Choroidal naevi are found in about 6% of individuals whereas only 6 people per million per year develop melanoma. At Oxford Eye Hospital, we have prepared the MOLES acronym and scoring system and established a virtual clinic to help practitioners differentiate choroidal melanomas from naevi. We hope these measures will reduce the referral of patients to hospital with common choroidal naevi without delaying the care of patients with melanoma. Any suggestions would be most welcome.

Bertil Damato (Bertil.Damato@OUH.NHS.UK)

MOLES Scoring Chart

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Severity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mushroom shape</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Unsure/Early growth through RPE</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>Orange pigment</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Unsure/Trace (i.e., dusting)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Confluent clumps</td>
<td>2</td>
</tr>
<tr>
<td>Large Size*</td>
<td>Thickness &amp; Diameter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thickness &lt; 1.0 mm (‘flat/minimal thickening’) and diameter &lt; 3 DD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Thickness = 1.0 – 2.0 mm (‘subtle dome shape’) and/or diameter = 3-4 DD</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Thickness &gt;2.0 mm (‘significant thickening’) and/or diameter &gt;4 DD</td>
<td>2</td>
</tr>
<tr>
<td>Enlargement</td>
<td>None (or lesion not documented or mentioned to patient previously)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Unsure (e.g., poor image quality)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Definite (confirmed with sequential imaging)</td>
<td>2</td>
</tr>
<tr>
<td>Subretinal fluid**</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Trace (if minimal and detected only with OCT)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Definite (if seen without OCT)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total Score:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| DD = disc diameter (=1.5 mm); *Ignore thickness if this cannot be measured; **Assume SRF if unexplained visual loss. |

Recommended Management

<table>
<thead>
<tr>
<th>MOLES Score</th>
<th>Management (i.e., in Oxfordshire)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Common naevus</td>
<td>Inform patients of lesion so that they organise usual self-care (i.e., with no surveillance other than usual visits to optometrist every 1-2 yrs). [Follow B3(modified) level of referral of College of Optometrists Clinical Management Guidelines (CMG) as done with congenital hypertrophy of the RPE (CHRPE)]</td>
</tr>
<tr>
<td>1 = Low-risk naevus</td>
<td>Refer NON_URGENTLY to the Virtual Clinic at Oxford Eye Hospital by completing the Choroidal MOLES Referral Form (downloadable from OEH website, v.i) and e-mailing it to <a href="mailto:OUH-tr.ocularmoles.oxon@nhs.net">OUH-tr.ocularmoles.oxon@nhs.net</a> with attached image(s) of lesion. [Follow B1(modified) referral protocol of College of Optometrists CMG].</td>
</tr>
<tr>
<td>2 = High-risk naevus</td>
<td>Refer urgently by e-mailing the 2WW Referral Form (downloadable from OEH website, v.i) to <a href="mailto:OUH-tr.ocularmoles.oxon@nhs.net">OUH-tr.ocularmoles.oxon@nhs.net</a> with attached image(s) of lesion.[Follow Level A3(modified) level of referral of College of Optometrists CMG]. Follow the SCAN and NHS FastTrack pathways. Encourage patients to accept the earliest appointment. Give them the FastTrack patient information sheet (v.i)*:</td>
</tr>
<tr>
<td>3 = Probable melanoma</td>
<td>Refer urgently by e-mailing the 2WW Referral Form (downloadable from OEH website, v.i) to <a href="mailto:OUH-tr.ocularmoles.oxon@nhs.net">OUH-tr.ocularmoles.oxon@nhs.net</a> with attached image(s) of lesion.[Follow Level A3(modified) level of referral of College of Optometrists CMG]. Follow the SCAN and NHS FastTrack pathways. Encourage patients to accept the earliest appointment. Give them the FastTrack patient information sheet (v.i)*:</td>
</tr>
</tbody>
</table>

Referral Tips

- If possible, include colour photographs and other images with referral form. Patients referred without attached images will undergo ocular photography at Oxford Eye Hospital without being seen by an ocular oncologist on that day. Subsequent management will be planned according to review of these images at our OEH Virtual Clinic.

Surveillance Tips

- Baseline imaging should consist of colour photography, if possible with optical coherence tomography (OCT) and/or fundus autofluorescence (FAF) imaging. Raised tumours need ultrasonography only if too thick or peripheral for OCT.
- Tumour surveillance usually requires only sequential colour photography, with other imaging only if growth is suspected.

Links

NICE guidance. Suspected Cancer: recognition and referral: https://www.nice.org.uk/guidance/ng12
Oxfordshire Local Optometric Committee: https://www.oxfordshireloc.org.uk/
Schematic drawings of melanocytic choroidal tumours

Normal

MOLES Score = 00000 = 0 = Common naevus

Common moles are small, flat, grey, and featureless. Proximity to disc is NOT a risk factor for malignancy.

Histology shows a small tumour composed of melanocytes with normal RPE and retina.

Autofluorescence imaging shows no abnormalities because the RPE over common naevi is normal.

