Uveal Melanoma National Guidelines

January 2015

Authors:


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1. Executive Summary

1.1. Care Pathway

Suspected primary uveal melanoma

REFER to one or 3 specialist ocular surgery centres

MAKE DIAGNOSIS:
For uveal melanoma use ophthalmoscopy, fundus photography and conventional ocular ultrasound
For ciliary body melanoma use UBM or anterior segment OCT
Fine needle aspiration biopsy can be performed with a direct transpalpebral approach or using a transvitreal approach

No

Diagnosis confirmed?

Consider PROGNOSTIC BIOPSY:
- Rare informed discussion with patients explaining theories of biopsy and risks and potential benefits:
  - Risk of having the biopsy
  - Limitations of the investigation
  - Benefits for future treatments
  - Impact on quality of life
  - Recruitment to trials

Yes

Consider TRIALS:
- Tests for novel prognostic serological biomarkers
- Collection of molecular genetic or cytophenetic data for research purposes as part of an ethically approved research programme

PROGNOSTICATION
- See Box 2

TREAT PRIMARY TUMOUR
- See Box 1

Use TNM staging system for prognostication
Use of multi-factorial prognostication systems should be considered

STAGE within 4 weeks using MRI (liver with diffusion weighting or liver ultrasound) plus MR if any abnormality seen

FOLLOW UP after primary tumour treatment:
- Monitor intensively for 2 years for tumour regression after treatment with plaque brachytherapy, proton beam radiotherapy or stereotactic radiotherapy
- Long term follow up intervals depend on the response to therapy and the complications experienced.

SURVEILLANCE
- For metastatic disease
- See Box 3

RECURRANCE?

No

Yes

See next page
## BOX 1 TREATMENT OPTIONS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Used for</th>
<th>Outcomes</th>
<th>Complications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RADIOTHERAPY</strong></td>
<td></td>
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<tr>
<td>Brachytherapy</td>
<td>Small/Medium/Large uveal melanoma &lt;20mm in basal diameter</td>
<td>Good local tumour control</td>
<td>Loss of vision</td>
<td>Dose and position of plaque can be adjusted to limit the loss of vision</td>
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<tr>
<td>Ruthenium 106</td>
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<td>Tumour recurrence</td>
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<tr>
<td>Iodine 125</td>
<td></td>
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</tr>
<tr>
<td>Proton Beam radiotherapy</td>
<td>Medium to Large uveal melanoma which can not be treated with brachytherapy or resection</td>
<td>Good local tumour control</td>
<td>Loss of vision</td>
<td>Not available in all ocular oncology units</td>
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<tr>
<td></td>
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<td></td>
<td>Loss of the eye from neovascular glaucoma</td>
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<tr>
<td>Stereotactic radiosurgery</td>
<td>Juxta papillary uveal melanoma ; patients unsuitable for ruthenium plaque or unfit for surgery</td>
<td>Good local tumour control</td>
<td>Loss of vision Radiation related complications. Tumour recurrence</td>
<td>Not available in all ocular oncology units</td>
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<tr>
<td><strong>PHOTOTHERAPY</strong></td>
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</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>
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<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>
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<tr>
<td><strong>SURGERY</strong></td>
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<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>Only performed in limited centres. Always performed with brachytherapy to reduce the risk of recurrence.</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>
</tr>
<tr>
<td>Enucleation</td>
<td>Large uveal melanoma Melanoma associated with neovascular glaucoma +/- 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>
</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>
</tr>
</tbody>
</table>
**BOX 2 PROGNOSTICATION**

The following features should be recorded:
- Age
- Gender
- Tumour location
- Tumour height
- Tumour Largest basal diameter
- Ciliary body involvement
- Extracocular melanoma growth

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).

A minimum dataset for uveal melanoma from the Royal College of Pathology should be recorded.

Any molecular testing should be carried out within an accredited laboratory with appropriate quality assurance in place to provide the standards of the diagnostic test.

The prognostic testing should take place within a tertiary referral centre.

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

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**BOX 3 SURVEILLANCE**

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

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

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.

Patients judged at high-risk (see Section 6.3.2) 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.

Liver function tests alone are an inadequate tool for surveillance.

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**COMMISSIONING OF CARE**

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

Surgeons who see a patient with a recurrence who was treated elsewhere should inform the treating centre.

Patients should be informed about and recruited into clinical trials wherever possible.

Supra-regional specialist multi-disciplinary teams (MDTs), using a network model, should be established that allow a coordinated approach for the care and follow-up of all patients with metastatic uveal melanoma. For advanced disease a specialist oncology MDT should consist of a medical or clinical oncologist, an interventional 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.

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.

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**PATIENT INFORMATION AND SHARED DECISION MAKING**

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

All available procedural and treatment options both locally and nationally should be discussed with the patient.

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.
1.2. **Recommendations**

Note: All of the recommendations are listed in this section and are not duplicated in the clinical chapter.

Within each clinical chapter there are hyperlinks to the relevant recommendations and a hyperlink to return to the chapter.

The grading of the recommendations is detailed in the methodology section.

1.2.1. **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]

1.2.2. **Service Configuration**

4. 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]

5. 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]

6. 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]

1.2.3. **General Guidance**

7. 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]

8. 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]
9. Each surgical ocular oncology centre should audit their results and share them nationally. [GPP]

10. 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

11. 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

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

13. 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]

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

15. 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]

1.2.4. Primary management

Pre-operative investigations

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

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

18. 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]

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

Staging before primary treatment

20. 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]

21. 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]

Treatment of the primary tumour

22. Patients should be informed that there is no proven survival advantage between any of the offered modalities. Grade A
23. 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>RADIOThERAPy</strong></td>
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<tr>
<td>Brachytherapy</td>
<td>Small/Medium /Large uveal melanoma* &lt;20mm in basal diameter</td>
<td>Good local tumour control</td>
<td>Loss of vision</td>
<td>Dose and position of plaque can be adjusted to limit the loss of vision</td>
<td>Grade A</td>
</tr>
<tr>
<td>Ruthenium 106</td>
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<td>Medium to Large uveal melanoma which cannot be treated with brachytherapy or resection</td>
<td>Good local tumour control</td>
<td>Loss of vision</td>
<td>Not available in all ocular oncology units</td>
<td>Grade C</td>
</tr>
<tr>
<td>Stereotactic</td>
<td>Juxta-papillary uveal melanoma ; patients unsuitable for ruthenium plaque or unfit for surgery</td>
<td>Good local tumour control</td>
<td>Loss of vision</td>
<td>Not available in all ocular oncology units</td>
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</tr>
<tr>
<td>radiosurgery</td>
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<tr>
<td><strong>PHOTOTHERAPY</strong></td>
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<tr>
<td>Transpupillary</td>
<td>Local recurrence and of adjuvant therapy of uveal melanoma</td>
<td>Improves local tumour control</td>
<td>Loss of vision</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>
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<tr>
<td>thermotherapy</td>
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<tr>
<td>Photodynamic</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>therapy</td>
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</table>

**SURGERY**
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Tumour Characteristics</th>
<th>Ocular Complications</th>
<th>Treatment Considerations</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exoresection +/- plaque</td>
<td>Medium to large melanoma with a narrow basal diameter</td>
<td>Variable</td>
<td>Retinal detachment&lt;br&gt;Loss of vision&lt;br&gt;Loss of the eye&lt;br&gt;Tumour recurrence&lt;br&gt;Risk of orbital dissemination of tumour</td>
<td>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>D</td>
</tr>
<tr>
<td>Enucleation</td>
<td>Large uveal melanoma&lt;br&gt;Melanoma associated with NVG +/- extensive retinal detachment</td>
<td>100% local tumour control if completely excised</td>
<td>Socket related complications&lt;br&gt;Orbital recurrence</td>
<td>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&lt;br&gt;Rarely performed in the UK</td>
<td>D</td>
</tr>
</tbody>
</table>

* = as defined by (Diener-West, Hawkins et al. 1992)

**Follow-up after primary treatment**

24. 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]

Return to chapter by clicking HERE

**1.2.5. Prognostication**

**Prognostic factors/tool**

25. 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]

**Prognostic biopsy**

26. 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]

27. 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

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

29. 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]

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

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

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1.2.6. **Surveillance**

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

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

34. 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]

35. Patients judged at high-risk (see Section 6.3.2) 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]

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

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1.2.7. Metastatic disease

Staging

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

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

39. Patients who have symptomatic bony pain should have a bone scan to assess the presence of bony disease. [GPP]

40. Contract enhanced MRI with diffusion weight imaging should be used to stage liver disease when assessing operability. Grade D

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

Prognostic method

42. 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]

43. A tissue sample should be taken to confirm the diagnosis of metastatic uveal melanoma unless contraindicated. [GPP]

44. Curative (R0) resection is the most important positive prognostic factor following liver resection. [GPP]
Management of systemic and oligometastatic-extrahepatic disease

45. Patients should be considered for clinical trials wherever possible and be informed of available trial options at other centres. [GPP]

46. 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]

47. Specialist centres should be involved in treatment decisions and review, but a patient may prefer to receive supportive care and systemic treatment locally. [GPP]

48. Patients with liver predominant disease should be considered for regional therapy. Grade D

49. Locoregional 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]

50. Ipilimumab can be offered in the UK following NICE approval of this drug for use in melanoma generically.

Management of liver metastases

51. For patients with technically resectable disease, assessment for curative intent hepatic resection should be offered. Grade D

52. Pre-operative diagnostic laparoscopy should be performed in patients with radiologically resectable liver metastases, as many of these patients will have a miliary pattern of disease. Grade D

53. Regional or systemic treatments may be considered in patients with liver dominant disease where resection is not suitable. [GPP]

Surveillance following liver treatment

54. Patients treated with curative intent should be followed with regular (3-4 monthly) hepatic MRI and CT of chest, abdomen and pelvis. [GPP]

55. Patient outcomes for this selected group should be collected centrally and prospectively. [GPP]
2. Background

2.1. Introduction

Uveal melanoma has an incidence of approximately 2-8 per million per year in Caucasians (Virgili, Gatta et al. 2007) 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. (McLaughlin, Wu et al. 2005, Damato and Damato 2012) The age at presentation peaks at approximately 60 years, except for iris melanomas, which usually present at a younger age. (Damato and Damato 2012) (Shields, Shields et al. 2001) Risk factors for uveal melanoma include light-coloured irides (Saornil 2004), congenital ocular melanocytosis (Singh, De Potter et al. 1998), melanocytoma (Reidy, Apple et al. 1985) and neurofibromatosis (Singh, De Potter et al. 1998). The role of sunlight is uncertain (Singh, Rennie et al. 2004). 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 (Smith, Padnick-Silver et al. 2007). Rare families carry germline mutations of the BAP1 gene on chromosome 3, which predisposes them to develop uveal melanoma, mesothelioma and other cancers (Cheung, Talarchek et al. 2013).

Staging for uveal melanoma follows the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system for eye cancer (Finger and The 7th Edition AJCC-Ophthalmic Oncology Task Force 2009, Kujala et al. 2013). 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% (Shields, Furuta et al. 2009). When grouping 7621 uveal melanomas into small (0-3mm 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 (Shields, Furuta et al. 2009).

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) (Damato, Eleuteri et al. 2011).

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, (Coupland, Lake et al. 2013). 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. (Sisley, Parsons et al. 2000, Patel, Edmondson et al. 2001) 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 (Kujala,

Outcomes are poor once metastatic disease occurs. The median survival from the time of the development of distant metastatic disease is 2 to 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 (Augsburger, Correa et al. 2009).

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 (Lorigan, Wallace et al. 1991, Willson, Albert et al. 2001). 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 (Willson, Albert et al. 2001). 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.

2.2. **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 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. The COMS study is discussed in more detail in section 4.

2.3. **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.

2.4. **Scope and purpose**

2.4.1. **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 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 has 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.

### 2.4.2. Clinical areas covered by the guideline

This guideline addresses the diagnosis and management of primary uveal melanoma, including iris and ciliary body melanoma in adults (>16 years). It does **not** address conjunctival melanoma, which has a pathogenesis and behaviour more in common with mucosal and cutaneous melanomas.

The guideline addresses four main clinical topics:

- Management of the primary tumour
- Prognostication
- Surveillance of patients at risk of recurrence
- Metastatic disease

### 2.4.3. Target population and target audience

The guideline is relevant to people with a confirmed or suspected diagnosis of uveal melanoma, as well as their family and carers.

The guideline will be helpful to all health professionals who provide care for people with uveal melanoma. This includes ophthalmologists, optometrists, liver surgeons, radiologists, pathologists, specialist cancer nurses and oncologists.

### 2.5. Acknowledgements

The GDG is grateful to Melanoma Focus for its support in funding the development of this guideline and for hosting the consultation and the final product on its web page http://melanomafocus.com/activities-2/um-guidelines-resources/. We would like to thank those people who helped with the searches and review of the evidence. These include: the Royal College of Physicians Library Services, who carried out the searches; Ruth Poulter, Clinical Trial Coordinator at University of Liverpool, who obtained papers; and Dr Rachel O’Mahony, who reviewed and extracted the evidence where the members of the GDG was unable to do so due to time constraints. The GDG members also express their gratitude to all those colleagues worldwide who gave their constructive comments on the draft. See Appendix E for the names of those who provided comments.

### 3. Methodology

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/um-guidelines-resources/). The development of the guideline was led by Dr Paul Nathan, who is a trustee of Melanoma Focus and a medical oncologist with an interest and expertise in the treatment metastatic melanoma. Other officers and trustees of Melanoma Focus played no part in the development of the guideline and did not comment on the guideline prior to the public consultation.

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) while 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 input 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 sub-groups 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.

A detailed description of the methodology is available in the document entitled Uveal Melanoma Guideline Development Methodology at http://melanomafocus.com/activities-2/um-guidelines-resources/

3.1. Levels of Evidence

The grading of the evidence is based on the Scottish Intercollegiate Guidelines Network (SIGN) grading system 1999-2012 http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

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
2- 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

3.2. **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

4. **Management of the primary tumour**

4.1. **Introduction**

Most uveal melanoma patients present with symptoms, including blurred vision, visual field loss, distorted vision, photopsia (i.e. flashing lights), visible tumour in iris or episclera, red eye and pain. In the UK approximately 30%-40% of patients are asymptomatic, their tumour being detected on routine ophthalmic examination by an optometrist or ophthalmologist (Damato 2001). Delay in referral leads to an increased likelihood that the patient will require an enucleation (removal of the eye) and as the result of more advanced disease stage at presentation (including disseminated melanoma) (Damato 2012).

