This study also suggests that assessment of largest basal diameter alone is adequate with every effort to measure this dimension accurately if this may influence the MOLES size score.

Statement of Ethics

Approval from the Audit Committee of Moorfields Eye Hospital was obtained (Approval No. 452). The need for informed consent was waived by the Audit Committee of Moorfields Eye Hospital. We adhered to the Tenets of the Declaration of Helsinki.

Data Availability Statement

All data generated or analysed during this study are included in the article. Any further enquiries can be directed to the corresponding author.

Conflict of Interest Statement

The authors have no conflicts of interest to report. This manuscript has not previously been submitted for publication. None of the authors have any financial disclosures to declare.

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Author Contributions

J.C. – Data acquisition, analysis, and interpretation, drafting of manuscript, final approval.

L. AH. – Conception, design, interpretation, drafting of manuscript, final approval.

M.S.S. – Conception, design, interpretation, drafting of manuscript, final approval.

B.D. – Conception, design, data acquisition, analysis, and interpretation, drafting of manuscript, final approval.

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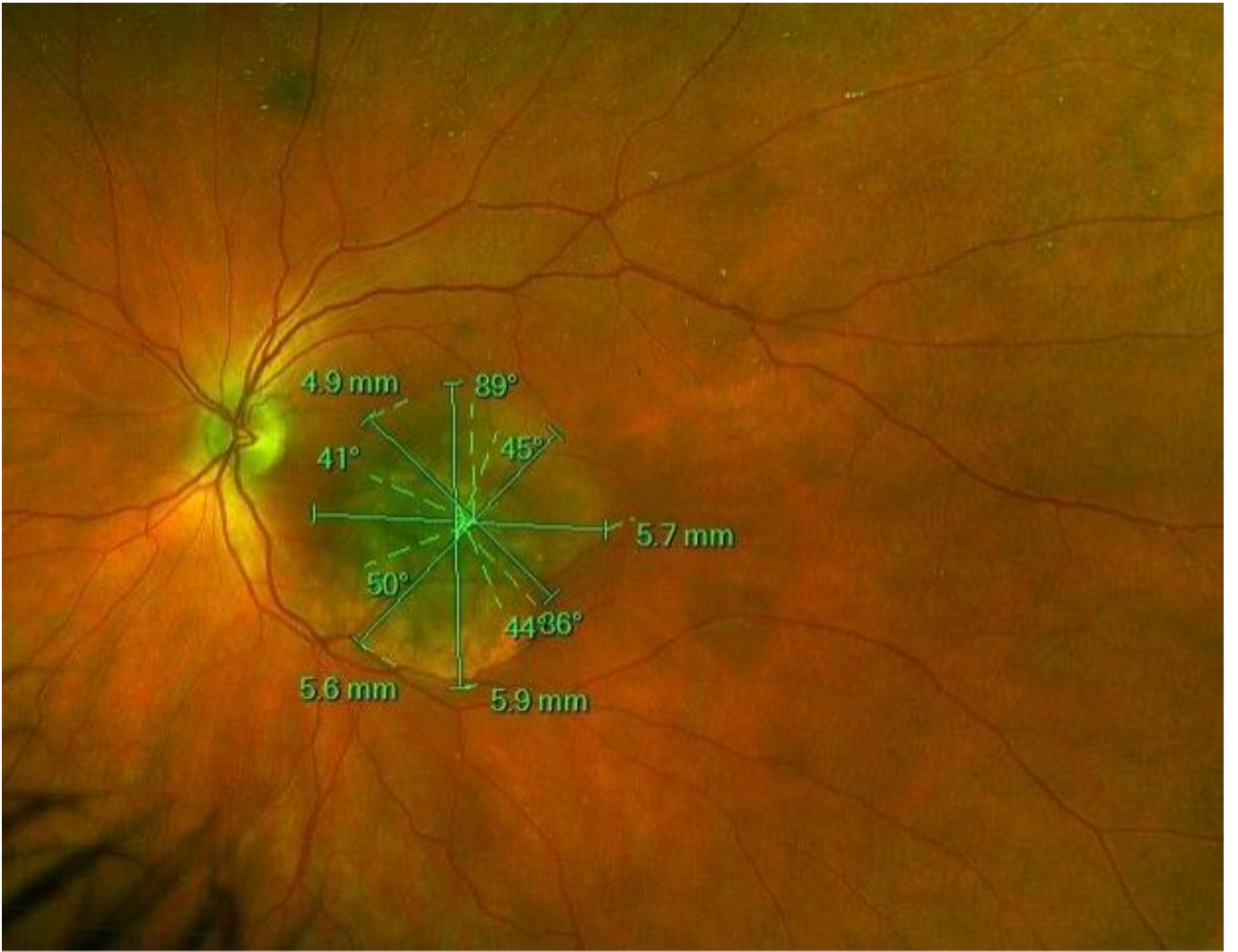
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Figure Legends