With OCT, naevi can be hyper- or hypo-fluorescent, depending on their degree of melanin pigmentation.
**MOLES Score = 00100 = 1 = Low-risk naevus**

This naevus is slightly larger than usual (i.e., 3-4 DD) without any other suspicious features and shows waxy, white drusen on its surface.

FAF shows the naevus to be darker than the surrounding choroid. Any drusen tend to fluoresce only dimly or not at all.

Histology would show swelling of the choroid by the naevus. Any drusen develop between the RPE and Bruch’s membrane.

OCT shows the naevus to be darker than the surrounding tissues. The RPE appears as a thick, white line and is draped over any drusen.

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**MOLES Score = 00101 = 2 = High-risk naevus**

This naevus is slightly larger than usual, with a small trace of subretinal fluid, which may not be visible except with OCT.

Autofluorescence imaging does not show up the retinal detachment.

Histology shows swelling of the choroid by the naevus and a small amount of subretinal fluid detaching the retina slightly over a limited area. This occurs because the function of the RPE is impaired by the naevus.

OCT shows the retina to be slightly detached by a small collection of subretinal fluid.
MOLES Score = 02202 = 6 = Probable melanoma

This tumour is larger than most naevi, with clumps of orange pigment and subretinal fluid that is abundant enough for the retinal detachment to be seen with an ophthalmoscope.

Histology shows the bulky tumour, with disruption of the overlying RPE, which causes fluid and lipofuscin to accumulate.

MOLES Score = 22202 = 8 = Probable melanoma

This melanoma has grown through the RPE so that its true colour is apparent. The tumour is tan because it has little melanin pigment. Congested blood vessels are seen in apical part of the tumour.

Histology would show growth of the tumour through Bruch’s membrane, which strangulates the tumour so that it becomes oedematous and swollen, to form a mushroom shape.

FAF shows the lipofuscin clumps to fluoresce brightly. The subretinal fluid gravitating from the tumour has damaged the RPE and retina inferior to the tumour so that these are hyper-fluorescent.

OCT shows thickening of the tumour as well as brightly fluorescent clumps of lipofuscin between the RPE and the retina, which is detached by abundant subretinal fluid.

FAF shows no fluorescence in the area where the tumour has grown through the RPE. The RPE inferior to the tumour is hyperfluorescent where it is damaged by longstanding retinal detachment.

Ultrasonography is required because the tumour is too thick for OCT. The oedematous tumour within the retina is highly reflective whereas the compact basal part of the tumour shows low reflectivity.
Introduction

Choroidal melanomas threaten patients with visual handicap, loss of the eye, and death from metastatic disease. Early diagnosis and treatment maximise any opportunities for preventing these outcomes.

Small melanomas can be difficult to distinguish from naevi. Such benign ‘moles’ are common, with a prevalence of approximately 6% (i.e., 1 in 17 adults).\(^1\) In contrast, choroidal melanomas are rare, with an annual incidence of approximately 1 in 400,000 at around the age of 40 years, increasing to almost 1 in 100,000 at 60 years and to 1 in 50,000 over the age of 65 years (Fig. 1).\(^1\) These rates are lower in individuals having a dark complexion.\(^1\) For these reasons, patient care needs to be individualised according to clinical features indicating any increased risk of malignancy. The author has devised the MOLES protocol to help clinicians remember these clinical signs and to plan patient care accordingly. Other systems, such as TFSOM-DIM (To find small ocular melanoma doing imaging) require ultrasonography and other imaging, which are not widely available in the community in the UK.\(^2\) The MOLES system can be based on ophthalmoscopy alone, ideally with colour fundus photography. Here, the rationale of the MOLES protocol is discussed.

**MOLES scoring system**

**Mushroom shape** is almost pathognomonic for choroidal melanoma. It occurs when the tumour extends through Bruch’s membrane and retinal pigment epithelium (RPE). When this happens, the tumour thickness increases so that the MOLES score exceeds 2. A score of 1 indicates that the tumour bulges slightly through a defect in Bruch’s membrane.

‘Orange pigment’, consisting of lipofuscin, accumulates on the retinal surface of the RPE, usually overlying rapidly growing tumours. Light dusting of orange pigment can occur over choroidal naevi and is given a MOLES score of 1; however, clumps of confluent orange pigment indicate more severe RPE dysfunction, which tends to occur with melanomas, hence the score of 2. Over amelanotic tumours, lipofuscin can appear brown. This pigment is bright on fundus autofluorescence imaging, which is performed routinely in specialist centres. On OCT, lipofuscin forms fluffy deposits on the retinal surface of the RPE, unlike drusen, which form discrete lumps between RPE and Bruch’s membrane. Note that orange pigment can appear over other tumours, such as metastases and haemangiomas.