Without timely treatment, uveal melanomas tend to make the eye blind, painful and unsightly as a result of retinal detachment, neovascular glaucoma (NVG) and uveitis. Despite successful ocular treatment, up to 50% of all patients with large ciliary body melanoma develop metastatic disease, which almost always involves the liver and which is usually fatal within a year of the onset of symptoms. With successful treatment of the primary, the outlook is excellent for many patients with uveal melanoma. In a cohort of 8033 patients, the 10-year metastatic rate for a 1-mm-thick uveal melanoma was 5%, while for a 2-mm-thick uveal melanoma it was 10%, and for a 6-mm-thick uveal melanoma it was 30% (Shields, Furuta et al. 2009). When grouping 7621 uveal melanomas into small (0-3mm 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 (Shields, Furuta et al. 2009). In the COMS study, the five-year survival figures for medium-sized choroidal melanoma were 91% in a group of patients randomized to radiotherapy and 89% in the group randomized to enucleation (Diener-West, Earle et al. 2001). At 12 years the survival figures were 79% in the radiotherapy group and 83% in the enucleation group. (COMS report no 28) (based on histopathologically confirmed melanoma metastasis alone). (Hawkins 2006)
The objectives of ocular treatment are to attempt to prevent metastatic disease and if possible to conserve the eye with as much useful vision as possible. Enucleation has therefore been replaced, whenever possible, by various forms of external radiotherapy, phototherapy and local resection, which are administered either individually or in combination. Many factors influence the choice of ocular treatment, including: tumour size and location, visual acuity in the affected eye and the fellow eye, and the patient’s general health as well as the patient’s visual needs, wishes and concerns.

### 4.2. Methods

#### 4.2.1. Questions addressed

The following questions were addressed.

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 1. What are appropriate pre-operative investigations for the primary tumour?</td>
<td>Patients with possible primary uveal melanoma</td>
<td>Biopsy B-ultrasound sonography (USS), ultrasound biomicroscopy, Photography Fluorescein angiogram Optical Coherence Tomography (OCT), fundus autofluorescence</td>
<td>With each other/ With observation only</td>
<td>Selection of appropriate treatment modality (see Q 3)</td>
</tr>
<tr>
<td>Q 2. Should patients be staged before primary treatment?</td>
<td>Patients with primary uveal melanoma</td>
<td>Any staging investigation</td>
<td>No staging</td>
<td>Change of treatment of primary tumour</td>
</tr>
<tr>
<td>• Which patients should be staged before primary treatment, and how and when?</td>
<td></td>
<td></td>
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<tr>
<td>• What is the benefit of staging before primary treatment?</td>
<td></td>
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<tr>
<td>• In what circumstances does investigation inform primary management?</td>
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<tr>
<td>Q 3. What is the optimal primary treatment?</td>
<td>Patients with primary uveal melanoma</td>
<td>Including: • Enucleation • Proton beam therapy • Plaque therapy • Endo-resection • Trans-scleral resection • Stereotactic radiotherapy • Thermotherapy</td>
<td>With each other or with usual care</td>
<td>Primary: 1. Survival/ Distal recurrence 2. Preserving eye 3. Preserving vision Secondary: 1. Quality of life 2. Visual Acuity 3. Local recurrence</td>
</tr>
</tbody>
</table>
4.2.2. Inclusion and Exclusion criteria for selecting evidence

Inclusion Criteria for all sections were: All study types in humans were considered but case-series had to be N>5. Older treatment forms, such as Xenon Arc photocoagulation that are no longer in use, were excluded.

4.2.3. Appraisal and Extraction

All references were sifted first by one individual. The primary reasons for excluding papers were that the papers did not address the question, or the techniques are now obsolete due to more recent advances, where techniques have changed, or that papers had been superseded by more contemporary results.

The four different reviewers (members of the GDG) appraised and reviewed the included papers, and the quality of the studies was assessed using the modified SIGN checklists. Most of the studies were case-series and, because SIGN does not have a quality checklist for this study type, additional criteria were used to assign an overall quality rating to these studies.

Information from each of the studies was extracted and presented to the GDG for discussion with an update of the evidence presented after an update search in June 2013. For full details of each of the included studies, see the evidence tables in Appendix B.

4.3. Evidence Summary

4.3.1. Question 1. What are appropriate pre-operative investigations for the primary tumour?

4.3.1.1. Choroidal melanoma

In most cases the diagnosis of choroidal melanoma is based on ophthalmoscopy, fundus photography and conventional ocular ultrasound. An early report on the diagnostic accuracy of ophthalmoscopy, fundus photography and conventional ocular ultrasound showed that the combination of these tests gave a diagnostic accuracy of 99.52% (Albert and Marcus 1990).

Conventional A and B scan ocular ultrasound is key to making the diagnosis (Wang, Yang et al. 2003), (Romani, Baldeschi et al. 1998). In the COMS trial, 99.7% (1559 of 1563) of medium sized and large ocular tumours were diagnosed to be melanoma using ocular ultrasound alongside other features, a diagnosis that was later confirmed by pathology (Collaborative Ocular Melanoma Study, Boldt et al. 2008). Diagnostic accuracy of ultrasound is likely to be lower in small uveal melanomas. Uveal melanoma demonstrates ultrasonographic hollowness, choroidal excavation and has a typical dome or ‘collar-stud’ configuration on B scan ultrasonography. Ultrasonographic hollowness or low internal reflectivity is also a suspicious sign in atypical choroidal naevi and helps to predict which naevi may progress to frank malignancy (Shields, Furuta et al. 2009). Evidence would suggest that ocular ultrasound sonography (USS) is better than computer tomography (CT) or
magnetic resonance imaging (MRI) at detecting extrascleral/orbital extension (Scott, Murray et al. 1998, Collaborative Ocular Melanoma Study, Boldt et al. 2008). Some have considered ocular positron emission tomography (PET/CT) as a diagnostic investigation because cutaneous melanoma demonstrates high metabolic activity and this can be demonstrated using Fludeoxyglucose positron emission tomography (FDG-PET)/CT (Finger, Kurli et al. 2004, Reddy, Kurli et al. 2005). However, uveal melanoma shows variable metabolic activity and, therefore, it is unlikely that an ocular PET/CT will be able to usefully distinguish between naeves and melanoma (Finger, Kurli et al. 2004, Reddy, Kurli et al. 2005). The reason for poor FDG uptake in uveal melanoma remains unknown (Strobel, Bode et al. 2009).

Other tests can be used to distinguish a choroidal naevus from a choroidal melanoma, tests that are especially useful when considering small melanoma or amelanotic melanoma. Autofluorescence is a property of lipofuscin (the orange pigment seen on top of melanoma which appears brown on the surface of an amelanotic melanoma). Quantification of autofluorescence images can distinguish a choroidal melanoma from a naevus with a sensitivity 89% and specificity of 93% (Albertus, Schachar et al. 2013). A study conducted by Ausberger in 1989 first described the presence of orange pigment clumps as a risk factor for predicting growth of melanocytic choroidal lesions (Shields, Shields et al. 1995)(Augsburger, Schroeder et al. 1989) Other risk factors (tumour thickness>2mm; the clinical presence of subretinal fluid; visual symptoms; and proximity to the optic disc <3mm) can all be determined with ophthalmoscopy and conventional ocular ultrasound. The significance of subretinal fluid on Optical Coherence Tomography (OCT) is yet to be determined, but OCT may be used to monitor suspicious choroidal lesions. As enhanced depth imaging with OCT improves, it is likely that a better understanding of the choroidal appearance of melanoma will be achieved, and this in turn is likely to assist in the differential diagnosis of choroidal tumours.

4.3.1.2. Ciliary body and iris melanoma
The evidence for investigation with more recently developed diagnostic tools is based on comparative case series. Bianciotto et al (Bianciotto, Shields et al. 2011) evaluated 200 iris and ciliary body tumours (47 were melanomas): they reported that Anterior Segment Optical Coherence Tomography (AS-OCT) was useful for iris melanoma but was not superior to Ultrasound Biomicroscopy (UBM) when considering ciliary body tumours. AS-OCT suffers from optically-related image shadowing with large, pigmented lesions (Razzaq, Emmanouilidis-van der Spek et al. 2011). Large iris pigment epithelium cysts and ciliary body lesions cannot be adequately imaged with AS-OCT. Recent evidence suggests that small anterior iris melanoma can be adequately imaged with AS-OCT (Hau et al in print). UBM with a 50MHz probe is considered to be the best tool to image the ciliary body (Gunduz, Hosal et al. 2007). Further, Conway et al compared UBM with conventional A/B scan ultrasound in 132 iris/ciliary body masses (55 were melanoma). They reported only 29% correspondence between the anatomical structures invaded by melanoma as identified by B-scan versus disease extent defined by UBM with UBM being superior (Conway, Chew et al. 2005). The disadvantages of UBM include patient discomfort due to the eye contact with a water bath, and the increased time taken to perform this test. However, more recent UBM machines are now fitted with probes that do not always require a waterbath.

4.3.1.3. Intraocular Biopsy for Diagnosis
If the diagnosis is still uncertain following the above investigations, then biopsy has a role in distinguishing small melanomas from naeves and amelanotic melanomas from metastases. Various methods have been described, using tools such as fine-needle aspiration, vitreous cutter and Essen Forceps, (Augsburger, Correa et al. 2002, Sen, Groenewald et al. 2006, Bornfeld 2007, Shields, Ganguly et al. 2007, Konstantinidis, Roberts et al. 2013). Biopsy is associated with a number of risks, which include: failure, especially with small tumours (Cohen,
Dinakaran et al. 2001, Augsburger, Correa et al. 2002; rhegmatogenous retinal detachment; and rarely endophthalmitis (Kvanta, Seregard et al. 2005). Seeding to extraocular tissues can also occur but this is exceptionally rare (Char, Kemlitz et al. 2006, Schefer and Abramson 2009, Caminal, Ribes et al. 2012).

Fine needle aspiration biopsy can be performed with a direct transcleral approach or using a transvitreal approach. Cohen et al reported a cohort of 83 patients who underwent 25-gauge fine needle aspiration biopsy for indeterminate choroidal lesions. Overall a diagnosis could be achieved in 88% but the small indeterminate lesions did not always yield sufficient cells to make a diagnosis especially if less than 2mm in thickness (<2mm 40% diagnostic 2-4mm 90% diagnostic) (Cohen, Dinakaran et al. 2001). (Konstantinidis, Roberts et al. 2013). In another cohort study of 34 patients in the ‘naevus versus melanoma category’ (1.5-3mm in thickness), who underwent a 25-gauge fine needle aspiration biopsy, the diagnostic yield was 65% (Augsburger, Correa et al. 2002). Transcleral conventional biopsy is best suited for anteriorly positioned tumours. Infrequent potential complications of biopsy include tumour seeding within the eye or orbit, infection and intraocular haemorrhage, although the latter is usually only transient (Kvanta, Seregard et al. 2005). Biopsy can be difficult to perform and the resulting specimen difficult to interpret. Therefore, these surgical procedures should only be undertaken in a specialist surgical ocular oncology centre by those with expertise and with the aid of a specialist ocular pathologist. (Cohen, Dinakaran et al. 2001, Augsburger, Correa et al. 2002, Konstantinidis, Roberts et al. 2013).

4.3.2. Question 2. Should patients be staged before primary treatment?

4.3.2.1. Incidence of metastases at staging

In the majority of patients with uveal melanoma, metastatic disease is not detectable at diagnosis. It is a rare finding at diagnosis being reported in less than 1% (70 out of 7,541) of patients screened for the COMS trial. (Diener-West, Reynolds et al. 2004). However, this study has limitations as only liver function tests (LFTs) and chest X-Rays (CXR) were used to stage patients. Using FDG-PET/CT, Finger et al. staged 52 patients with the diagnosis of primary uveal melanoma, and metastases were only found in 2 patients (3.8%) (Finger, Kurli et al. 2004). More recently, Feinstein et al used abdominal CT to stage 91 patients with uveal melanoma, and metastases were found in 3 patients (3.3%) (Feinstein, Marr et al. 2010). In a study by Freton et al, 333 patients with uveal melanoma were screened with PET/CT and 7 patients (2.1%) were found to have metastatic melanoma. (Freton, Chin et al. 2012)

There is evidence to suggest that the risk of detecting metastatic disease at diagnosis can be stratified according to the size of the uveal melanoma. The incidence of liver metastases at diagnosis in 911 British patients from 2007-2011 was only 0.6% in the small-to-medium uveal melanoma group compared to 7.7% in those patients scheduled for enucleation [Papastefanou et al 2012, conference presentation]. These patients were all staged with an abdominal ultrasound and LFTs: if an abnormality was detected, they had further imaging with either PET/CT, CT or MRI of the abdomen. None of the patients with metastatic disease had a normal abdominal ultrasound, although 40% of patients with CT-confirmed metastatic disease had normal LFTs. This is in concordance with a large body of literature questioning the value of LFTs in uveal melanoma staging and surveillance (see below and Chapter 6).

4.3.2.2. Staging investigations

If staging is performed, there is still debate regarding the optimum staging investigation to select and to date no prospective trials have compared different staging systems. Unlike cutaneous melanoma, the liver is almost
always the first site where metastases are seen (Finger, Kurli et al. 2005). Therefore, imaging should be targeted towards the liver.

**Liver Function tests**

Liver function tests are widely performed in staging of uveal melanoma. However, all authors accept the low sensitivity of this blood test. In the COMS trial, an abnormal LFT was reported if it was at least twice the upper limit of normal. This prompted liver imaging or a biopsy to confirm metastatic disease. The sensitivity and specificity of at least one abnormal liver enzyme in predicting metastatic disease were 15% and 92% respectively (Diener-West, Reynolds et al. 2004). Alkaline phosphase was suggested to be the enzyme with the highest diagnostic accuracy; however the combination of abnormal alkaline phosphase (ALP) and Gamma-glutamyltransferase (GGT) raised the likelihood of detecting metastatic disease (Hicks, Foss et al. 1998). These same authors however reported that LFTs had a positive predictive power of <50%, and therefore found them of little value.

