Distinguishing Choroidal Nevi from Melanomas using the MOLES Algorithm: Evaluation in an Ocular Nevus Clinic

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Running title: MOLES scoring system for choroidal moles

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Objective. The aim of this study was to determine the sensitivity and specificity of MOLES scoring system in differentiating choroidal melanomas from nevi according to Mushroom shape, Orange pigment, Large tumor size, Enlarging tumor, and SRF.

Methods and Analysis. Color photographs, fundus-autofluorescence images, and optical-coherence tomography of 222 melanocytic choroidal tumors were reviewed. Each MOLES feature was retrospectively scored between 0 and 2 and tumors categorized as 'common nevus', 'low-risk nevus', 'high-risk nevus' and 'probable melanoma' according to the total score. MOLES scores were compared with the experts' diagnosis of melanoma.

Results. The MOLES scoring system indicated melanoma in all 81 tumors diagnosed as such by ocular oncologists (100% sensitivity) and nevus in 135 of 141 tumors given this diagnosis by these experts (95.7% specificity). Of the 6 tumors with discordant diagnoses, 4 had basal diameters exceeding 6 mm, all with SRF and/or orange pigment; and 2 small tumors showed either significant SRF with traces of orange pigment, or vice versa.

Conclusions. The MOLES system for diagnosing melanocytic choroidal tumors compares well with expert diagnosis but needs to be evaluated when deployed by ophthalmologists and community optometrists in a wide variety of working environments.

Early treatment of choroidal melanoma optimizes opportunities for conserving the eye and vision. There is tentative evidence that treatment of small choroidal melanomas may prevent metastatic spread in some patients.(1, 2) It can be difficult, however, to distinguish choroidal nevi from small melanomas. Patients with a benign lesion may therefore undergo excessive surveillance, experiencing undue anxiety and incurring unnecessary expense. Management of these patients can be burdensome to healthcare services because of the high prevalence of choroidal nevi, especially in the White population (i.e. ~6%)(3). This can delay the care of patients with serious conditions, including choroidal melanoma.(4)

Various mnemonics and acronyms have been developed to aid differentiation between choroidal nevi and melanomas(5, 6); however, these necessitate assessment of internal acoustic reflectivity by ultrasonography. There is scope for aids enabling practitioners to estimate likelihood of malignancy from widely used imaging, such as color photography, optical-coherence tomography (OCT) and fundus-autofluorescence imaging (FAF) when ultrasonography is not possible, as in virtual clinics and in optometric and general ophthalmic clinics.

The senior author (BD) has devised the acronym, MOLES, which represents Mushroom shape, Orange pigment (i.e., lipofuscin), Large tumor size, Enlarging tumor, and Subretinal fluid (SRF). Each of these features is scored between 0 and 2 and tumors are diagnosed according to their sum total as 'common nevus', 'low-risk nevus', 'high-risk nevus' or 'probable melanoma' as described previously (Table 1).(7)

The aim of this study was to determine the sensitivity and specificity of the MOLES scoring system in differentiating choroidal melanomas from nevi.

Patients and Methods

Patients were included if seen at the Nevus Clinic of Moorfields Eye Hospital between January 2013 and December 2018. They were excluded if diagnosed with melanocytoma or congenital ocular melanocytosis or if the tumor extended anterior to ora.

Initial assessment was performed by an ocular oncologist and included measurement of Snellen visual acuity, binocular indirect ophthalmoscopy, fundus photography with Optos (Optos, Dumfermline, UK) or Topcon (Topcon fundus camera, Topcon Corporation, Tokyo, Japan), FAF (Optos, Dumfermline, UK), OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany), and, in selected cases, B-scan ultrasonography.

Patients were monitored or treated with photodynamic therapy, ruthenium plaque radiotherapy, proton beam radiotherapy, or enucleation.

Medical records and digital images were retrospectively scored and tumors categorized according to the MOLES system as 'common nevus', 'low-risk nevus', 'high-risk nevus' and 'probable melanoma'.(7) This was done according to clinical features documented at the patient's first visit at our hospital as described In Table 1, except that enlargement was documented if tumor growth was mentioned in the charts or referral letter. The experts' diagnosis was retrospectively categorized as melanoma if this was specified at initial assessment or if the patient underwent radiotherapy or other treatment for this condition. The MOLES scores were compared with the expert diagnosis to compute sensitivity and specificity in differentiating melanomas from nevi (i.e., common, low-risk, and high-risk lesions).