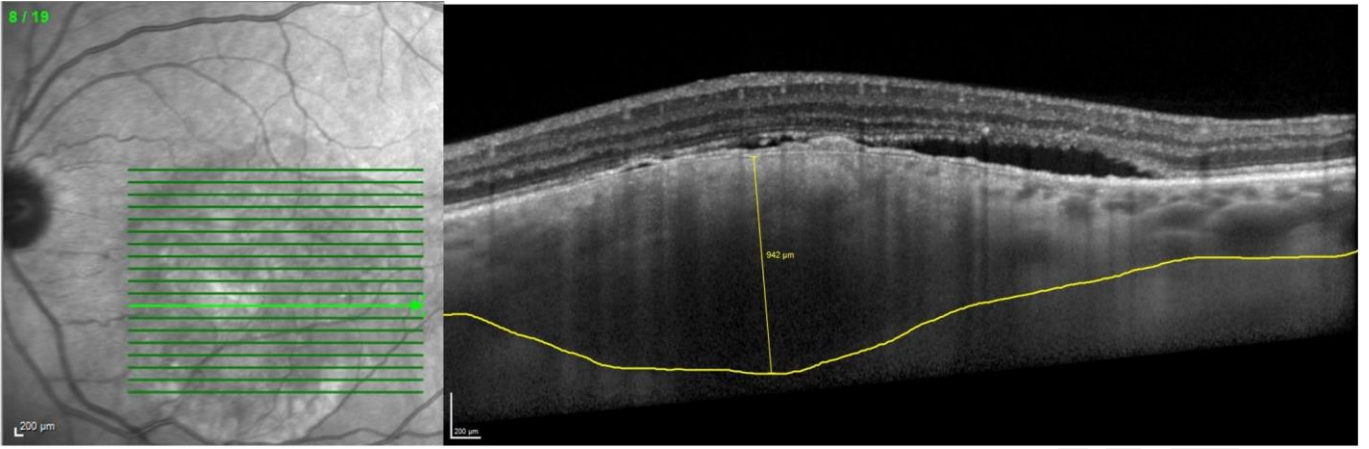
Figure 1. Ultra-wide field cropped image demonstrating multiple measurements using callipers of a round melanocytic choroidal tumour to determine the largest diameter of the lesion.

Figure 2. EDI-OCT image of a choroidal melanocytic tumour with overlays demonstrating manual segmentation of the choroidal-scleral interface and maximal thickness measurement with callipers.

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Table 1.: Demographics of patients whose tumour size category was determined by ultrasound measured tumour thickness.

Patient Number	Age	Sex	Eye	Mushroom shape	Orange pigment	Tumour diameter (dd)	Tumour thickness (mm)	Enlargement	Subretinal fluid	Total MOLES score	Diagnosis
1	25.5	Female	Left	Absent	Absent	1	1.2	None	Absent	1	CN
2	60.1	Female	Right	Absent	Absent	2.5	1.1	None	Trace	2	CN
3	73.3	Female	Left	Absent	Absent	2	1.2	None	Absent	1	CN
4	84	Female	Left	Absent	Absent	2.5	1.2	None	Absent	1	CN
5	77.8	Female	Right	Absent	Absent	1.5	1.1	None	Absent	1	CN
6	55.5	Female	Left	Absent	Absent	1.5	1.2	None	Significant	3	CMM
7	55.1	Male	Right	Absent	Trace	2	1.1	None	Absent	2	CN
8	43.5	Female	Right	Absent	Absent	3	2.3	None	Trace	3	CN
9	54.6	Female	Left	Absent	Trace	3	2.3	None	Trace	4	CMM
10	57.7	Male	Left	Absent	Confluent	4	2.3	None	Significant	6	CMM
11	74	Female	Left	Absent	Confluent	3	2.6	None	Trace	5	CMM
12	57.2	Male	Left	Absent	Absent	4	2.6	None	Trace	3	CMM
13	69.9	Male	Right	Absent	Absent	4	3.1	None	Trace	3	CMM
14	78.3	Male	Right	Absent	Confluent	2	1.2	None	Significant	5	CMM
15	53.5	Female	Right	Absent	Trace	2	2	None	Significant	4	CMM
16	59.6	Female	Left	Absent	Absent	3	2.2	None	Significant	4	CMM
17	67.4	Male	Left	Absent	Absent	4	2.7	None	Significant	4	CMM
18	41	Male	Right	Absent	Confluent	2	1.1	None	Significant	5	CMM
19	85	Female	Left	Absent	Trace	2	1.7	None	Trace	3	CMM

CN – Choroidal Naevus, CMM – Choroidal malignant melanoma.