Kaiserman et al recorded serial LFTs in 30 uveal melanoma patients who subsequently developed metastases and compared this group with 80 uveal melanoma patients without metastatic disease (Kaiserman, Amer et al. 2004). They found that liver enzymes rose 6 months prior to the detection of metastatic disease but 50% still remained within normal limits. These authors recommended staging/screening with combined liver imaging and sequential LFTs.

**Abdominal Ultrasound**

Eskelin et al recommended abdominal ultrasound combined with LFTs with a semi-annual screening detecting >95% of metastasis while they are still asymptomatic. They reported that abdominal USS revealed unequivocal hepatic metastases in 36 of 46 patients (78%) with metastatic disease, of whom 12 (33%) had normal LFTs. Ultrasound was suggestive of metastases in 5 additional patients (11%), all of whom were confirmed to have hepatic metastases by fine-needle aspiration biopsy, CT, or both. Liver USS was negative (false negative) in only 2 patients (4%), both of whom had liver metastases and at least 1 abnormal LFT. Ultrasound is the preferred imaging modality in many centres due to its lower cost and ease of accessibility (Eskelin, Pyrhonen et al. 1999). If an abnormality is detected in the liver on USS, further qualification is performed with either CT or MRI. Hicks et al found the specificity of 100% and positive predictive power of greater than 50% of abdominal ultrasound in detecting metastatic disease. (Hicks, Foss et al. 1998).

**Abdominal CT scan**

Feinstein and associates reviewed the records of 91 patients who underwent CT scanning within 1 month of uveal melanoma diagnosis. CT scan detected a large variety of benign hepatic lesions such as cysts and fatty liver: 90% of hepatic lesions could be classified. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of a CT scan in detecting metastatic disease were 100%, 91%, 27%, and 100% respectively. The low PPV was attributable to a variety of benign hepatic lesions detected with CT. Patients with multiple lesions on abdominal CT scanning were significantly more likely to have metastatic disease (Feinstein, Marr et al. 2010).

**Abdominal MRI with or without contrast**
There has been no published assessment of the value of an MRI of the liver for staging of patients presenting with a primary uveal melanoma. In the follow up of patients with a ‘high risk’ of metastatic disease, MRI has proved to be an accurate method for staging (Marshall, Romaniuk et al. 2013).

**Fludeoxyglucose (FDG)-PET/CT**

The value of FDG-PET in detecting metastatic disease in uveal melanoma remains uncertain. In a study of 27 patients 6/13 patients with liver metastases from UM were PET avid, whilst 7/13 were not (Strobel, Bode et al. 2009). In an earlier study 2/52 patients presenting with primary choroidal melanoma had FDG avid metastases at diagnosis (Finger, Kurli et al. 2005). False positives were seen in 3/52 (3.8%) patients when further evaluated by histopathology and/or additional imaging; 7 patients (13.4%) had PET detected inflammatory or benign lesions elsewhere. No comparison was made in this study with other imaging techniques, specifically high resolution CT, MRI or USS. Further studies comparing PET/CT to other imaging modalities would be useful to evaluate the detection rate and specificity of FDG-PET in the staging of uveal melanoma.

**Chest radiography**

The sensitivity and specificity of chest radiography (CXR) in a series of 235 choroidal melanoma patients undergoing preoperative testing were reported to be 1.8% and 100% respectively (Hicks et al). In the COMS, restricting the analysis to chest x-rays (CXR) obtained within the 90-day period before diagnosis of metastasis, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 35%, 98%, 65%, and 93%.

The COMS and other studies have recommended pre-operative CXR to rule out a primary lung tumour, but no routine follow-up CXR. (Hicks et al, 1998) However, since the PPV of the test prior to local treatment is even lower than when used for follow-up, the usefulness of this test at diagnosis or follow-up is questionable.

4.3.2.3. Does detection of metastatic disease at diagnosis influence management of the eye?

No evidence was found to address this question.

4.3.3. Question 3. What is the optimal primary treatment?

4.3.3.1. Enucleation

Prior to the advent of radiotherapy, the traditional treatment of choroidal melanoma was enucleation of the affected eye as soon as the diagnosis was established with reasonable clinical certainty. The number of patients needing enucleation has diminished with the availability of alternative globe-sparing treatment options. In spite of this, enucleation is required in up to one-third of patients due to the tumour being too large for treatment by other means, the potential complications of treatment being too great, or patient choice. Enucleation entails the complete removal of the eyeball, thus avoiding any disturbance of the intraocular tumour. In the event that there is extraocular spread, complete tumour excision should be attempted where possible. If this is not achievable during surgery, adjuvant orbital radiotherapy is required. Up to 50% of uveal melanoma patients develop metastatic disease because the tumour has disseminated at an early stage before detection and treatment of the ocular tumour (Kujala, Makitie et al. 2003). Zimmerman et al (Zimmerman, Mclean et al. 1978) previously suggested that enucleation surgery was associated with acceleration of metastatic death. This hypothesis was not supported by the COMS report 24 (Hawkins 2004), which indicated that pre-enucleation radiotherapy did not show an advantage. Gambrelle et al (Gambrelle,
Grange et al. 2007) found the 5-year melanoma-specific survival rate was around 32% after primary enucleation (Isager, Ehlers et al. 2004).

After enucleation, there is an obviously reduced visual field to the side of the artificial eye along with loss of depth perception. Many of the skills of depth perception are relearned with time and most patients continue with their same jobs and activities without difficulty. Steeves et al (Steeves, Gonzalez et al. 2008) suggest that one-eyed individuals maintain perfectly normal lives and are not limited by their lack of binocularity. Quality of life studies have shown that following enucleation, patients have lower levels of anxiety compared to patients treated with radiotherapy (Melia, Moy et al. 2006).

4.3.3.2. Brachytherapy
In most centres, brachytherapy is the first choice of treatment. The procedure involves suturing of a radioactive plaque to the episclera (usually under general anaesthesia or deep sedation) and a second operation, following a specific period of time during which the prescribed dose is delivered, to remove the plaque. Treatment is completed once the plaque is removed. It may take up to 6 months before regression can be recorded. In Europe, ruthenium-106 is the most popular isotope whereas in the USA iodine-125 is generally preferred. Currently ruthenium-106 is the only radioisotope prescribed for the treatment of uveal melanoma in the UK, and therefore these guidelines will consider, first, the published evidence for ruthenium-106 plaque brachytherapy.

Ruthenium

Ruthenium plaque brachytherapy can be used to treat small to medium sized melanoma, with excellent 5-year local control rates of 95.6%, 93.6% and 98% being reported (Verschueren, Creutzberg et al. 2010, Marconi, de Castro et al. 2013). However, no 10-year local control rates were reported in these studies. A meta-analysis of 1066 patients with uveal melanoma treated by ruthenium plaque brachytherapy recorded the 5-year mortality for small/medium T1/T2 tumours (small tumours: height 1-3 mm, diameter more than 5mm; medium tumours: height 2.5-10.0mm and diameter <=16 mm; T1, T2 and T3 reflect particular subcategories of the 6th edition of AJCC TNM Staging system used at the time) as 6%, and for large T3 tumours (height >=10 mm or diameter >=16 mm) as 26% (Seregard 1999). For the population as a whole, the 5- and 10-year mortalities were 14% and 22% respectively (Seregard 1999). This reflects the tumour selection criteria for ruthenium plaque brachytherapy, as many ocular oncologists do not select this treatment for larger tumours. Ruthenium plaque brachytherapy is used for thick posterior uveal melanomas only in some centres where alternative modalities such as I-125 or teletherapy such as proton beam or stereotactic radiosurgery are not available to treat thick tumours. In one small, non-randomised study, thick posterior uveal melanomas (thickness>=8mm) were treated with enucleation or ruthenium plaque brachytherapy (Kaiserman, Kaiserman et al. 2009). Despite a low 71% control rate in the ruthenium plaque group and the thicker tumours being in the enucleation group (p=0.001), melanoma-related mortality rates were the same in both groups (at 5 years 20.5% and 28.1% p=0.6 and at 10 years 46.2% and 44.0% p=0.9). The authors concluded that ruthenium plaque brachytherapy is a safe alternative treatment that does not compromise survival (Kaiserman, Kaiserman et al. 2009). Local tumour control is compromised when ruthenium plaque brachytherapy is applied to thicker tumours, with control rates of 71%, 82% and 86% in three studies (Bergman, Nilsson et al. 2005, Kaiserman, Kaiserman et al. 2009, Ritchie, Gregory et al. 2012). Lack of response to ruthenium plaque brachytherapy was associated with uveal melanomas >5mm in height (Papageorgiou, Cohen et al. 2011). The selection criteria for ruthenium plaque brachytherapy vary between European centres but there is general consensus that ruthenium plaque brachytherapy should be
restricted to uveal melanoma below 7-8mm in height (Bergman, Nilsson et al. 2005, Isager, Ehlers et al. 2006, Ritchie, Gregory et al. 2012). Other risk factors for local recurrence/poor tumour control are large basal diameter, anterior location, young patient age and foveal location (Isager, Ehlers et al. 2006, Papageorgiou, Cohen et al. 2011). Transpupillary thermotherapy TTT can be combined with primary ruthenium plaque therapy to improve tumour control and globe preservation rates (see section on TTT) (Yarovoy, Magaramov et al. 2012).

Visual complications from ruthenium plaque brachytherapy are less severe than those recorded from the collateral damage of iodine plaque brachytherapy or proton beam radiotherapy (PBR). Patients are warned about the risk of postoperative diplopia but the risk is very low. The incidence of ocular motility disorders following ruthenium plaque brachytherapy in a cohort of uveal melanoma cases treated in London was rare at 1.7% over 8 years (Dawson, Sagoo et al. 2007). The incidence of radiation cataract is low at 16% (Marconi, de Castro et al. 2013). The incidence of NVG is only 3% and related to the TNM stage (6th edition of TNM staging of AJCC) of the tumour, i.e., it increased after treatment of larger tumours (Summanen, Immonen et al. 1996, Marconi, de Castro et al. 2013). In the long term, radiation damage to the optic disc and macular can destroy central vision. Predictive factors for visual deterioration from radiation maculopathy include: a) proximity of the posterior tumour border to the fovea; b) poor presenting visual acuity; and c) age <40 years (Summanen, Immonen et al. 1996, Rouberol, Roy et al. 2004, Bergman, Nilsson et al. 2005). Predictive factors for loss of light perception were proximity to the optic disc and increasing size of the tumour (Summanen, Immonen et al. 1995). Visual deterioration, cataract and vitreous haemorrhage is associated with increasing tumour height, as these tumours require a higher dose of radiation to achieve tumour control (Summanen, Immonen et al. 1995, Summanen, Immonen et al. 1996). The plaque can be positioned eccentrically with its posterior edge aligned with the posterior tumour margin to reduce the radiation dose to the optic disc and fovea (Russo, Laguardia et al. 2012) Tumour control was not compromised using this technique even at 4 years follow up. However, in general, good visual results are seen following ruthenium plaque brachytherapy, especially for anterior tumours. Damato and his group (Damato, Kacperek et al. 2005) reported visual conservation of 20/40 or better in 55% at 9 years; loss of vision correlated with: posterior tumour extension (p < 0.001), temporal tumour location (p = 0.001), increased tumour height (p = 0.01), and older age (p < 0.01).

After plaque brachytherapy for uveal melanoma, ophthalmological follow up entails regular ocular examinations and investigations for radiotherapy complications, which typically manifest 2-5 years after primary treatment. Tumour regression is recorded with serial ocular ultrasound and dilated fundus examination with visits to the respective Ocular Oncology service, especially in the first and second year after completing primary treatment. Tumour regression rates are variable (Shields, Shields et al. 1998). Kivela and associates were unable to correlate time to 25% or 50% reduction in tumour size following ruthenium plaque brachytherapy with time to metastatic disease (Rashid and Kivela 2012). Therefore, it appears that tumour response to brachytherapy cannot be relied upon with certainty as a prognostic indicator.

**Iodine-125**

I-125 episcleral plaque therapy is an effective, low morbidity treatment for medium and small sized but rapidly growing choroidal melanomas (Vullaganti, DeVilliers et al. 2011) (Badiyan, Rao et al. 2012) It circumvents an intraocular procedure and provides a margin of safety in the treatment of clinically undetectable disease). It is a safe and effective alternative to enucleation with regard to survival and local tumour control (Badiyan, Rao et al. 2012) and provides a fair chance of preserving the eye with acceptable cosmesis and a reasonable chance of
conserving useful vision for 1 to 2 years in these patients with large choroidal melanomas. (Puusaari, Heikkonen et al. 2003, Krohn, Monge et al. 2008).

The use of brachytherapy to treat choroidal melanoma is heavily influenced by evidence from COMS. There were three main trial arms:

1. The COMS “Small” study: No RCT exists for small uveal melanoma, the publications from this group for small uveal melanoma were from observations only. 204 patients with small choroidal melanomas (height 1-3 mm, diameter more than 5mm) were prospectively observed. This study showed that with prospective follow-up, overall survival was comparable to the general population (COMS report No 4 and 5) (Hawkins and Melia 1997, Melia, Diener et al. 1997).

2. The COMS “Medium” randomized trial: 1317 patients with medium tumours (height 2.5-10.0mm and diameter <=16 mm) were randomized to either treatment with l-125 plaque brachytherapy (85 Gy) or enucleation. The overall survival and risk of death from metastatic disease were comparable between the two groups, thus establishing plaque brachytherapy as a reasonable primary treatment for choroidal melanomas. At 5, 10 and 12 years, the mortality rates for patients treated with brachytherapy were 10%, 18% and 21% and for patients treated with enucleation, they were 11%, 17% and 17% respectively (COMS report 16,17,18, 28) (Diener-West, Earle et al. 2001, Hawkins, Vine et al. 2001, Hawkins 2001, Melia, Abramson et al. 2001, Hawkins 2006).