Follow-up was measured from the first clinic date to the 2nd November 2019, when this analysis was performed.

Data were analyzed with Stata (StataCorp, College Station, Texas, USA). Approval from the Audit Committee of Moorfields Eye Hospital was obtained (Number: 452). Patient consent was not required. We adhered to the Tenets of Helsinki.

Results

The cohort comprised 222 patients (61.7% female) with a median age of 62.5 years (range, 17.3 – 89.9) (Table 1). The tumors had a median basal diameter of 3 DD (Disc diameters) (range, 0.3 – 19) and a median thickness of 0.9 mm (range, 0 – 11). One tumor had broken through retinal pigment epithelium (RPE) but had not developed a mushroom shape. Confluent orange pigment and significant SRF were present in 37 (16.7%) and 61 (27.5%) eyes respectively. Growth was documented in 13 (5.9%) tumors, all with MOLES scores exceeding 4 and all having undergone treatment (Table 1). According to MOLES, the tumors were categorized as 'common nevus', 'low-risk nevus', 'high-risk nevus' and 'probable melanoma' in 71 (32%), 36 (16.2%), 28 (12.6%) and 87 (39.2%) respectively.

Table 2 itemizes tumor features according to MOLES score. Table 3 lists the clinical features in 18 tumors whose size category was determined by tumor thickness, resulting in a higher risk category in 6 nevi.

The ocular oncologists diagnosed 79 tumors as melanoma and 143 as nevus; however, two diagnosed as nevi subsequently received brachytherapy so that diagnosis was revised to melanoma

and nevus in 81 and 141 tumors respectively. One nevus received PDT to improve vision by reducing SRF. The melanomas were treated with PDT (6), brachytherapy (68), proton beam radiotherapy (5) or enucleation (2) (Table 1).

Three (25%) of the 12 tumors with a MOLES score of 3 and three of 75 with higher MOLES scores were not treated, because the oncologists had diagnosed nevus (Fig. 1) (Table 4). Four of these six tumors had basal diameters exceeding 6 mm, all with SRF and/or orange pigment, and two small tumors showed either significant SRF with traces of liposfuscin, or vice versa.

These results indicate that MOLES correctly identified all 81 melanomas (100% sensitivity) and 135 out of 141 choroidal nevi (95.7% specificity; 95% Confidence Interval 92.4 – 99.1).

Discussion

Main findings

The main finding of this study is that the MOLES score correlated well with the experts' diagnoses of choroidal melanoma and nevus, with sensitivity and specificity levels of 100% and 96% respectively. Another finding was that ultrasonographic measurement of tumor thickness influenced the MOLES category in only 6/222 (2.7%) tumors.

Strengths and weaknesses

The strengths of this study are the large number of patients and the multimodality imaging. There are several weaknesses. First, the retrospective data collection from patients' charts prevented us from determining the oncologists' estimate of risk of malignancy, which was not always documented. Second, we do not know how many untreated tumors would have grown with long-term monitoring. We also cannot know how many treated tumors would have remained unchanged if left alone. It would have been unethical to leave diagnosed melanomas untreated, because of the risk of metastasis. This problem is compounded by the lack of consensus amongst ocular oncologists as to which suspicious tumors should be diagnosed as melanoma. Third, MOLES scores were based on images not live examinations; this is an advantage, because it replicates the way images are assessed remotely in virtual clinics. Fourth, the oncologists' diagnosis was not confirmed histologically. It is not conventional practice to biopsy small melanocytic choroidal tumors to confirm malignancy, except in rare, selected cases. This is because with small tumors it is difficult to obtain sufficient tissue for analysis and because of the risk of complications.

Discussion of methods

We included all consecutive patients irrespective of tumor size, because some large melanocytic choroidal tumors are benign (i.e., 'giant nevi').(8) We excluded melanocytomas and patients with congenital ocular melanocytosis because the need for monitoring these is accepted and because the MOLES scoring system is not applicable to such lesions.

The follow-up period was computed from the first clinic visit to the date of our study closure because we assumed that all patients with tumor growth would be referred back to our care.

