Review

Uveal Melanoma UK National Guidelines

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Abstract  The United Kingdom (UK) uveal melanoma guideline development group used an evidence based systematic approach (Scottish Intercollegiate Guidelines Network (SIGN)) to make recommendations in key areas of uncertainty in the field including: the use and effectiveness of new technologies for prognostication, the appropriate pathway for the surveillance of patients following treatment for primary uveal melanoma, the use and effectiveness of new technologies in the treatment of hepatic recurrence and the use of systemic treatments. The guidelines were sent for international peer review and have been accredited by NICE. A
1. Introduction

1.1. Aim of the guideline

The aim of these guidelines is to optimise patient care by providing recommendations based on the best available scientific evidence. These guidelines should assist the planning of patient care and provide an indication of the likely clinical outcomes, as well as facilitating patient counselling and informed decision-making. Where adequate evidence is lacking, the guideline development group (GDG) has, where possible, arrived at an expert consensus. The Group recognises, however, that each patient is an individual. These guidelines should therefore neither be prescriptive nor dictate clinical care; however, where care significantly differs from the guidelines, it should be justifiable. Our review also identifies gaps in current evidence, thereby defining scope for further research and audit.

The GDG reviewed the evidence, where available, for the key areas of uncertainty in the field, which include:

- The use and effectiveness of new technologies such as cytogenetics/genetic analysis for prognostication.
- The appropriate pathway for the surveillance of patients following treatment for primary uveal melanoma.
- The use and effectiveness of new technologies in the treatment of hepatic recurrence.
- The use of systemic treatments.

1.2. Background

Uveal melanoma has an incidence of approximately 2-8 per million per year in Caucasians [23] these tumours are even less common in races with brown eyes. More than 90% involve the choroid, the remainder being confined to iris and ciliary body. Both sexes are affected in equal numbers [12,5]. The age at presentation peaks at approximately 60 years, except for iris melanomas, which usually present at a younger age [5,18]. Risk factors for uveal melanoma include light-coloured irides [15], congenital ocular melanocytosis [19], melanocytoma [14] and neurofibromatosis [19]. The role of sunlight is uncertain [20]. Familial cases are very rare but some patients may have familial atypical mole and melanoma syndrome; these cases require monitoring by a dermatologist as they are also at risk of cutaneous melanoma [22]. Rare families carry germline mutations of the BAP1 gene on chromosome 3, which predisposes them to develop uveal melanoma, mesothelioma and other cancers [2].

Staging for uveal melanoma follows the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) staging system for eye cancer [7,8]. Outcomes for patients with uveal melanoma vary widely, but for patients with early tumours they are excellent. In a cohort of 8033 patients, the 10-year metastatic rate for a 1-mm-thick uveal melanoma was 5%, for a 2-mm-thick uveal melanoma it was 10%, and that for a 6-mm-thick uveal melanoma it was 30% [16,17]. When grouping 7621 uveal melanomas into small (0-3 mm thick, 29.8%), medium (3.1-8 mm thick, 49%) or large (>8 mm thick, 20.9%) tumours, the 10-year rates of detecting metastases were 11.5%, 25.5% and 49.2% respectively [16,17].

An online tool, the Liverpool Uveal Melanoma Prognosticator Online (LUMPO), has been developed and is freely available. It generates an all-cause mortality curve according to age, sex, AJCC TNM size category (based on basal tumour diameter and tumour height), ciliary body involvement, melanoma cytomorphology, closed loops, mitotic count, chromosome 3 loss and presence of extraocular spread (www.ocularmelanomaonline.com) [4].

Cytogenetic and molecular genetic features of the uveal cells have been demonstrated to have strong prognostication value in uveal melanoma. The most striking abnormality in uveal melanoma is the complete or partial loss of chromosome 3. Other common genetic abnormalities of uveal melanoma include loss on the short arm (p) of chromosome 1, and gains on 6p and 8q (see review, [3]. The above-mentioned chromosomal alterations in primary UM are clinically relevant because of their correlation with the risk of metastatic death. Chromosome 3 loss is associated with a reduction of the 5-year survival probability from approximately 100% to about 50%. Similarly, chromosome 8 gains and loss of chromosome 1 significantly correlate with reduced survival [21,13]. Conversely, gains in chromosome 6p correlate with a good prognosis, suggesting this aberration may have a functionally protective effect.