3. The COMS “Large” randomized trial: 1003 patients with large tumours (height >=10 mm or diameter >=16 mm) were randomized to pre-enucleation external beam radiation therapy (EBRT) 20/5 or enucleation only without EBRT. This study showed that pre-enucleation radiotherapy does not provide any additional benefit (COMS report 9, 10, 11, 15, 24) (Schachat 1998, Willson, Albert et al. 2001, Hawkins 2004).

**Treatment dose and parameters:**

The American Brachytherapy Society recommends a minimum tumour l-125 dose of 85 Gy at a dose rate of 0.60-1.05 Gy/h. It has been shown that treatment of choroidal melanomas less than 5mm in apical height with l-125 brachytherapy to the true apical height is equally effective when compared to treatment with 85Gy to 5.0mm (as performed in the COMS trial) and has a lower incidence of radiation-related complications (Vullaganti, DeVilliers et al. 2011, Murray, Markoe et al. 2013).

**Local control:**

l-125 brachytherapy is effective in tumour control in 92-97%, allowing preservation of the eye and useful visual function for the majority of patients. (Jensen, Petersen et al. 2005, Garcia-Alvarez, Saornil et al. 2012). It allows for safe and effective therapy in patients with ocular melanoma of various sizes depending on location (Fontanesi, Meyer et al. 1993).

**Anterior location:** The use of 125I plaque brachytherapy to treat melanomas situated anterior to the equator allows good local and systemic control with a low rate of macular and optic disc complications. The most frequent complication is cataract formation. (Lumbroso, Charif et al. 2004). Shields et al. have shown that better visual outcomes are seen after plaque radiotherapy for choroidal melanoma in younger patients with small tumours at sites remote from the optic disc and foveola (Shields, Shields et al. 2000).
**Juxtapapillary location:** Sagoo et al demonstrated that juxtapapillary choroidal melanoma can be treated with brachytherapy with 80% tumour control at 10 years and adjuvant TTT did not add to the success rate (Sagoo, Shields et al. 2011). Slotted or notched plaques can be used for tumours within 1.5 mm, touching or surrounding the optic disc. Krema et al showed that both I-125 brachytherapy and stereotactic radiotherapy demonstrate comparable efficacy in the management of juxtapapillary choroidal melanoma. Stereotactic radiotherapy (see section 4.6.3) showed statistically significantly higher radiation-induced ocular morbidities at 4 years post-radiotherapy but I-125 had higher recurrence rate (11% compared to 7%) (Krema, Heydarian et al. 2013), (Krema, Heydarian et al. 2013).

**Melanomas with extraocular extension:** Small and medium-sized ciliary body and choroidal melanoma with clinically visible extraocular extension less than 3 mm in thickness can, in selected cases, be treated successfully with plaque radiotherapy (Gunduz, Shields et al. 2000).

**Melanomas with thickness between 5-7 mm:** The management of choroidal melanoma with a thickness of 5-7 mm is controversial. Iodine seems to provide higher local tumour control, while ruthenium induces less radiation complications. I-125 may represent a better option in this subgroup of tumours, especially for preventing metastatic disease (Tagliaferri, Smaniotto et al. 2012).

**Treatment failure:**

There is a low risk of local treatment failure or secondary enucleation after definitive I-125 brachytherapy for choroidal melanoma. Jampol et al have shown the risk factors for local recurrence include older age at time of treatment, greater apical height, and proximity to the foveal avascular zone (Jampol, Moy et al. 2002). Char et al have also shown that late recurrence is possible five or more years later in patients treated with radioactive plaque (Char, Kroll et al. 2002) Risk factors for enucleation following I-125 plaque radiotherapy in these studies included: male gender; greater apical height of the tumour; longer basal dimension; poorer visual acuity in the tumour-containing eye at baseline; collar-button tumour shape; presence of retinal detachment over the tumour; lower radiation dose to the tumour apex; and higher dose to the sclera. In patients with large posterior uveal melanomas (> or =8-mm thick) the rate of enucleation was 24% at 5 years and 34% at 10 years (Shields, Naseripour et al. 2002).

**Visual loss after I-125 brachytherapy:**

The COMS report number 16 showed that the visual acuity during the first 3 years after I-125 plaque radiotherapy for choroidal melanoma declined on average at a rate of approximately two lines per year (Melia, Abramson et al. 2001): 49% of patients had substantial loss of visual acuity at 3 years. High risk characteristics for visual loss were: tumour height >5.0 mm; distance between tumour and foveal avascular zone <2.0 mm; diabetes; non–dome-shaped tumour; and presence of tumour-associated retinal detachment. In patients with large posterior uveal melanomas (> or =8-mm thick), Shields et al. have shown the most important risk factors for poor visual acuity include retinal invasion by melanoma, increasing patient age, use of I- 125 isotope, and <2 mm distance to the optic disc (Shields, Shields et al. 2000).

A study from New Zealand showed that a high percentage of patients retaining mobility vision following I-125 brachytherapy (>6/12 in 35% patients and >6/60 in 51% patients) (Stack, Elder et al. 2005).

**Radiation retinopathy, neuropathy and cataract:**
Radiation retinopathy and cataract formation are common toxicities 3 years following I-125 plaque brachytherapy for medium-sized choroidal melanomas (COMS criteria)(Badiyan, Rao et al. 2013). Three-year rates of radiation retinopathy, radiation papillopathy, and exudative retinal detachment were 45%, 14%, and 10%, respectively. The 3-year rates of cystoid macular oedema, vitreous haemorrhage, and enucleation due to radiation toxicity were 17%, 12%, and 4% respectively. The risks of anterior segment complications were much higher in patients treated for large melanomas (COMS criteria). In these patients the 5-year rates of cataract formation, neovascularization of the iris and NVG were 69%, 62% and 60%, respectively (Puusaari, Heikkonen et al. 2004).

Development of complications was related to the tumour location and dose to non-tumour structures. A dose of more than 90 Gy to the macula gave a 63% chance of developing maculopathy (P < 0.01). A tumour larger than 4 mm significantly increased the risk of developing radiation maculopathy. Development of radiation cataract was also dose-related; >25 Gy to the lens gave a 44% risk of cataract development (P < 0.001). For tumours less than 4 mm from the disc margin there was a 50% risk of optic neuropathy (Stack, Elder et al. 2005).

Bianciotto et al showed that proliferative radiation retinopathy developed in 7% of eyes by 10 years after I-125 plaque radiotherapy for uveal melanoma. The main factors for development of proliferative radiation retinopathy included young age, pre-existent diabetes mellitus and shorter tumour distance to the optic disc (Bianciotto, Shields et al. 2010). The use of bevacizumab has reduced the need for enucleation due to I-125 radiation toxicity (Badiyan, Rao et al. 2013). Treatment modalities for radiation retinopathy include intravitreal injections of triamcinolone and bevacizumab, laser photocoagulation, hyperbaric oxygen treatment, photodynamic therapy and oral pentoxyphylline.

Metastasis risk:

The risk of metastasis was found to be 10% at 5 years and 27% at 10 years in a study of patients treated with I-125 (1163) In patients treated for large posterior melanomas (> or =8-mm thick), the tumour-related metastases rate was 30% at 5 years and 55% at 10 years (Shields, Naseripour et al. 2002).

Other factors influencing choice of brachytherapy:

The COMS report number 3 looked at quality of life after I-125 brachytherapy or enucleation for choroidal melanoma. Patients treated with brachytherapy reported significantly better visual function than patients treated with enucleation with respect to driving and peripheral vision for up to 2 years following treatment. This difference diminished by 3 to 5 years post-treatment, paralleling the decline in visual acuity in brachytherapy-treated eyes. Patients treated with brachytherapy were more likely to have symptoms of anxiety during follow-up than patients treated with enucleation. Given that no significant differences in survival between enucleation and brachytherapy have been found, the differences demonstrated here for driving and anxiety will allow the individual patient and physician to make informed choices regarding treatment based on personal preferences (Melia, Moy et al. 2006).

Compared to ruthenium plaque treatment, the cost price of iodine treatment is much higher owing to the requirement for frequent replacement of the iodine grains due to a short half-life of 60 days in comparison with the 374 day half-life of ruthenium (Ru-106). The deeper penetration of the γ rays of I-125 (compared to β-rays of Ru-106) allows treatment of larger and thicker tumours (up to 10mm height by I-126 compared to up to 5-7mm height by Ru-106), but at the cost of causing more radiation damage to healthy surrounding tissues, hence
optic neuropathy, maculopathy, and visual loss. Successful use of other isotopes, such as palladium, has been demonstrated by Finger et al, and others (Shields, Cater et al. 2002, Finger, Chin et al. 2009).

4.3.3.3. Stereotactic radiosurgery
Stereotactic radiosurgery (SRS) usually consists of a single-session delivery of ionizing radiation to a stereotactically localized volume of tissue. Certain centres use fractionated SRS for uveal melanoma (Muller, Naus et al. 2012).

The patient receives standard retrobulbar anaesthesia to prevent globe movement during SRS. Based on the MRI, the target volume for each patient’s tumour is identified stereotactically and the radiation parameters are calculated. A stereotactic frame is attached to the skull for the treatment and the entire treatment is completed in a matter of hours. Advantages of this procedure are that it is minimally invasive (needing only local anaesthesia); it is particularly useful in patients unfit for general anaesthesia as it does not involve any surgery; and is performed as an outpatient.

SRS is particularly useful in juxtapapillary choroidal melanomas (Zorlu, Selek et al. 2009, Al-Wassia, Dal Pra et al. 2011) and those tumours not suitable for ruthenium plaque therapy. Dunavoelgyi et al (Dunavoelgyi, Dieckmann et al. 2011) have demonstrated an excellent local tumour control rate of 95.9% after 5 years and 92.6% after 10 years in patients with uveal melanoma treated with SRS.

In the UK, SRS has been used for the treatment of ocular melanomas since the 1990s at the Sheffield Ocular Oncology Centre. In 1996, Rennie et al. published their initial experience in the use of SRS (Rennie, Forster et al. 1996). The initial use of a high isodose at 70Gy was found to be effective but associated with a high incidence of radiation related adverse reactions. Reducing the isodose from 70 Gy to 35 Gy led to a dramatic decrease in complications, vision loss and salvage enucleation, whilst not compromising patient survival. Cohen et al (Cohen, Carter et al. 2003) have shown that the metastasis-free survival after SRS was comparable to that after enucleation in patients treated at Sheffield (74% in the stereotactic treatment group versus 51% in the enucleation treatment group at 5-years, with no significant difference after multi-variant analysis). A retrospective analysis comparing the outcomes of patients from Sheffield treated with SRS versus proton beam is currently under way.

In centrally-located choroidal melanomas, Dunavoelgyi et al demonstrated that hypo-fractionated SRS showed a low to moderate rate of adverse long-term side effects comparable to those after PBR. Future fractionation regimens should seek to further reduce adverse side effects rate while maintaining excellent local tumour control. Suesskind et al (Suesskind, Scheiderbauer et al. 2013) found that SRS combined with tumour resection might be associated with increased tumour control and fewer radiation complications than SRS alone as monotherapy. However, the protocol was stopped after 3 unexplainable deaths following tumour resection surgery.

Modorati et al (Modorati, Miserocchi et al. 2009), in a 12-year study from Italy have demonstrated a survival rate with SRS of 81.9% at 5 years. The median tumour thickness reduction after treatment was 1.96 mm (-32.1%). The most frequent treatment-related complications were: exudative retinopathy (33.3%), NVG (18.7%), radiogenic retinopathy (13.5%) and vitreous haemorrhages (10.4%). A reduction of visual acuity was observed but the eye was retained in 90% patients, and the authors concluded SRS should be considered as an alternative to enucleation surgery. Chabert et al (Chabert, Velikay-Parel et al. 2004) demonstrated no difference in quality of life scores between plaque brachytherapy and SRS for the treatment of uveal melanoma.
4.3.3.4. Proton beam radiotherapy

PBR offers a more targeted delivery of radiation compared to conventional external beam radiotherapy. This precision is achieved by the highly collimated beams with their destructive ionising radiation peaking at the depth where the charged particles stop travelling (the Bragg peak), hence it targets the discrete area with limited damage to surrounding tissues. The treatment dose prescribed is fractionated, typically four sessions are required and treatment is completed in one week. Treatment planning (simulation) is an important aspect of proton beam radiotherapy that must be performed several weeks ahead. Tantalum markers are sutured to the eye and intraoperative measurements are taken so that the tumour position and shape can be recorded. An ocular X-ray reveals the location of the tantalum markers. Detailed ultrasound measurements of tumour height are required for accurate modification of the proton beam. PBR is custom-designed for each individual patient with uveal melanoma.

Protons achieve high rates of local tumour control in patients considered unsuitable for other forms of conservative treatment. Multiple studies are consistent in demonstrating this high rate of local control of PBR: between 87% and 96% at 5 years (Damato, Kacperek et al. 2005, Dendale, Lumbroso-Le Rouic et al. 2006, Aziz, Taylor et al. 2009, Caujolle, Mammar et al. 2010), and between 92.1%-96.8% at 10 years (Mosci, Polizzi et al. 2001, Damato, Kacperek et al. 2005, Caujolle, Mammar et al. 2010). There is only one publication to date comparing local tumour control following PBR, ruthenium and iodine plaque brachytherapy. Wilson et al reported that patients treated with ruthenium plaque brachytherapy had significantly greater risk of local tumour recurrence than did those patients treated with either 125-Iodine plaque brachytherapy (P = 0.0133; confidence interval [CI], 1.26-7.02; risk ratio, 2.97) or proton beam radiotherapy (P = 0.0097; CI, 1.30-6.66; risk ratio, 2.94) (Wilson and Hungerford 1999). There was no significant difference in tumour control between PBR and 125- Iodine plaque brachytherapy. Risk factors for failure of local tumour control following PBR were identified as a reduction of the safety margin, large tumours infiltrating the ciliary body, the presence of an eyelid within the irradiation field, inadequate delimitation of the tumour border by tantalum clips, and male gender (Egger, Schalenbourg et al. 2001).