We measured basal tumor diameter in horizontal DD, accepting that this does not always correspond to 1.5 mm; this is because with thin and flat tumors this method is more accurate than ultrasonography. It is also a method that is easy to replicate outside of specialist centers.

The MOLES scoring system is based on clinical signs that are well accepted as features that differentiate choroidal nevi from melanomas. A study of more than 3000 cases by Shields et al confirmed orange pigment ($p=0.0004$), diameter >5 mm ($p=0.0275$), thickness >2 mm ($p<0.0001$) and SRF ($p<0.0001$) to be statistically associated with tumor growth, which was taken to indicate malignancy.(6) Choroidal nevi only rarely perforate RPE, and when they do, they do not develop a mushroom shape.(9) With such strong evidence in the published literature, further studies to show associations between the MOLES signs and malignancy in melanocytic choroidal tumors would have been redundant.

Some points regarding the MOLES scores require discussion. Although almost pathognomonic for melanoma, mushroom shape is given a MOLES score of only 2 to simplify scoring; this is justified because mushroom-shaped tumors inevitably have a total score exceeding 2 because of thickness. This should ensure that patients are referred for specialist opinion even in the rare event that mushroom shape is the only sign of melanoma. None of the tumors in this study had a mushroom shape and this is because tumors with this sign were triaged directly to our oncology clinic and not the nevus clinic.

Orange pigment can develop over hemangiomas and metastases(10, 11); however, the MOLES system is not designed to differentiate between melanomas and such lesions.

The size categories used by the MOLES system are mostly based on a study by Augsburger et al.(12) Although there is a size overlap between choroidal nevi and melanomas, the MOLES system adjusts for this by including other risk factors.

Enlargement is included in MOLES because growth is such a strong indicator of malignancy and because in some cases it is the only suspicious feature. Some nevi can enlarge in adulthood; however, such growth is rare and tends to be subtle (i.e., <0.5 mm/year).(13, 14) Growth before adulthood is not usually a sign of malignancy but nevertheless requires monitoring as choroidal melanoma can developed at a young age.(15) Some patients present with what appears to be a common nevus that was not noted previously. Monitoring of such lesions usually reveals no growth, suggesting that these nevi were missed previously. For this reason, the MOLES system requires enlargement to be confirmed by sequential imaging.

SRF can develop over choroidal nevi but is usually minimal; the MOLES scoring system therefore scores this feature as 2 only if it is visible ophthalmoscopically.

The MOLES system omits several features considered to indicate increased risk of malignancy. Statistical studies show that tumor proximity to the optic disc is not an indicator of malignancy.(6) Many nevi do not show drusen on their surface and, conversely, these deposits can develop on melanomas. A recent study has shown haloes to be statistically insignificant as indicators of malignancy.(6) Assessment of internal acoustic reflectivity requires ultrasonography;(6) however, as mentioned, this is not widely available outside specialist units.

The TFSOM mnemonics categorize signs of malignancy in a binary fashion.(6, 16); however, it may not be possible to decide categorically whether a particular feature is present. The MOLES scoring system therefore includes an intermediate category for borderline and uncertain findings.

Tumors with a high MOLES score are categorized as ‘probable melanomas’ and not ‘melanomas’ because non-oncologists may not feel confident or qualified to distinguish melanomas from other tumors.

Discussion of results

The discrepancy between the MOLES score and the experts’ diagnosis in 6 tumors is not surprising considering that there is no consensus as to how patients with indeterminate lesions should be diagnosed.(5, 12) MOLES has a relatively low threshold for indicating malignancy; this is to reduce the risk of misdiagnosing choroidal melanomas as nevi in situations where expertise and equipment are limited and also because it is only designed to guide investigation and monitoring, not treatment.

The ultrasound measurements of tumor thickness increased the MOLES category in 6/222 (2.7%) tumors. This may have been spurious as it is known that ultrasonographic thickness measurements tend to be greater than those obtained by OCT or histology.(17, 18)

Previous studies

Roelofs et al evaluated the MOLES system in 450 choroidal melanomas treated at our center and found a MOLES score <3 in only one patient, whose tumor was located pre-equatorially.(7) This indicates that when used by an expert the risk of misdiagnosing choroidal melanomas as nevi is low. The present study extends the findings of that investigation, also including nevi to investigate the specificity of the MOLES scoring system.