Table 2.: Interobserver comparison between melanocytic choroidal tumour diameter measurement on Optos widefield fundal images.

Patient Number	Observer 1			Observer 2			Interobserver difference of revised MOLES diameter score
	Optos measurement of tumour diameter (mm)	Optos measurement of tumour diameter (DD)	Revised MOLES diameter score	Optos measurement of tumour diameter (mm)	Optos measurement of tumour diameter (DD)	Revised MOLES diameter score	
1	2.196	1.464	0	2.161	1.441	0	0
2	5.164	3.443	1	4.872	3.248	1	0
3	4.153	2.769	0	3.896	2.597	0	0
4	4.940	3.293	1	5.648	3.765	1	0
5	2.337	1.558	0	2.500	1.667	0	0
6	5.387	3.591	1	5.908	3.939	1	0
7	4.460	2.973	0	4.590	3.060	1	-1
8	6.100	4.067	2	6.662	4.441	2	0
14	4.667	3.111	1	4.548	3.032	1	0
18	3.054	2.036	0	3.264	2.176	0	0
19	4.297	2.865	0	4.301	2.867	0	0

Patient Number	Original tumour diameter (dd)	Original MOLES diameter score	Optos measurement of tumour diameter (mm) – average of observer 1 and 2	Optos measurement of tumour diameter (DD)	Revised MOLES diameter score	Difference between original and revised MOLES diameter score
1	1	0	2.179	1.452	0	0
2	2.5	0	5.018	3.345	1	1
3	2	0	4.025	2.683	0	0
4	2.5	0	5.294	3.529	1	1
5	1.5	0	2.419	1.612	0	0
6	2	0	5.648	3.765	1	1
7	2	0	4.525	3.017	0	0
8	3	1	6.381	4.254	2	1
14	2	0	4.608	3.072	1	1
18	2	0	3.159	2.106	0	0
19	1.5	0	4.299	2.866	0	0

Table 3.: Difference between original and revised MOLES diameter score based on the average of the measurements between Observer 1 and 2.

Table 4.: Interobserver comparison of revised melanocytic choroidal tumour thickness measurements

	Observer 1		Observer 2		
Patient number	OCT thickness measurement (um)	Revised MOLES thickness score	OCT thickness measurement (um)	Revised MOLES thickness score	Interobserver difference in MOLES score according to revised thickness measurements
1	266	0	262	0	0
2	584	0	664	0	0
3	1156	1	1277	1	0
4	1336	1	1154	1	0
5	376	0	351	0	0
6	337	0	943	0	0
7	559	0	718	0	0
8	501	0	700	0	0
14	1213	1	1110	1	0
18	863	0	723	0	0
19	1308	1	1066	1	0

Table 5.: Differences between the revised and original MOLES thickness measurements

Number	Original MOLES thickness score	Revised MOLES thickness score	Difference between revised and original MOLES thickness score
1	1	0	-1
2	1	0	-1
3	1	1	0
4	1	1	0
5	1	0	-1
6	2	0	-2
7	1	0	-1
8	2	0	-2
14	1	1	0
18	1	0	-1
19	1	1	0

Table 6.: Original MOLES score compared to revised MOLES score according to OCT thickness

Original MOLES score	Revised MOLES score						Total
	0	1	2	3	4	5	
1	2	2	0	0	0	0	4
2	0	2	0	0	0	0	2
3	0	0	2	0	0	0	2
4	0	0	0	2	0	0	2
5	0	0	0	0	0	1	1
6	0	0	0	0	0	0	0
Total	2	4	2	2	0	1	11

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Number	Observer 1	Observer 2	Previous total MOLES score	Observer 1	Observer 2	Interobserver difference
	MOLES score according to revised thickness and diameter measurements	MOLES score according to revised thickness and diameter measurements		Difference between revised and previous MOLES score	Difference between revised and previous MOLES score	
1	0	0	1	-1	-1	0
2	2	2	2	0	0	0
3	1	1	1	0	0	0
4	1	1	1	0	0	0
5	0	0	1	-1	-1	0
6	3	3	4	-1	-1	0
7	1	2	2	-1	0	-1
8	3	3	3	0	0	0
14	5	5	5	0	0	0
18	4	4	5	-1	-1	0
19	3	3	3	0	0	0

Table 7.: Interobserver comparison of revised melanocytic choroidal tumour diameter and thickness measurements combined.

Table 8.: Original MOLES score compared to revised MOLES score according to revised diameter and OCT thickness

Previous MOLES score	Revised MOLES score						Total
	0	1	2	3	4	5	
1	2	2	0	0	0	0	4
2	0	0	2	0	0	0	2
3	0	0	0	2	0	0	2
4	0	0	0	1	1	0	2
5	0	0	0	0	0	1	1
6	0	0	0	0	0	0	0
Total	2	2	2	3	1	1	11

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