Metastasis-free survival after PBR was 88.3% at 5 years and 76.4% at 10 years (Caujolle, Mammar et al. 2010), (Damato, Kacperek et al. 2005). Similarly, Dendale et al (Dendale, Lumbroso-Le Rouic et al. 2006) showed 5-year overall survival and metastasis-free survival rates were 79% and 80.6% respectively. When considering patients with large choroidal melanoma, there was no significant difference between enucleation or PBR for cumulative all-cause mortality, melanoma-related mortality and metastasis-free survival (log-rank test, p = 0.56, p = 0.99 and p = 0.25, respectively) (Mosci, Lanza et al. 2012).

Another survival study on the relative rates of metastatic death, cancer death, and all-cause mortality between enucleation and PBR revealed a statistically significant survival benefit in the PBR group in the first two years of treatment. However, by the sixth year the survival benefit was not maintained. Results suggest that treatment choice has little overall influence on survival in patients with uveal melanoma (Seddon, Gragoudas et al. 1990).

4.3.3.5. Complications of Proton Beam Radiotherapy (PBR)

One early main complication after PBR is intraocular inflammation. Lumbroso et al (Lumbroso, Desjardins et al. 2001) found 28% of patients developed ocular inflammation. Inflammation following PBR is not unusual, but is usually limited to mild anterior uveitis, which rapidly resolves with topical steroids and cycloplegics. It is correlated with larger initial tumours (tumour height and irradiation of a large volume of the eye) and may be related to an exudative retinal detachment and tumour necrosis, both of which in turn are thought to lead to an
associated release of cytokines and neovascular glaucoma (NVG) (termed, ‘toxic tumour syndrome’). The good local control results are tempered somewhat by the appreciable ocular morbidity, which may necessitate removal of the eye (secondary enucleation) usually as a result of NVG. Secondary enucleation rates following PBR correlate strongly with tumour size (Foss, Whelehan et al. 1997, Damato, Kacperek et al. 2005). The overall eye retention rate in 2648 uveal melanoma patients (tumour diameter 4mm-27.5 mm and tumour height 0.9-15.6 mm) treated with proton beam radiotherapy was 88.9% at 5 years, 86.2% at 10 years and 83.7% at 15 years (Egger, Zografos et al. 2003). After optimization of the technique, retention rates at 5 years increased from 97.1% to 100% for small tumours, from 86.7% to 99.7% for medium, and from 71.1% to 89.5% for large tumours (Egger, Zografos et al. 2003). Similar rates from Scotland were reported for ciliary body and choroidal melanomas, where proton beam treatment is mainly used in the treatment of medium and large uveal melanomas. Of the 147 patients identified, 22.4% required enucleation (Macdonald, Cauchi et al. 2011). Mean time to enucleation was 23.8 months and the main reasons were suspected recurrence (48%) and NVG (42%). The actuarial 5-year eye retention rate was 71.3% (Macdonald, Cauchi et al. 2011). In a larger study of 1406 patients with uveal melanoma treated by proton beam radiotherapy, the 5-year enucleation rate for complications was 7.7%, the main indication being NVG. Independent prognostic factors for enucleation for complications of PBR were tumour thickness (p < 0.0001) and lens volume receiving at least 30 Cobalt Gray Equivalent (CGE) (p = 0.0002) (Dendale, Lumbroso-Le Rouic et al. 2006). Foss et al demonstrated that the presence of retinal detachment and large tumour dimensions, i.e., those tumours too large to be treated by ruthenium plaque, are important risk factors in predicting NVG (Foss, Whelehan et al. 1997). If both are present the risk of NVG at 4 years is 88%, if one is present the risk is 37% and, if neither are present, there was no risk of developing NVG.

An alternate to enucleation in the event of ‘toxic tumour syndrome’ development following PBR secondary include local resection and endoresection (Cassoux, Cayette et al. 2013); (Konstantinidis, Groenewald et al. 2014); (McCannel 2013). These procedures have been introduced recently by a few ocular oncology centres with good effect.

Prognosis for vision is less positive: 18.5% of patients had vision less than 3/60 pre-treatment, compared to 74% post-irradiation (p < 0.0001) (Aziz, Taylor et al. 2009). Preservation of acuity is influenced by the stage of the tumour. Results from Genoa show that visual acuity better than 2/10 was 30% in T1 and T2 tumours, and 21% in T3 tumours (Mosci, Polizzi et al. 2001). An early report on 538 patients treated with high energy proton beam showed one-third of patients with adequately scored visual acuity pre- and post-treatment had stable, if not improved vision, and half the patients retained useful vision post-treatment, despite two-thirds having posterior pole tumours (Courdi, Caujolle et al. 1999, Mosci, Polizzi et al. 2001). In Liverpool, of 349 patients with choroidal melanoma treated with PBR, 79.1% had post-treatment vision of counting fingers or better, 61.1% had vision of 20/200 or better and 44.8% achieved 20/40 or better. Visual loss can be unpredictable due to toxic tumour syndrome (Damato, Kacperek et al. 2005). Progressive visual field deficits have also been reported following PBR for parapapillary choroidal melanoma, and not unexpectedly, the scotoma usually correlates with the area of the retina exposed to irradiation (Park, Walsh et al. 1996).

A systematic review and meta-analysis of PBR concluded that a strong recommendation favouring PBR above enucleation or plaque brachytherapy could not be made from the currently published evidence (Wang, Nabhan et al. 2013). The overall quality of the evidence was low (Wang, Nabhan et al. 2013). Other important factors need to be considered for comparative effectiveness decisions. Patients’ opinions and preferences should
heavily influence the decision, including their feelings about enucleation, their willingness to try a therapy without extensive prospective outcome data (PBR), their willingness to travel to tertiary care centres, and in some cases their financial and other resources. In Europe, the availability of PBR is currently limited to a few tertiary care centres.

4.3.3.6. Transpupillary thermotherapy
Transpupillary thermotherapy (TTT) is another method of treating uveal melanoma. The heat from a laser induces ischaemia, free radical damage and tumour necrosis. The treatment is delivered in the clinic using a modified infrared diode laser at 810 nm with an adjustable beam width of 1.2 mm, 2.0 mm and 3.0 mm. The infrared delivery system is adapted to a slit-lamp biomicroscope and delivered through a contact lens. The end point of treatment is a colour change in the tumour, and this is best seen at the first treatment of a pigmented uveal melanoma. Intravenous indocyanine green can be given just before TTT to increase the laser energy uptake by amelanotic uveal melanoma (Sagoo, Shields et al. 2011). Intravenous indocyanine green administration before TTT does not alter the tumour regression pattern (De Potter and Jamart 2003). Several treatment sessions are required to achieve total tumour destruction (Kociecki, Pecold et al. 2002).

TTT has been used as primary treatment for small uveal melanoma with some success. Shields et al reported 4% recurrence at 1 year, 12% at 2 years, and 22% at 3 years (Shields, Shields et al. 2002). Of serious concern is that there have been accounts of extraocular extension following primary TTT (Shields, Shields et al. 2002). It is vital therefore that tumours are carefully selected for this primary treatment. The following maximum cut off values for selecting tumours for primary TTT have been recommended: tumour height not greater than 3.0 mm, basal diameter not greater than 10 mm and maximum systolic velocity of the tumour on Doppler ultrasound not greater than 11.7 cm/s (Yarovoy, Magaramov et al. 2010). Other risk factors for local recurrence include amelanotic pigmentation, presence of subretinal fluid, tumours abutting or overhanging the optic disc, tumour requiring more than 3 sessions of TTT and incomplete regression following primary TTT (Shields, Shields et al. 2002, Parrozzani, Boccassini et al. 2009, Yarovoy, Magaramov et al. 2010).

Transpupillary thermotherapy can cause damaging effects to the retina, leading to visual loss shortly after treatment. Shields et al. reported visual outcomes in their first 100 cases (Sagoo, Shields et al. 2011). The visual acuity was worse in 42 eyes (42%). The main reason for poor vision was treatment of a subfoveal tumour with induction of a visual scotoma in the treated area (Kociecki, Pecold et al. 2002). Retinal traction was seen in 10% of cases. It was most frequently associated with treatment of uveal melanoma distal and temporal to the optic disc (Shields et al. 2011). Other visual threatening complications include macular pucker 11%, macular oedema 4%, vitreous haemorrhage 3%, vein occlusion 8%, exudative retinal detachment and NVG in 3% (Kociecki, Pecold et al. 2002, Parrozzani, Boccassini et al. 2009).

The concern about poor local control rates and extraocular recurrence with primary TTT led researchers to suspect that the depth of penetration of the diode laser was insufficient to treat the majority of uveal melanomas. Deeper tumour necrosis at the base of the uveal melanoma was more likely to be achieved with simultaneous plaque radiotherapy (Kociecki, Pecold et al. 2002). Hence in centres where TTT is used, it is used in conjunction with plaque brachytherapy, known as ‘sandwich’ therapy to improve local tumour control (Gragoudas, Li et al. 2002); (Shields, Cater et al. 2002). 5-year recurrence rates as low as 3% have been achieved using ‘sandwich’ therapy (Gragoudas, Li et al. 2002), (Shields, Cater et al. 2002). This combination treatment appears to provide better 5-year local tumour control (96% versus 83% p=<0.034), a better globe preservation (98% versus 87% p=<0.024) and recurrence free survival rate (89% versus 67% p=<0.017) than ruthenium plaque
brachytherapy alone in medium sized tumours (COMs criteria) (Yarovoy, Magaramov et al. 2012). There was no difference in overall patient survival/metastatic rate (Yarovoy, Magaramov et al. 2012). TTT is widely used to manage radiotherapy complications such as ‘toxic tumour syndrome’ (see above under 4.3.3.5) and local tumour recurrence (Yarovoy, Magaramov et al. 2012). When early plaque brachytherapy-related vision loss is accounted for, the addition of TTT did not result in significantly worse visual acuity (Drury, Chidgey et al. 2012). However at 1 and 4 years follow up, the visual outcome was worse in patients who had received ‘sandwich’ therapy compared to those who had received plaque brachytherapy alone (Drury, Chidgey et al. 2012). Adjuvant TTT did not improve the local tumour control of juxtapapillary uveal melanoma treated by iodine-125 plaque brachytherapy (Sagoo, Shields et al. 2011).

TTT has also been used in conjunction with PBR: in a randomized study of 151 patients, PBR was combined with TTT for the treatment of large uveal melanomas (Desjardins, Lumbroso-Le Rouic et al. 2006). Patients who received adjuvant TTT had a significantly lower risk of secondary enucleation (p=0.02) and had a more marked reduction in tumour thickness (p=0.06). No statistically significant difference was observed between the 2 groups in terms of cataracts, maculopathy, papillopathy and glaucoma.

4.3.3.7. Exoresection
Exoresection (also termed ‘local resection’ or ‘choroidectomy’) involves removal of the tumour ‘en bloc’ through a large sclera opening. Previously, full-thickness sclera excision was advocated but this has been replaced by methods using a lamellar sclera flap to close the eye. Exoresection of choroidal melanomas is a difficult procedure, demanding considerable surgical experience. Furthermore, it requires significant systemic hypotension to control haemorrhage. For these reasons, this operation is performed by only a very few surgeons around the world. Exoresection of small, ciliary body tumours (cyclectomy) is less difficult and is therefore undertaken more widely. Exoresection of iris melanomas (iridectomy) is in turn easier than either of the above procedures, but is increasingly being replaced by radiotherapy (e.g. PBR and ruthenium plaques; see below).

The largest exoresection series reported to date was published by Damato et al over 20 years ago (Damato, Paul et al. 1993). In 163 completed resections, the tumours had a mean diameter of 13.3 mm and a mean thickness of 7.4 mm, with 38 tumours extending to within 1 disc diameter (DD) of the optic disc, fovea or both. Cox multivariate analysis showed that the most significant preoperative factors for predicting retention of good vision (6/12 or better) were nasal tumour location (p = 0.002) and distance of more than 1 DD between the tumour and the optic disc or fovea (p = 0.010). The most significant predictive risk factor for severe visual loss (hand movements or worse) was posterior tumour extension to within 1 DD of the optic disc and/or fovea (p = 0.009). One year post-operatively, all 28 patients with medial tumours not extending to within 1 DD of the optic disc or fovea retained the eye with 57% having vision of 6/12 or better and 93% having vision of counting fingers or better. In 68 patients with lateral tumours, 90% retained the eye at 1 year with preservation of vision of counting fingers or better in 82% of 56 eyes without posterior tumours extension and in 50% of 12 eyes with posterior tumour extension (Damato et al 1993). There were 24 patients (14%) with residual tumour in this cohort. Forward stepwise logistic regression analysis indicated that posterior extension to within 1 DD of the optic disc or fovea was the sole best indicator of the risk of residual disease (p < 0.001). After excluding these cases, 286 patients were studied for the development of delayed local recurrence, which occurred in 57 cases. Forward stepwise multivariate analysis showed statistically significant predictors for recurrent tumour to be epithelioid cellularity (p = 0.002), posterior tumour extension to < 1 disc diameter of disc of fovea (p = 0.002), large tumour diameter > or = 16 mm (p = 0.019) and lack of adjunctive plaque radiotherapy (p = 0.018) (Damato,
Paul et al. 1996). Rhegmatogenous retinal detachment occurred in 28 (18%) eyes and was significantly more common in patients with thick tumours (Cox univariate analysis, P = 0.001) and in males (Cox univariate analysis, P = 0.013), with posterior tumour extension being of borderline significance (Cox univariate analysis, P = 0.069). Surgical treatment of the retinal detachment was performed in 25 patients. Anatomic success was achieved in 21 (84%) of these 25 patients, with 7 patients retaining counting fingers vision, and 3 seeing 6/60 or better. Ten eyes treated for retinal detachment were enucleated because of recurrent tumour (four eyes), retinal detachment (three eyes), wound dehiscence (one eye), phthisis (one eye), and poor visual acuity (one eye). Eleven eyes known to have a retinal tear underwent prophylactic vitreoretinal surgery at the end of the local resection, with only one (9%) of these subsequently developing retinal detachment (Damato, Groenewald et al. 2002).