Roelofs et al also evaluated MOLES in a cohort of 99 patients who were treated for choroidal melanoma after a period of surveillance found that tumor progression was detected without ultrasonography in 98 cases(19).

Clinical implications

The MOLES acronym should make it easier for ophthalmologists and optometrists to remember the key signs differentiating melanomas from nevi, which in lay parlance are called 'moles'.

As mentioned, MOLES should be useful to a wider range of practitioners than mnemonics and acronyms that require ultrasonography to assess internal tumor reflectivity.

MOLES enables practitioners to concisely describe melanocytic choroidal tumors, encouraging more detailed documentation. For example, a MOLES score of '02201 = 5' succinctly conveys that the tumor is probably a melanoma with a basal diameter >6 mm and/or a thickness >2 mm together with confluent orange pigment and traces of SRF but no mushroom shape and no documented growth.

The scope of MOLES has been increased by the COVID-19 pandemic, which at least in the UK is encouraging practitioners to shift the care of patients with melanocytic choroidal tumors from ocular-oncology centers to ophthalmic units closer to the patients' home and from these clinics to community optometrists.(20) This trend reduces the risk of coronavirus infection to patients and healthcare providers as well as minimizing traveling costs for patients and conserving healthcare resources.

Research implications

This investigation pertains only to the performance of MOLES when used by ocular oncology experts (e.g., as in virtual clinics); further studies are needed to validate this diagnostic aid when deployed by optometrists and other ophthalmologists, who may lack the expertise and equipment needed to identify the clinical features of malignancy. Spurious MOLES scores may result if practitioners fail to recognize incipient mushroom formation or SRF, or if orange pigment is missed or mistaken for drusen, or if basal tumor diameter is not measured accurately (e.g., omitting calipers or a ruler). The present investigation suggests that there is scope for such studies, which would take this algorithm for testing in a wider context, also indicating which patients should be referred for specialist opinion and whether expert advice can reliably be based solely on images submitted with the referral documentation, with or without ultrasonography.

To this end, we intend to investigate the ability of optometrists and ophthalmologists to assess tumor diameter and thickness and to detect orange pigment and SRF with and without special imaging. In keeping with the use of telemedicine during the Covid-19 pandemic, we will perform this investigation online. The planned investigation and other studies may also determine whether tumor thickness can be omitted from the MOLES scoring system as implied by our finding that this feature only rarely influences tumor categorization.

There is a need for evidence from long-term outcomes studies on which to base categorization of orange pigment and SRF in MOLES scoring. Albertus and associates have developed a method of image analysis that compares autofluorescence of the tumor with that of a control region in the adjacent fundus (i.e., Index of Retinal Autofluorescence)(21); however, a simple system not requiring special software would be more likely to gain acceptance.

The successful deployment of the MOLES system will depend on the efficiency of educational initiatives aimed at improving awareness and detection of clinical indicators of malignancy.

Conclusions

MOLES scores of melanocytic choroidal tumors correlate well with expert diagnosis. Further studies are needed to evaluate this system in general ophthalmic clinics and optometric practice.

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Table Legend

Table 1: Patient demographics according to MOLES score and expert diagnosis of choroidal lesion

Table 2: Clinical findings according to MOLES score

Table 3: Clinical features of 16 tumors whose size category was determined by thickness

Table 4: Clinical features of 6 tumors with a MOLES score exceeding 2 and diagnosed by the expert as nevus

Figure Legend

Fig. 1. OCTs and fundus autofluorescence images of 6 tumors with a MOLES score >2 and diagnosed by experts as nevus. a–c Case 141 (MOLES = 00201 = 3), with basal diameter >4 DD and trace SRF. d-f Case 142 (MOLES = 00201 = 3), with basal diameter >4 DD and trace SRF. g–i Case 147 (MOLES = 01200 = 3), with trace orange pigment and basal diameter >4 DD. j–l Case 159 (MOLES = 00202 = 4), with basal diameter >4 mm and significant SRF. m–o Case 148 (MOLES = 01102 = 4), with trace orange pigment, thickness >1 mm and significant SRF. p–r Case 153 (MOLES = 02101 = 4), with confluent orange pigment, basal diameter 3 mm, and trace SRF.