The natural history of uveal melanoma is characterised by the frequent development of metastases and patients develop metastatic disease at any time from the initial diagnosis of the primary to several decades later [9,6,11]. The risk of metastatic relapse for an individual varies greatly dependent on primary tumour characteristics and genetic alterations.

summary of key recommendations is presented. The full documents are available on the Melanoma Focus website.

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Outcomes are poor once metastatic disease occurs. The median survival from the time of the development of distant metastatic disease is 2–12 months and 1-year survival 10–15%. This range reflects a number of prognostic factors including the burden of metastatic disease and the effect of metastatic screening programmes [1].

The liver is the most common site for uveal melanoma metastases, with 50% of patients having liver-only disease, and 90% of those with metastases elsewhere (bowel, bone, lung and lymph nodes) also having liver metastases [10,24]. Liver disease is usually multifocal, often in a miliary distribution, but some patients may develop isolated metastases, enabling surgical removal. Liver involvement is the cause of death in most patients with metastatic uveal melanoma [24]. Most patients die from parenchymal liver failure, but obstructive jaundice may result from liver metastases compressing the common hepatic or intrahepatic ducts or, less commonly, from porta hepatis nodal disease compressing the extrahepatic duct.

1.3. Strengths and limitations of the evidence

Due to the rarity of uveal melanoma and associated poor prognosis, there is limited clinical evidence guiding the optimal treatment of metastatic disease. Most reports in the literature are of small case series of ten or fewer patients. Larger non-randomised studies were scrutinised carefully for a survival bias as mortality is so high. With regard to treatment of primary tumours, each United Kingdom (UK) centre tends to have specific areas of interest and no centre offers all potential treatment options. Whilst the centres compare their results in regular meetings, there are no randomised comparative trials (RCT) from the UK. The COMS study (Collaborative Ocular Melanoma Study (http://www.jhu.edu/wctb/coms/)) in the US has provided a valuable source of data; however, overall, the limitations of the evidence base in the literature are considerable.

1.4. Risks versus benefits

In weighing up the risks and benefits of any intervention, the guideline development group (GDG) has concentrated on an analysis of clinical benefit and, where appropriate, toxicity. It has not performed any cost-effectiveness analyses as this falls outside the remit of these guidelines.

2. Methods

The guideline was convened under the UK Melanoma Study Group, a precursor of Melanoma Focus, now a national charity with a professional core membership undertaking research and education in the field of melanoma and skin cancers. The guideline and supporting documentation are available on the Melanoma Focus website http://melanomafocus.com/activities-2/ocular-melanoma-project/).

The number of health professionals who provide care to patients with uveal melanoma in the UK is relatively small and the aim was to reflect the views of a significant proportion of these within the GDG. There are three ocular oncology referral centres in England that deliver primary treatment (surgery) for patients with uveal melanoma (Liverpool, London and Sheffield) whilst a handful of other centres have a specialist interest in the treatment of uveal melanoma metastatic disease. GDG members were selected to represent these centres as well as the professions involved in delivering care. In addition to the thirteen health professionals, including a trainee, there were originally three patient representatives (one of whom resigned for personal reasons) and a project manager on the GDG. The guideline was started in February of 2012, with the first Guideline Development Group meeting held in April 2012; in all, seven GDG meetings were held over a period of two years. GDG members completed a Declaration of Interest form prior to the first meeting, which was subsequently updated. All interests were declared at the first meeting and it was agreed that members who had a commercial interest in a drug or technology under discussion could remain in the room and answer questions from GDG members but could not participate in the discussion or the formulation of recommendations.

As the clinical area and the associated body of literature is small, it was decided to do one all-encompassing initial literature search and then to sift references for each question within the database. The original search was carried out by the Royal College of Physicians on 27 March 2012, with the search repeated to identify new evidence on 21 June 2013 and again 16 April 2014. Questions were drafted based on inputs from GDG members. Subgroups of content experts on the GDG worked on each topic, agreeing the criteria for including papers, then appraising and extracting references using a ‘Scottish Intercollegiate Guidelines Network’ (SIGN)) checklist as a guide. However as most of the evidence consisted of small case series, for some questions additional criteria were applied to appraise quality, in particular whether the case series included patients from more than one centre. The subgroups were supported and advised by a guideline methodologist. The subgroups presented the evidence review and extraction tables to the full GDG at the group’s meetings. The full GDG discussed the evidence and formulated evidence statements and recommendations. A great deal of work was done electronically and following update search revisions all GDG members were sent several drafts of chapters for comment.