Technical improvements have occurred more recently (Damato 2012, Damato 2012). Techniques have been developed for conserving the integrity of the ciliary epithelium over the pars plana and for ‘top-slicing’ tumour adherent to retina, dramatically reducing rates of retinal detachment (Damato 2012, Damato 2012). Rates of local tumour control have improved greatly, as a result of adjunctive brachytherapy with a 25 mm ruthenium plaque in all cases (Damato 1997). Such routine adjunctive brachytherapy has reduced the need for wide surgical margins. These measures have significantly improved ocular outcomes, particularly conservation of vision (Damato 1997). Outcomes of local resection of uveal melanoma depend greatly on the experience of the surgeon and on the anaesthetist’s ability to provide profound hypotensive anaesthesia.

Even with earlier resection techniques, various authors have shown that with large uveal melanomas, the results of local resection are superior to those achieved with radiotherapy (Shields, Cater et al. 2002, Shields, Naseripour et al. 2002, Puusaari, Damato et al. 2007, Bechrakis, Petousis et al. 2010).

4.3.3.8. 

Endoresection

With endoresection, the choroidal melanoma is removed piecemeal, using a vitreous cutter. This is done either through a retinotomy over the tumour or after raising a retinal flap. The technique is evolving, with advances such as bimanual surgery and the use of heavy liquids. Endolaser treatment is applied to destroy any residual tumour and to achieve retinopexy. The eye is filled with silicone, which is removed after twelve weeks. Adjunctive radiotherapy can be applied, either in all patients or if histology and genetic studies indicate that the tumour is aggressive. Some centres perform endoresection only after neo-adjuvant radiotherapy, because of concerns about iatrogenic tumour seeding (Bechrakis and Foerster 2006, Schilling, Bornfeld et al. 2006).

In a series of 52 endoresections by Damato, the tumours had a mean largest basal diameter of 8.2 mm and a mean tumour thickness of 3.9 mm (Damato, Groenewald et al. 1998). Forty tumours extended to within 2 disc diameters of the optic disc, with 17 involving the disc. Follow-up ranged from 40 days to 7 years (median 20 months). At the last visit, 90% of eyes were retained, with vision of 6/6-6/12 (two), 6/18-6/36 (three), 6/60 to counting fingers (18), hand movements (nine), and light perception (four). The main complications were retinal detachment in 16 and cataract in 25 patients. Secondary endoresection (n=11) was performed after plaque radiotherapy (four), photocoagulation (four), trans-scleral local resection (two), and PBR (one), with retention of the eye in nine cases. By the close of the study, no patients developed definite local tumour recurrence but one died of metastatic disease 41 months postoperatively. The Liverpool Ocular Oncology Centre experience in local resection of an additional 71 patients is reported in a recent publication (Konstantinidis, Groenewald et al. 2014).
The only other major series is that reported by Garcia et al in 2008 (Garcia-Arumi, Zapata et al. 2008). In a series of 38 patients, the authors reported outcomes after a follow-up time ranging from 23 to 129 months (mean 70.63 months). Preoperative visual acuity ranged from ‘hand-movements’ to 20/20 (mean, 20/60). In primary cases, mean tumour thickness was 10.1 mm and mean base diameter 9.9 mm. At the latest visit, 92.1% patients still retained the eye. Final visual acuity ranged from ‘no light perception’ to 20/30 (mean 20/300). Two patients experienced local recurrence before 3 years of follow-up. Metastatic disease was found in two patients at 5 years of follow-up. Kaplan-Meier survival analysis for all causes was 88.2% at 5 years. Specific survival was 90.9% at 5 years.

4.3.3.9. Treatment of Iris Melanoma
These tumours have the best survival outcomes, if the ciliary body is not involved the 10-year survival data is close to 100%. Nevertheless, treatment is still recommended as an enlarging iris tumour will produce ocular complications.

Resection of small iris tumours is a very successful treatment option especially if there is no ciliary body involvement. Iris sector defects can result in visual side effects such as photophobia, glare and halo formation around lights, which make night driving difficult. Pupilloplasty (i.e. reconstruction of the iris) can be performed to minimise this problem. PBR has been used but in this subgroup of patients the eye retention rates are worse than for ciliary body or choroidal melanoma. In a recent review of 15 cases, eye retention following PBR was 80% (Rundle, Singh et al. 2007). 53% of patients with iris melanomas following proton beam treatment had glaucoma, although this was a pre-existing condition in 33% of the original group of 15 patients (Rundle, Singh et al. 2007). Damato et al reported complication rates from a larger series of 88 patients with iris melanomas. Glaucoma was present before treatment in 13 patients and developed after treatment in another 3, and in several patients it was difficult to control (Damato, Kacperek et al. 2005). Post-irradiation cataract is a common although treatable complication following PBR of iris melanoma. Lumbroso et al found 45% of these patients developed cataract within 24 months of treatment (Lumbroso-Le Rouic, Delacroix et al. 2006). In another series of 78 iris melanomas treated by PBR, 51% developed cataract (8873). Both Damato et al (Damato, Kacperek et al. 2005) and Rundle et al (Rundle, Singh et al. 2007) found 20% of patients developed cataract following proton beam irradiation for iris melanomas, and the latter group also reported 27% of patients developed dry eye.

Ruthenium plaque brachytherapy resulted in 100% tumour control in a series of 15 pure iris melanomas from London with a long median follow-up of 96 months (Tsimpida, Hungerford et al. 2011). The eye retention rate was also 100%, as no cases of NVG were reported. Like PBR cataract was reported in 60% and dry eyes were seen in 20% of patients. Slightly higher rates of cataract formation have been recorded following Iodine plaque brachytherapy.

4.4. Evidence Statements

4.4.1. Pre-operative investigations
Uveal melanoma is a rare cancer and the combination of a multi-disciplinary skill set together with specialist expertise is required. Level 4 - Government advice

Delay in referral results in more advanced disease at presentation and an increased likelihood that the patient will require an enucleation. Level 3
The diagnosis of uveal melanoma made using ophthalmoscopy, fundus photography and conventional ocular ultrasound has an accuracy of 99% in medium sized to large melanomas. Level 1+

Conventional A and B scan ocular ultrasound is key to making the diagnosis. Level 3

Ocular Oncology Centres tend to have more experienced ocular ultrasonographers and better ultrasound equipment. Level 4

The evidence for investigation with more recently developed diagnostic tools, based on comparative case series, demonstrate that anterior segment OCT is useful for iris melanoma but is not superior to UBM when considering ciliary body tumours. Level 3

UBM with a 50MHz probe is the best tool to image the ciliary body. Level 3

If the diagnosis is still uncertain then biopsy has a role. Level 3

Small indeterminate lesions may not yield sufficient cells to make a diagnosis especially if less than 2mm in thickness. Level 2+

4.4.2. Staging before primary treatment

Tumour size at diagnosis is associated with incidence of metastasis and therefore can be used to aid stratification. Level 2+

Knowledge of the presence of metastatic disease only affects management of the primary tumour when considering enucleation of a painless asymptomatic eye. In this situation, it may be appropriate after careful counselling of the patient to postpone primary treatment or to not perform the operation, to avoid needless mutilation. Level 4

LFTs are highly specific but not sensitive in detecting metastatic disease. Level 2+

When evaluating biochemical markers of liver function combined GGT and ALP were the most helpful in predicting patients with metastatic disease. Level 3

A rising trend in liver enzyme levels over time is more important than the absolute value, which may be within the normal range. Level 2-

Abdominal ultrasound, abdominal CT and PET/CT have been used to stage uveal melanoma patients at the time of diagnosis of the primary tumour. Level 2

Although there is evidence that MRI is the best imaging modality for assessing the volume and distribution of liver metastatic disease once it has occurred (Level 2), no reports were found that evaluated the use of MRI to stage uveal melanoma patients at diagnosis of the primary tumour.

4.4.3. Primary Treatment

Choice of primary treatment has not been demonstrated to have a significant impact upon patient survival in uveal melanoma. Level 1

There was no significant difference for cumulative all-cause mortality, melanoma-related mortality and metastasis-free survival (log-rank test, $p = 0.56$, $p = 0.99$ and $p = 0.25$, respectively) in patients with large choroidal melanoma after primary treatment with enucleation compared to PBR. Level 2+
Five-year local control rates of over 95% have been reported for Ruthenium plaque brachytherapy. **Level 2**

Risk factors for local recurrence/poor tumour control include large basal diameter, anterior location, young patient age and foveal location. **Level 3**

Visual complications of ruthenium plaque brachytherapy are less severe than those recorded from the collateral damage of iodine plaque brachytherapy or PBR. **Level 3**

Visual deterioration, cataract and vitreous haemorrhage is associated with increasing tumour height following brachytherapy, as these tumours require a higher dose of radiation to achieve tumour control. **Level 3**

Tumour response to brachytherapy may not be a reliable prognostic indicator. **Level 3**

There is a risk of later extraocular extension following primary TTT, particularly in larger tumours. **Level 3**

TTT used in conjunction with plaque brachytherapy, known as “sandwich” therapy, provides better 5-year local tumour control (96% versus 83% p=<0.034), a better globe preservation (98% versus 87% p=<0.024) and recurrence free survival rate (89% versus 67% p=<0.017) than ruthenium plaque brachytherapy alone in medium sized tumours (COMS criteria) but there was no difference in overall patient survival/metastatic rate. **Level 2+**

At 1- and 4-years follow-up the visual outcome was worse in patients who had received ‘sandwich’ therapy compared to those who had received plaque brachytherapy alone. **Level 2+**

In patients with tumour diameter ranging from 4 to 27.5 mm, and tumour height from 0.9 to 15.6 mm receiving PBR, the overall eye retention rate post-treatment at 5 years was 88.9%, 86.2% at 10 years and 83.7% at 15 years. **Level 3**

Eye retention rates following PBR are lower for iris melanoma with a higher incidence of post-irradiation cataract and NVG. **Level 2**

### 4.5. Recommendations

Refer to recommendations related to this chapter which in Section 1.2 by clicking HERE

### 4.6. Linking evidence to recommendations

In formulating these recommendations, the GDG appraised the data where available. Where data were lacking, the GDG considered how best to combine what data were available with data and experience from similar situations in other oncological areas, as well as their own experience of managing the disease. The GDG did not formally assess the cost of any of the recommendations as the focus of these guidelines is on the identification of those clinical management changes that could be: a) clinically justified; and b) lead to improved health outcomes. However, the GDG was generally aware that recommendations need to be practical if they are able to result in a change of practice. An example was discussions regarding imaging technology to stage patients presenting with ‘high risk’ primary uveal melanomas. Whilst we agreed that contrast-enhanced MRI is the optimal modality for assessing the burden of metastatic liver disease, many centres perform an initial hepatic assessment using USS performed by highly experienced operators and only progress to other modalities when USS-detected abnormalities are seen. Whilst the GDG agreed that USS provides less accurate information regarding disease burden than MRI, using it as an initial screening tool may be entirely reasonable if it has a low false negative rate. USS also has major advantages regarding speed of assessment and cost, and without evidence that patients were at a disservice by having an MRI scan only following an abnormal ultrasound, the
GDG was unable to recommend MRI staging for all ‘high risk’ patients. This is an area that would benefit from further investigation.

The GDG believes that our recommendations regarding patient access to information about options available at each of the surgical centres, the development of a national uveal melanoma database, education of health care professionals who are likely to detect primary uveal melanoma, and timely referral to medical oncology will combine to significantly improve the quality of patient care.
5. Prognostication

5.1. Introduction

Uveal melanoma can arise in the iris, ciliary body and the choroid, with the latter being the most common site. Despite successful treatment of the primary tumours in most cases, approx. 40%-50% of patients will develop disseminated disease, predominantly in the liver, but also in the lungs, bone and elsewhere. Early surgical removal of metastases has improved patient survival in some cases (Frenkel, Nir et al. 2009, Mariani, Piperno et al. 2009); however, in general, the prognosis of UM patients with metastatic disease is currently poor because of the lack of effective systemic agents.

Several parameters have been identified in the literature, which have prognostic significance with varying degrees of strength that predict metastasis and therefore survival in uveal melanoma patients. These can be grouped into: a) clinical; b) histomorphological; c) immunohistochemical; d) genetic; and e) serological features (see references below). Some of these have been reviewed in depth by the AJCC TNM staging committee and have been included into this staging system for prognostication purposes (Finger and The 7th Edition AJCC-UICC Ophthalmic Oncology Task Force 2009, Kivela and Kujala 2013). Others have undergone extensive analysis using large data sets, either as part of a one-centre or multicentre analysis either as single parameters or in combination. Finally, other prognostic parameters noted in the literature have undergone less robust evaluation and their true significance remains unclear. The purpose of the following Chapter is to review the proposed prognostic parameters, determine whether there is a preferred prognostic tool and to suggest the role for prognostic biopsy.

5.2. Methods

5.2.1. Questions addressed

The questions that the developer(s) aimed to address were:

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Is there a preferred prognostic tool?</td>
<td>Patients with diagnosed primary uveal melanoma with and without clinical evidence of metastatic disease</td>
<td>Clinical variables Histomorphological features Immunohistochemical features Genetic data Serological markers</td>
<td>Each other</td>
<td>Survival (hazard ratio for prognostic factors)</td>
</tr>
<tr>
<td>What is the role of the prognostic biopsy?</td>
<td>Patients with uveal melanoma with and without clinical evidence of metastatic disease</td>
<td>Intraocular biopsy</td>
<td>With no biopsy</td>
<td>Patient surveys and satisfaction</td>
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5.2.2. Inclusion and exclusion criteria for selecting evidence

All papers regarding prognostic parameters predicting survival outcome described for primary uveal melanoma were included. Preclinical and animal studies, in vitro cytogenetic markers and cell line studies, single centre unvalidated series and single case reports were excluded.

5.2.3. Appraisal and extraction

Information from each of the investigation was extracted and presented to the Guideline Development Group for discussion on July 10 2013, with an update of the evidence presented after the update search. Tables 1-4 show the papers that were reviewed. For full details of each of the included studies, see the evidence tables in Appendix A.