**Larger size.** Choroidal melanomas tend to be wider and thicker than naevi, although there is some overlap. A study by Augsburger et al indicates that there are 125 choroidal naevi for every melanoma in the thickness range of 1.5 to 2 mm, 25 naevi for every melanoma in the thickness range of 2 to 2.5 mm, and 5 naevi for every melanoma in the thickness range of 2.5 to 3 mm, approximately.\(^3\) Erring on the side of caution, the tumour thickness is given MOLES scores of 0, 1 and 2 if the tumour thickness is <1 mm, 1-2 mm or >2 mm respectively (i.e., ‘flat/minimally thickened’, ‘slightly dome shaped – seen with difficulty on ophthalmoscopy’, and ‘significantly elevated- easily visible on ophthalmoscopy’). If possible, the thickness of small, posterior lesions should be documented by performing optical coherence tomography (OCT). Ultrasonography may be useful when OCT is not possible because of large tumour size or peripheral location.

Augsburger et al found that there are 70 naevi for every choroidal melanoma in the basal diameter range of 5 to 6 mm, 10 naevi for every melanoma in the diameter range of 6 to 7 mm, and 3 naevi for every melanoma in the range 7 to 8 mm, approximately.\(^3\) The MOLES system therefore scores basal diameter as 0, 1 or 2 if measurements are <3 DD, 3-4 DD, and >4 DD respectively. Tumours rarely become thicker without also showing an increase in diameter; colour photography should therefore be sufficient to assess size when OCT and ultrasonography are not possible.
In a series of >3500 choroidal melanomas treated in Liverpool, the basal diameter was less than 6.0 mm (i.e., 4 DD) in 3% of cases (unpublished data). These tumours are likely to have a MOLES score exceeding 2 because of other ophthalmoscopic signs of malignancy (i.e., mushroom shape, orange pigment, enlargement, and/or subretinal fluid).

**Enlargement** of choroidal naevi is rare after the age of 25 years, and when it occurs it is minimal and slow, developing over many years. Fundus photography makes it easier to detect tumour growth. Sequential fundus photography is ideal but not essential as long as a baseline photograph is available. Tumour enlargement confirmed photographically is given a MOLES score of 2. If photography is suggestive of growth but inconclusive, because of poor image quality, a score of 1 is given. A score of 0 is given if a lesion is detected and its absence previously not confirmed photographically. A score of 0 is given also if the patient was not informed of any naevus in previous ocular examinations. This is because the lesion may have been missed or because the clinician did not mention the presence of the lesion to the patient. In the author’s opinion, when monitoring suspicious lesions, ultrasonography is not required if sequential colour photography does not suggest growth. This is because it is rare for tumours to grow thicker without becoming wider.

**Subretinal fluid (SRF)** develops when RPE function is disturbed by an underlying choroidal tumour, as usually happens with melanomas. The retina is flat over common naevi (i.e., MOLES score = 0) but some larger lesions may show minimal or localised detachment; these features are given a score of 1. Cystoid spaces within the retina indicate chronicity so that a score of 0 is given unless SRF is also present. Significant and extensive retinal detachment that is visible ophthalmoscopically is given a MOLES score of 2. Subretinal fluid is best detected with OCT. When such imaging is not available, it is reasonable to assume that SRF is present if the patient reports metamorphopsia or other visual symptoms for which no other cause can be found. The inferred presence of SRF is given a MOLES score of 1.

**Management**

In an ongoing audit by the author, most choroidal naevi referred to the Oxford Eye Hospital ocular tumour diagnostic clinic were common naevi (i.e., MOLES score of 0), with almost no risk of malignancy. The referral of large numbers of common naevi is placing a burden on hospital resources, possibly delaying the care of patients requiring urgent treatment for diseases such as uveal melanoma. Unnecessary referrals are also causing distress to many patients, who may also incur loss of income and expenses for travel, etc.

The author suggests that all patients be informed of any pigmented fundus lesions, ideally being provided with an information sheet and a photograph of the lesion. Patients with a common naevus need no special arrangements (i.e., usual self care, such as review every 2 years as is recommended for patients without pigmented fundus lesions).

Patients with low-risk or high-risk naevi should ideally receive baseline colour photography as well as autofluorescence imaging and OCT (or ultrasonography if a raised lesion is too large or peripheral for OCT). Long-term surveillance by our ocular oncologist is indicated, with followup every 6 to 12 months depending on the estimated risk of malignancy. Patients should be referred non urgently to the OEH Virtual Clinic by e-mailing the relevant referral form with attached images. Such images may enable our ocular oncologist to provide a diagnosis without the patient having to travel to hospital. If adequate images are not received with the referral letter, the patient will need to attend our Ocular Moles Photography Clinic for imaging studies, which will be reviewed by our ocular oncologist a few days later at the Virtual Clinic with the patient being given an appointment at our OEH ocular tumour diagnostic clinic if the clinical features suggest malignancy.

If the MOLES score is more than 2 (i.e., ‘probable melanoma’), the patient should be referred urgently to the OEH Virtual Clinic to be seen within 2 weeks (see page 1). The onus is on the referring practitioner to ensure that relevant guidelines are followed (see links on page 1). The oculist oncologist will then decide whether to discharge or monitor the patient or to refer on to a specialist oculist oncology service for definitive diagnosis and treatment.

**References**