The evidence was appraised and extracted into tables; see Appendix A, which includes many references that were reviewed but not included in the final document.

2.1. Levels of evidence


1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1− Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++ High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
1− Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3 Non-analytic studies, e.g. case reports, case series.
4 Expert opinion.

2.2. Grade of recommendations

The grading of recommendations is also based on SIGN 199-2012:

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.
GPP Recommended best practice based on the clinical experience of the guideline development group.

3. Recommendations

3.1. Patient Choice and Shared decision-making

1. All specialist surgical ocular oncology multidisciplinary teams (MDTs) should collaborate to produce an information leaflet on the options available nationally. [GPP]

2. All available procedural and treatment options, local, national and international should be discussed with the patient. [GPP]

3. The risks and benefits of any procedures and treatments being considered should be fully discussed with the patient, including their impact on quality of life. [GPP]

3.2. Service configuration

1. Supra-regional specialist multi-disciplinary teams (MDT), using a network model, should be established that promote a coordinated approach for the care and follow-up of all patients with uveal melanoma. For advanced disease, a specialist oncology MDT should consist of a medical or clinical oncologist, an interventional radiologist, a diagnostic radiologist a histopathologist, a liver surgeon and a clinical nurse specialist, all with experience in treating uveal melanoma and with direct links to ocular surgical oncology centres. The MDT should make recommendations on an individual patient’s tumour staging and management, and have available all treatments and trials locally or by referral. [GPP]

2. Any molecular testing should be carried out within an accredited molecular pathology laboratory with appropriate quality assurance in place to provide the required standards and experienced interpretation of the diagnostic test, in compliance with national requirements. [GPP]

3. A national register, based on a standardised minimum data set, should be established where details of every patient with a diagnosis of uveal melanoma are entered, with follow-up data collected at least annually. [GPP]

3.3. General guidance

1. All local recurrences of the primary uveal melanoma should be reported to the surgical ocular oncology centre where treatment for the primary tumour took place. [GPP]

2. All Optometrists and Ophthalmologists should receive training in the recognition of uveal melanoma, in order to allow earlier detection and timely referral of patients with uveal melanoma. [GPP]

3. Each surgical ocular oncology centre should audit their results and share them nationally. [GPP]

4. The suspected diagnosis of uveal melanoma by the referring clinician should follow the same pathways as for any other suspected cancer. The ocular
oncology centre should be notified within 48 hours of presentation and the patient seen by the specialist within two weeks. Grade C

5. Suspicious lesions or lesions diagnosed as uveal melanoma should be referred to a consultant surgical ocular oncologist in one of the surgical oncology centres for ocular malignancies. Grade D

6. Specimens should be reported by an ophthalmic pathologist within a specialist centre. [GPP]

7. All patients with a new diagnosis of uveal melanoma should be offered referral to a medical or clinical oncologist with a specialist interest in the disease. [GPP]

8. Patients should be informed about and recruited into clinical trials wherever possible. [GPP]

9. Patients should be offered the opportunity to participate in uveal melanoma specific research. With patient consent, samples should be taken surplus to diagnostic requirements and stored in an ethically-approved quality biobank for research purposes. [GPP]

3.4. Primary management

3.4.1. Pre-operative investigations

1. Make a diagnosis of uveal melanoma using ophthalmoscopy, fundus photography and conventional ocular ultrasound. Grade A

2. Ciliary body melanoma should be imaged with Ultrasound Biomicroscopy (UBM) or anterior segment Optical Coherence Tomography (OCT). Grade D

3. If the clinical diagnosis is uncertain following the above-mentioned techniques then diagnostic biopsy should be considered and balanced against potential risks of the procedure. [GPP]

4. Fine needle aspiration biopsy can be performed either with a direct transcleral approach or using a transvitreal approach. Grade D