All references were sifted initially by one individual, and grouped according to whether the prognostic parameter(s) described was/were of the following types: a) clinical; b) histomorphological; c) immunohistochemical; d) genetic; or e) serological. Where several or combinations of prognostic parameters described, these were also evaluated. The primary reasons for excluding papers were that they did not address the question. The reviewer appraised and reviewed the included papers, and the quality of the studies was assessed using the SIGN checklists as a guide.

5.3. Review of Evidence

5.3.1. Is there a preferred prognostic tool?

When evaluating the literature with respect to this question, it became apparent that the definition of the word ‘tool’ had to be addressed. Ultimately, it was decided that the word ‘tool’ had several meanings but principally referred to a ‘method’ or ‘methods’, including clinical, histomorphological, immunohistochemical, genetic, serological and ‘combined’ methods, which had been applied to determine the prognosis of uveal melanoma patients.

Clinical factors that have been consistently demonstrated in the literature to have strong statistical significance when predicting the risk of metastasis (and therefore have a role in prognostication) include:


Most of these parameters have been included in the 7th Edition of the AJCC TNM staging system (Kivela and Kujala 2013). http://www.springer.com/medicine/surgery/book/978-0-387-88440-0

Histomorphological factors shown in numerous papers to be prognostic significance comprise:


Immunohistochemical parameters described to be of prognostic significance in uveal melanoma include:


Cytogenetic and molecular genetic features of the tumour 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 1p, 6q, 8, and 9p as well as gain on 1q, 6p, and 8q (see review, Coupland, Lake et al. 2013). The above-mentioned chromosomal alterations in primary uveal melanoma 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% (Prescher, Bornfeld et al. 1992, Prescher, Bornfeld et al. 1994, Damato,

Different methods (i.e. techniques or ‘tools’) can be applied to assess the genetic alterations of uveal melanomas. The most commonly used tests are fluorescent in situ hybridization (FISH), multiplex ligation dependent probe amplification (MLPA), microsatellite analysis (MSA), single nucleotide polymorphisms (SNP) array (aSNP) and a PCR-based 12-gene assay based on gene expression profiling (GEP) (see Review by (Coupland, Lake et al. 2013)). The latter technique divides uveal melanoma into two ‘classes’ on the basis of an mRNA expression signature: class 1 and class 2 (Onken, Worley et al. 2010, Onken, Worley et al. 2012). Essentially, ‘Class 1’ uveal melanoma often show 6p and 8q gain. ‘Class 2’ uveal melanoma tend to show more aneuploidy with 1p loss, 3 loss, 8p loss, and 8q gain. Class 2 UM are also strongly associated with inactivating mutations of ‘BRCA1-associated protein-1 (BAP1), located at 3p21 (see below) (Harbour, Onken et al. 2010). The GEP-based test has been patented (DecisionDx-UM; www.castlebiosciences.com/test_UM.html). To date, there has been a paucity of studies that directly compare prognostic techniques in uveal melanoma (Singh, Aronow et al. 2012).

Only limited comparative analyses have been performed (Onken, Worley et al. 2007, Young, Burgess et al. 2007), (Young, Rao et al. 2007, Petracchi, Martus et al. 2008, Onken, Worley et al. 2012, Singh, Aronow et al. 2012, Vaarwater, van den Bosch et al. 2012, Coupland, Damato et al. 2013, Coupland, Lake et al. 2013), each with their respective flaws, and therefore no statement regarding superiority of a particular technique over another can be made.

Some serological markers have been proposed to be associated with poorer prognosis and ‘high-risk’ uveal melanoma: these include MIA-1 (Schaller, Bosserhoff et al. 2002, Reiniger, Schaller et al. 2005, Barak, Frenkel et al. 2007, Missotten, Korse et al. 2007); S-100B (Missotten, Beijnen et al. 2003, Barak, Frenkel et al. 2007, Missotten, Korse et al. 2007), osteopontin (Kadkol, Lin et al. 2006), (Barak, Frenkel et al. 2007); TPS (Barak, Frenkel et al. 2007); GDF-15 (Suesskind, Ulmer et al. 2011); B2-microglobulin (Triozzi, Achberger et al. 2012); and circulating cell free DNA (Mets, Scheulen et al. 2013). Most of these serological biomarkers are being investigated as a research tool but to date are not being used to influence clinical management.

Combined prognostic models have been designed and validated by some ocular oncology centres (Taktak, Fisher et al. 2004, Kaiserman, Rosner et al. 2005, Damato, Eleuteri et al. 2008, Damato, Eleuteri et al. 2011). The prognostic models take into account a number of the stronger prognostic parameters in uveal melanoma, which have been incorporated into statistical systems (e.g. conditional hazard estimating neural network; artificial neural networks; and accelerated failure time) using test and validation sets, for individualised prediction of prognosis. It has been demonstrated that these models increase the accuracy of prognosis prediction rather than using one single prognostic parameter. In some centres, the prognostication model is being used for
patient counselling and to determine screening frequency and the ultimate modality for screening (e.g. MRI versus ultrasound) applied (Marshall, Romaniuk et al. 2013).

5.3.2. What is the role of prognostic biopsy?

The proposed roles of prognostic biopsy are:

1. The identification of a high-risk group allows for: a) determination of liver scan frequencies and studies comparing screening methodologies; b) early surgical intervention of metastatic disease; and c) development of systemic adjuvant therapies using either two-stage or multistage phase II studies (Whitehead, Tishkovskaya et al. 2012).

Whilst genetic testing may alter management of patients at ocular oncology centres (Damato, Eleuteri et al. 2011), to date there is only one documented prospective single-arm study in the literature, whereby those asymptomatic uveal melanoma patients with a predicted 5-year mortality of greater than 50% underwent 6-monthly screening using MRI (Marshall, Romaniuk et al. 2013). This resulted in metastases being detected before symptoms in 83 (92%) of 90 patients developing systemic disease, with 49% of these having less than five hepatic lesions all measuring less than 2 cm in diameter. Of these 90 patients, 12 (14%) underwent hepatic resection, all surviving for at least a year afterwards. Whether this results in prolongation of life after taking lead-time bias into account, requires further follow-up and investigation.

2. Aid patient counselling – Patient demand is increasing for prognostication biopsies in uveal melanoma. Some studies (Beran, McCannel et al. 2009, Cook, Damato et al. 2009) have demonstrated that one of the main benefits perceived by patients is that they would have greater control knowing the genetic ‘type’ of their tumour, and that screening for metastatic disease and early treatment might enhance chances of survival. Further, psychological status did not vary significantly as a function of cytogenetic test result. Prognostic information was important to patients with choroidal melanoma, even in the absence of prophylactic measures that might improve prognosis (Beran, McCannel et al. 2009).

5.3.2.1. Tumour biopsy complications

Opinions vary about the scope of ocular tumour biopsy and the balance between the benefits of performing the biopsy and the theoretical risk of affecting tumour growth and/or the small risk of seeding. To date, there is no evidence in the literature suggesting that performing a biopsy of a uveal melanoma (and indeed any malignancy) affects the subsequent behaviour of the tumour – e.g. stimulating a high-grade transformation of an initially low-grade melanoma. On the other hand, episcleral seeding of uveal melanoma following biopsy has been reported, albeit it is rare (Raja et al. 2011, Caminal et al. 2006, Glasgow, B.J et al. 1988). In such cases, these have been treated by excision of any nodules with adjunctive cryotherapy.

Other complications of intraocular biopsy, such as transient or persistent vitreous or subretinal haemorrhage, retinal detachment, infectious endophthalmitis and rhegmatogenous retinal detachment (Shields, Ganguly et al. 2007) (Eide N et al. 2009, Grixti A et al. 2014). With the exception of transient vitreous haemorrhage after trans-vitreal biopsy, all of these complications are rare in the hands of an experienced surgeon, and are treated in the usual fashion (Grixti et al. 2014).
5.3.2.2. Tumour Heterogeneity
The use of fine needle biopsy in uveal melanoma prognostication relies on the assumption that the sampled tissue is representative of the entire tumour. Concern has been raised regarding tumour biopsy, as sampling error can potentially be introduced as a result of tumour heterogeneity. FISH analysis performed on paraffin sections has revealed some heterogeneity of monosomy 3 in uveal melanoma (Sandinha, Farquharson et al. 2006, Maat, Jordanova et al. 2007, Mensink, Vaarwater et al. 2009, Schoenfield, Pettay et al. 2009). This was also examined using MLPA using formalin-fixed enucleated globes; however, in the latter study it was found in most uveal melanomas that despite some variation in results of the individual loci examined in differing sites, the interpretation of the overall chromosome 3 status was consistent across the tumour (Dopierala, Damato et al. 2010). Indeed preliminary data demonstrate a very high concordance rate between MLPA and MSA results of intraocular biopsies of uveal melanomas that were subsequently enucleated and re-examined using these techniques (Coupland et al. 2014). Some rare cases are exceptions to the rule (Callejo et al. 2011). To date, there are no reports examining uveal melanomas using other techniques, including gene expression profiling. In general, it is highly recommended that interpretation of the cytogenetic or molecular results take into consideration the clinical data and history as well as the histomorphological features of the specimen examined. Disomy 3 or Class I results are to be interpreted with caution if the sample has not been examined for cellular content or cell type.

5.4. Evidence Statements
5.4.1. Prognostic factors/tool
- Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological, immunohistochemical and genetic features. Level 1++
- There are a number of different cytogenetic and molecular techniques for evaluating genetic changes in uveal melanoma but there is insufficient comparative data. No evidence was found that demonstrated one technique was superior to another. Level 1+
- A number of novel serological biomarkers are being investigated but not informed clinical management. Level 2

5.4.2. Prognostic biopsy
- Biopsy provides powerful prognostic information but there is as yet inadequate evidence to demonstrate that changing management as a result of this information affects survival. Level 4

5.5. Recommendations
Refer to recommendations related to this chapter, which are in Section 1.2 by clicking HERE

5.6. Linking Evidence to Recommendations
The GDG had a lengthy discussion regarding the risks and benefits of a prognostic biopsy. Some of the clinicians regarded the biopsy as collecting information for research purposes only, with no therapeutic benefit; others
were of the opinion that a biopsy assists in identifying patients at ‘high risk’ of metastasis and who could benefit from more intensive follow-up with the aim of potentially detecting metastases earlier. There was additional prolonged discussion on how to define a ‘high risk’ uveal melanoma patient (with respect to the development of metastasis) given the variety of genetic testing methods and their varying degrees of accuracy. Further, the GDG discussed what the definition of a ‘high risk’ uveal melanoma patient would be without the genetic data.

Currently two of the three ocular oncology referral centres in the UK do not routinely perform prognostic biopsy as it does not alter patient management in those two particular centres. There is some concern about the accuracy of the results and about the risks of the procedure. These include the risk of tumour seeding, intraocular haemorrhage as well as the possibility of a non-diagnostic result. This is in contrast to the third centre (Liverpool) where routine prognostication has been part of patient management since 1996, and where considerable expertise has been accumulated.

The discussion focused on patient preferences. The patient representatives were in favour of patients being informed about and being offered an intraocular biopsy, as this gave them more information on which to base decisions including future treatment options. They argued that if the biopsy is not performed, this information would not be available at a later date, particularly if the uveal melanoma was treated by radiotherapy in the absence of tissue sampling. Without accurate genotyping of their tumours through a biopsy, patients may not be eligible to be recruited into clinical trials. This was regarded by the patient representatives as a major handicap. There was a discussion about whether all patients wanted to know the results of the intraocular biopsies. Experience at the Liverpool Ocular Oncology Centre (and elsewhere) would suggest that most patients do; however, this information is only incorporated into the pathology reports, if the patient has consented for the prognostic testing to be done. It was agreed that there should be an informative and neutral discussion between the patient and surgical ocular oncologist about the risks of intraocular biopsy prior to treatment of the primary tumour, and these were to be considered against the potential benefits.

6. Surveillance of patients at risk of recurrence

6.1. Introduction

Uveal melanoma is a rare cancer, with a propensity for liver metastasis. Management of localised disease with either surgery or radiotherapy achieves a high rate of local control; however, about 50% of patients relapse with predominantly liver metastases. The risk of metastatic disease can be predicted relatively accurately through the use of clinicopathological features and molecular genetics (see above). Prognosis in the metastatic setting remains poor, with a median survival of less than 6 months for patients who receive no active treatment; and 6 to 24 months for treated patients. Surgical management of liver metastases offers the only real likelihood of long-term disease control at present for some patients with isolated metastatic tumours (Frenkel, Nir et al. 2009, Mariani, Piperno-Neumann et al. 2009), particularly as there are currently no proven systemic therapies that change outcome in patients with disseminated uveal melanoma. This has led to the introduction of surveillance programmes for patients with a high-risk of developing disease, with the aim of identifying metastases early, allowing for resection or clinical trial entry. It has been previously shown that surveillance allows early detection of metastases prior to the development of symptoms, and that this facilitates trial entry and surgery in a limited proportion of patients. Although a survival benefit to screening has not been proven, many centres (nationally
and internationally) now perform periodic screening of patients with high-risk uveal melanoma, and screening is now considered to be good clinical practice. However the optimal screening method (e.g. CT scanning, MRI, US), timing, patient selection and overall advantage of surveillance remain under debate. More sensitive imaging modalities such as PET/CT and contrast-enhanced MRI have been proposed and are increasingly used internationally. This has been on the assumption that such technologies improve the detection and expedite detection of metastases and improve resection and hence survival. However this benefit remains to be demonstrated, and there are clear financial and clinical implications.

**Aim – purpose is to identify patients who have relapsed. – i.e. who have developed metastatic disease.**

The GDG agreed that the aim is to detect small volume, pre-clinical disease rather than first identifying large volume, clinically detectable, metastatic disease.

**Aim – to detect metastatic disease as early as possible.**

The GDG agreed that there is a need to assess whether early detection makes a difference. There is evidence in Section 7 that small volume treatment has better outcome. Early treatment potentially may influence benefit and number of lines of treatment.

### 6.2. Methods

#### 6.2.1. Questions addressed

1. Should all patients be offered surveillance?
2. Should there be a risk-adapted strategy for surveillance?
3. What is the optimal imaging modality for surveillance?
4. What is the interval?
5. What is the duration of surveillance?