3.4.2. Staging before primary treatment

1. A decision on staging should be made based on the individual circumstances of the patient, but staging should not delay the primary management of the tumour. [GPP]

2. Staging should be considered in the following circumstances:
   - The patient is at particularly high risk because of the clinical features of their presentation.
   - The patient is particularly anxious and requires reassurance. [GPP]

3.4.3. Treatment of the primary tumour

1. Patients should be informed that there is no proven survival advantage between any of the offered modalities. Grade A

2. Treat patients using table below
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Used for</th>
<th>Outcomes</th>
<th>Complications</th>
<th>Comments</th>
<th>Grade of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phototherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transpupillary thermotherapy</td>
<td>Local recurrence and of adjuvant therapy of uveal melanoma</td>
<td>Improves local tumour control</td>
<td>Loss of vision Extraocular tumour recurrence</td>
<td>Very occasionally used by some centres for small melanoma nasal to the optic disc. When considering preservation of vision, for example in a one eyed patient; as it avoids radiotherapy complications. However, it is no longer recommended routinely as a sole primary treatment.</td>
<td>Grade C</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>Small melanoma</td>
<td>Uncertain</td>
<td>Tumour recurrence</td>
<td>Avoids radiotherapy complications New treatment option not widely used for uveal melanoma. This is an experimental treatment.</td>
<td>Grade D</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exoresection ± plaque</td>
<td>Medium to large melanoma with a narrow basal diameter</td>
<td>Variable</td>
<td>Retinal detachment Loss of vision Loss of the eye Tumour recurrence Risk of orbital dissemination of tumour</td>
<td>Rarely performed in the UK. Only performed in limited centres. Always performed with brachytherapy to reduce the risk of recurrence</td>
<td>Grade C</td>
</tr>
<tr>
<td>Endoresection ± radiotherapy</td>
<td>Medium-sized uveal melanoma. Toxic tumour syndrome post PBR</td>
<td>Variable</td>
<td>Transient intraocular haemorrhage; Rarely tumour seeding</td>
<td>Only performed in limited centres in the UK</td>
<td>Grade D</td>
</tr>
<tr>
<td>Enucleation</td>
<td>Large uveal melanoma Melanoma associated with NVG ± extensive retinal detachment</td>
<td>100% local tumour control if completely excised</td>
<td>Socket related complications Orbital recurrence</td>
<td>Cosmetic results are reasonably good with an orbital implant and artificial eye</td>
<td>Grade A</td>
</tr>
<tr>
<td>Exenteteration</td>
<td>Large extra-ocular extension after uveal melanoma</td>
<td>100% local tumour control if completely excised</td>
<td>Orbital recurrence</td>
<td>Rarely performed in the UK.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>

* = as defined by (Diener-West, Hawkins et al., 1992)
3.4.4. Follow-up after primary treatment

1. Patients treated with plaque brachytherapy, proton beam radiotherapy or stereotactic radiotherapy should be monitored for tumour regression intensively over the first two years following treatment. Long-term follow up intervals depend on the response of the tumour to brachytherapy and the radiotherapy complications experienced. [GPP]

3.5. Prognostication

3.5.1. Prognostic factors/tool

1. Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological and genetic features. The following features should be recorded:
   - Age
   - Gender
   - Tumour location
   - Tumour height
   - Tumour largest basal diameter
   - Ciliary body involvement
   - Extraocular melanoma growth (macroscopic)

   The following features should be recorded if tissue is available:
   - Cell type (modified Callender system)
   - Mitotic count (number/40 high power fields in H&E stained sections)
   - Presence of extravascular matrix patterns (particularly closed connective tissue loops; enhanced with Periodic acid Schiff staining). Grade A
   - Presence of extraocular melanoma growth (size, presence or absence of encapsulation). [GRADE A]

3.5.2. Prognostic biopsy

1. There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
   - Risk of having the biopsy
   - Limitations of the investigation
   - Benefits for future treatments (including possible recruitment to trials)
   - Impact on quality of life
   - Recruitment to trials
   - Follow-up. [GPP]

2. The minimum dataset for uveal melanoma from the Royal College of Pathology should be recorded. http://www.rcpath.org/publications-media/publications/datasets/uveal-melanoma.htm. Grade D

3. Tests for novel serological biomarkers should only be used within clinical trials or research programmes. [GPP]

4. Consider collecting molecular genetic and/or cytogenetic data for research and prognostication purposes where tumour material is available and where patient consent has been obtained as part of an ethically approved research programme. [GPP]

5. Use of the current (i.e. 7th) Edition of the TNM staging system for prognostication is highly recommended. Grade A

6. Use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features – should be considered. Grade D

3.6. Surveillance

1. Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [GPP]

2. Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features. [GPP]

3. All patients, irrespective of risk, should have a holistic assessment to discuss the risk, benefits and consequences of entry into a surveillance programme. The discussion should consider risk of false positives, the emotional impact of screening as well as the frequency and duration of screening. An individual plan should be developed. [GPP]

4. Patients judged at high-risk (see Section Error! Reference source not found.) of developing metastases should have 6-monthly life-long surveillance incorporating a clinical review, nurse specialist support and liver-specific imaging by a non-ionising modality. [GPP]

5. Liver function tests alone are an inadequate tool for surveillance. Grade C

3.7. Metastatic disease

3.7.1. Staging

1. Patients should have whole body staging (chest, abdomen and pelvis) with CT scan or PET CT. Grade D

2. Brain imaging should not be carried out in the absence of symptoms. [GPP]

3. Patients who have symptomatic bony pain should have a bone scan to assess the presence of bony disease. [GPP]
4. Contract enhanced MRI with diffusion weight imaging should be used to stage liver disease when assessing operability. Grade D

5. Contrast-enhanced CT scan should be used to stage extrahepatic disease. Grade D

3.7.2. Prognostic method

1. This minimum data set should be collected for all patients with systemic disease (Stage IV) for future validation:
   - Metastatic Tumour Burden (site, diameter and number),
   - LDH
   - ALP
   - GGT
   - Bilirubin
   - Presence or absence of ascites
   - Gender
   - Age
   - Performance status,
   - DFS following definitive primary therapy. [GPP]
2. A tissue sample should be taken to confirm the diagnosis of metastatic uveal melanoma unless contraindicated. [GPP]
3. Curative (R0) resection is the most important positive prognostic factor following liver resection. [GPP]

3.7.3. Management of systemic and oligometastatic-extrahepatic disease

1. Patients should be considered for clinical trials wherever possible and be informed of available trial options at other centres. [GPP]
2. Patients with good performance status (PS 0-2) who decline trials or for whom no suitable clinical trials are available should be offered systemic treatments and managed in specialist centres with appropriate oncology expertise in uveal melanoma. [GPP]
3. Specialist centres should be involved in treatment decisions and review, but a patient may prefer to receive supportive care and systemic treatment locally. [GPP]
4. Patients with liver predominant disease should be considered for regional therapy. Grade D
5. Loco-regional treatment for the management of oligometastatic disease (i.e. when metastases are limited to a single or limited number of organs) should be considered. This may include surgery, stereotactic treatment or other forms of ablation. [GPP]
6. Ipilimumab can be offered in the UK following NICE approval of this drug for use in melanoma generically.

3.7.4. Management of liver metastases

1. For patients with technically resectable disease, assessment for curative intent hepatic resection should be offered. Grade D
2. Pre-operative diagnostic laparoscopy should be performed in patients with radiologically resectable liver metastases, as many of these patients will have a miliaiy pattern of disease. Grade D
3. Regional or systemic treatments may be considered in patients with liver dominant disease where resection is not suitable. [GPP]

3.7.5. Surveillance following liver treatment

1. Patients treated with curative intent should be followed with regular (3-4 monthly) hepatic MRI and CT of chest, abdomen and pelvis. [GPP]
2. Patient outcomes for this selected group should be collected centrally and prospectively. [GPP]

Conflict of interest statement

GDG members completed a Declaration of Interest form prior to the first meeting, which was subsequently updated. All interests were declared at the first meeting and it was agreed that members who had a commercial interest in a drug or technology under discussion could remain in the room and answer questions from GDG members but could not participate in the discussion or the formulation of recommendations. All declarations of interest are available with the full guidelines document online.

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References