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Test/Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should all patients be offered surveillance?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>LFT, USS, MRI (liver, contrast enhanced)</td>
<td>With each other</td>
<td>Metastasis Survival</td>
</tr>
<tr>
<td>Should there be a risk-adapted strategy for surveillance?</td>
<td>Patients who have been treated for a primary uveal melanoma, and who have a ‘high risk’ of developing metastatic disease, according to clinical, histomorphological</td>
<td>LFT, USS, MRI (liver, contrast enhanced)</td>
<td>Comparing different risk levels to each other</td>
<td>Sensitivity and specificity of metastasis detection Survival</td>
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and genetic features.

<table>
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<tr>
<th>Question</th>
<th>Patients who have been treated for a primary uveal melanoma</th>
<th>Compared to each other</th>
<th>Sensitivity and specificity of metastasis detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the optimal imaging modality for surveillance? What is the interval?</td>
<td>USS MRI (liver, contrast enhanced) CT Scan</td>
<td></td>
<td>Survival</td>
</tr>
<tr>
<td>What is the duration of surveillance?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>Compared to each other</td>
<td>Sensitivity and specificity of metastasis detection</td>
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<tr>
<td></td>
<td>USS MRI (liver, contrast enhanced) CT Scan</td>
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<td>Survival</td>
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<td>5 years versus 10 years versus life-long</td>
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6.2.2. Inclusion and exclusion criteria for selecting evidence

Included were Case control studies, Case series >3 patients and Review articles combined with case reports. Only studies with adult patients were included. Preclinical and animal studies were excluded, as were case reports (1-3 cases) and review articles without any original case information.

6.2.3. Appraisal and extractions

All references were sifted first by one individual. Two reviewers appraised and reviewed the included papers, and the quality of the studies was assessed using the modified SIGN checklists as a guide.

Most of the studies were case reports (close to 30%) with only about 10% representing descriptive case series.

Information from each of the studies was extracted and presented to the Guideline Development Group for discussion on March 14 2014 with an update of the evidence presented after the update search. For full details of each of the included studies, see the evidence tables in Appendix A.

No studies were found that addressed the duration of surveillance review question.

6.3. Evidence summary

6.3.1. Question 1: Should all patients be offered surveillance?

A recent and very detailed review of studies that investigated periodic surveillance from 1980 to 2009 by Augsburger et al. (Augsburger, Correa et al. 2011) failed to find evidence of a survival benefit associated with regular surveillance. Therefore it could be argued that it is futile offering uveal melanoma patients' surveillance examinations to detect metastatic disease. However, the majority of the studies reported in this review (n = 31 in total) were small, retrospective, and from single institutions. In addition, a wide and very variable range of screening methods and strategies were described, further complicating the comparison. Notably, none of the articles was a report of a randomized or nonrandomized comparative clinical trial of total post-treatment survival in subgroups assigned to regular periodic surveillance for metastasis versus no surveillance testing (Augsburger, Correa et al. 2011).
On the other hand, several studies have clearly demonstrated that periodic liver imaging allows the identification of liver metastases prior to the development of symptoms (Eskelin, Pyrhonen et al. 1999, Maeda, Tateishi et al. 2007, Kim, Lane et al. 2010, Marshall, Romaniuk et al. 2013). For example, in the study by Marshall et al. 92% of patients who developed metastases, were asymptomatic at the time of diagnosis using 6-monthly non-contrast MRI surveillance (Marshall, Romaniuk et al. 2013). Furthermore, liver surveillance allowed detection of liver metastases in the majority of patients prior to changes in serum biochemistry.

Liver metastasectomy is currently only possible in approximately 10% of cases using historical screening programmes (Sato 2010, Marshall, Romaniuk et al. 2013) and reflecting the burden of disease at diagnosis of metastases. However, the resection rate may be increased with strategic planning of screening, using more sensitive tools.

6.3.2. Question 2: Should there be a risk-adapted strategy for surveillance? If so, what is a high-risk and or low-risk uveal melanoma?

As mentioned above in the “Prognostication” section (section 5), the risk of metastatic relapse in uveal melanoma is determined by multiple factors, including clinicopathological features such as tumour size and location (Shields, Furuta et al. 2009) and molecular genetic abnormalities, most notably the loss of chromosome 3 (Prescher, Bornfeld et al. 1996, Damato, Eleuteri et al. 2011). In addition, the risk of metastatic disease may be assessed using multigene expression assays (Onken, Worley et al. 2010). This has enabled the development of sophisticated prognostic tools, which allow the identification of patients with a high risk of developing metastases, (Onken, Worley et al. 2010) for whom surveillance is most likely to be beneficial. For example, the Liverpool Uveal Melanoma Prognosticator Online (LUMPO) is used on a routine basis to stratify uveal melanoma patients into low- and high-risk groups, and is used in patient counselling, management and screening (www.ocularmelanomaonline.com) (Damato, Eleuteri et al. 2011).

Targeted screening, in the highest risk patients with the greatest needs, also offers a practical setting where clinical trials may be most helpful in elucidating the role of follow-up. In the study by Marshall et al (Marshall, Romaniuk et al. 2013) for example, only patients with monosomy 3 were enrolled, thus limiting surveillance to patients with a high risk of recurrence, which is reflected in the development of metastases in 48% of patients, after a median follow-up period of approximately 29 months. Conversely, patients for whom relapse is very unlikely may be reassured and discharged early. However, the level of risk that is employed as a cut-off is clearly subject to debate. The risk-versus-benefit ratio of screening in ‘low metastatic risk’ disease poses additional challenges and must be carefully weighed against potential harm from false positive findings, potential radiation exposure, psychological morbidity and the economic impact.

The definition of ‘high risk’ uveal melanoma poses difficulties since not all centres apply the molecular genetic testing, or only in very few selected cases, e.g. enucleation samples. Consequently, a definition of ‘high risk’ cannot in the UK be based only on molecular genetic abnormalities, but must include clinical and histomorphological features of the tumours, when assessable. A ‘high risk group’ may therefore entail inclusion of uveal melanomas with:

a. Large tumour size (based on a TNM tumour size and stage cut off - e.g. T3 tumour with a stage IIIA, corresponding to a 5-year mortality rate of 34%) (Finger and The 7th Edition AJCC-UICC Ophthalmic Oncology Task Force 2009, Kivela and Kujala 2013)

b. with or without (+/-) Ciliary body involvement
c. +/- Epithelioid cells

d. +/- Closed connective tissue loops (also termed extravascular matrix loops)

e. +/- High mitotic count (>5 per 40 HPF)

f. +/- Monosomy 3

g. +/- Polysomy 8

h. +/- GEP Class 2

i. +/- A risk of death of 30% at 5 years or higher (i.e. TNM 7th edition Stage III (either A, B or C) (Kujala et al. 2013).

Discussion is required to agree on this definition before any prospective study addressing the usefulness of surveillance in uveal melanoma subgroups can be commenced. Further, the endpoints of this study would have to be carefully considered: e.g. time to detection of metastases, time to resection, survival outcomes.

6.3.3. Question 3: What is the optimal imaging modality for surveillance, overall and of the liver?

Many different imaging modalities are in use or have been suggested including, but not limited to, liver imaging with USS, CT or MRI (with or without contrast enhancement) or body imaging with CT or PET-CT. The choice of imaging modality currently reflects local practice access, and also whether or not to exclusively image the liver or include extrahepatic sites.

The principal hypothesis behind screening in the surveillance of uveal melanoma patients is the detection of resectable liver metastases, based on the assumption that a significant proportion of patients have liver-only metastases at first relapse. Consequently, this has led to the use of liver imaging as the primary modality used for screening. In an imaging study of 110 uveal melanoma patients at different time points following diagnosis of the primary tumour, 55% had liver-only metastases, and the liver was involved in 92% overall (Lorigan, Wallace et al. 1991). Several other studies have similarly reported high rates of liver involvement (Einhorn, Burgess et al. 1974, Gragoudas, Egan et al. 1991). However, in a series evaluating distribution of metastases at death, the liver was involved in 93%, with 87% of cases showing multiple sites of metastases (Willson, Albert et al. 2001). Other autopsy series showed liver-only metastases in between 22%-30% of patients with other sites being affected in up to 90% of patients. (Patel, Didolkar et al. 1978, Borthwick, Thombs et al. 2011). The incidence of brain metastases is low at 1%.

Therefore, in advanced metastatic disease liver-only uveal melanoma metastases are less common; extrahepatic metastases at first relapse in the presence of liver metastases can occur (Lorigan, Wallace et al. 1991), but the frequency is unclear. Recent case series utilising PET-CT have illustrated that UM metastases can be widely disseminated and include unusual sites such as cardiac, muscle, and thyroid etc. (Klingenstein, Haug et al. 2010) and (Kurli, Reddy et al. 2005). Extrahepatic relapse in the absence of liver metastases appears uncommon. Prolonged survival has been described following solitary extrahepatic metastatectomy (Aoyama, Mastrangelo et al. 2000). The low frequency of isolated extrahepatic relapse would not appear to justify routine imaging beyond the liver: this would require long-term CT follow-up, which is potentially associated with harmful radiation effects.
Liver imaging: Although there has been very limited formal evaluation of imaging in uveal melanoma, a meta-analysis in gastrointestinal cancer reported the highest weighted sensitivity in the detection and assessment of liver metastases with either MRI or PET-CT (Niekel, Bipat et al. 2010). Two uveal melanoma-specific studies suggest that MRI may be superior to PET-CT in detecting small hepatic metastases (lesions <10 mm in diameter) (Servois, Mariani et al. 2010, Orcurto, Denys et al. 2012). However, MRI still remains an imperfect preoperative modality, given the pattern of miliary liver metastases that can be seen in uveal melanoma. Contrast-enhanced MRI can further increase high spatial resolution and sensitivity and is the preferred liver-imaging technique for potentially operable malignant liver disease. The role in routine surveillance is less clear and potentially offset by high costs, long procedure time and a recognised but low incidence of potentially adverse reactions. A direct comparison between MRI with and without contrast has not been published in uveal melanoma. Investigation into the utility of PET-MRI in this setting is also required. This is a relatively new technology that is not in general use at present. However, PET-MRI has potential advantages, most notably a lower dose of ionising radiation in comparison to PET-CT.

The choice of modality clearly has implications on the cost-effectiveness of any surveillance programme. The current estimated costs to the NHS are £85-£125, £380, £370, £450 and £900 for liver USS, contrast CT, non-contrast MRI, contrast MRI and PET-CT, respectively. (Estimated costs in 2014). In the absence of cost-effectiveness data, the choice of modality has been based upon a relatively subjective assessment of efficacy in relation to cost and the scope of the surveillance programme (all patients versus a targeted high-risk population).

6.3.4. Question 4: What is the optimal surveillance interval?

There is very little evidence on which to base decisions regarding either frequency or duration of follow-up.

In a study by Eskelin et al. (Eskelin, Pyhonen et al. 1999) surveillance was performed annually using liver USS and 59% of metastases were detected at an asymptomatic stage. The authors hypothesised that 6-monthly imaging would increase the percentage of asymptomatic detection to 95%. In the study by Marshall et al. (in which surveillance was performed every 6 months), 92% of patients were detected before the development of symptoms (Marshall, Romaniuk et al. 2013).

Nonetheless, the general consensus in the field is that 6-monthly imaging is preferable. Advice must take into account the individual’s risk weighted against the cost and resource implications of shorter scanning intervals as well as the possible psychological impact on patient and family from more frequent (e.g. 3monthly) testing.

6.3.5. Question 5: What is the duration of surveillance?

Uveal melanoma may continue to relapse for many decades following primary diagnosis, with 20%-33% of deaths attributed to metastatic recurrence even at 15-42 years (Coupland, Sidiki et al. 1996, Kujala, Makitie et al. 2003). The Liverpool dataset suggests an almost linear continuation of recurrence over time and beyond 10 years without a visible plateau in risk of recurrence. (Damato and Damato 2012) The role of lifelong screening is unknown, but it is pertinent to note that surgical resection series report that the outcome appears most favourable in later relapsing patients, perhaps arguing for prolonged follow-up in some instances. Lifelong screening in all patients would appear unjustified and expensive, and supports the concept of targeted screening of higher risk subgroups. Marshall et al. reported that 65% of high-risk patients had relapsed at 5 years on non-contrast liver MRI surveillance, and thus focusing surveillance on this period would appear sensible (Marshall,
Romaniuk et al. 2013). However, a further period of screening, may also prove to be of value in the detection of resectable disease.

6.4. **Evidence Statements**

- To date, an effect of screening on survival of uveal melanoma patients has not been demonstrated. **Level 2**
- If a substantial and clinically meaningful survival benefit were truly associated with periodic surveillance testing for uveal melanoma metastases, such benefit would be demonstrated most convincingly by means of a prospective comparative clinical trial in which subgroups of patients with uveal melanoma (after treatment of their primary intraocular tumour) were subjected to either regular periodic surveillance testing by some consistent regimen or no surveillance testing at all and then followed until death from any cause. It seems unlikely that this could be tested practically. **Level 4**
- Despite the lack of evidence there is general consensus that surveillance testing is not worthless, and indeed is performed in virtually all centres in a periodic manner using differing methods for differing lengths of periods. **Level 4**
- Surveillance clearly identifies many patients with metastasis at a substantially less advanced disease burden than would occur if only postsymptomatic testing were employed. **Level 2**
- Targeted surveillance is likely to bring more benefit. A consensus definition of ‘high-risk’ uveal melanoma is required, incorporating clinical, histomorphological and genetic features of the tumours. **Level 4**
- Most surveillance testing for metastatic uveal melanoma concentrates on the liver, with the effect that highly-sensitive modalities for liver imaging are chosen. **Level 2**
- The role of extrahepatic imaging in surveillance is unclear, particularly as the frequency of extrahepatic metastatic relapse remains unknown. **Level 2**
- Hepatic surveillance of uveal melanoma has resulted in an increased detection rate of metastases in the liver, resulting in increased locoregional treatment in some centres and trial recruitment. **Level 2**
- Surveillance is intuitively advantageous, allowing locoregional management of liver-only metastases, and facilitating early systemic treatment and particularly trial enrolment before the disease burden causes deteriorations in general health and performance status. **Level 4**
- Additionally, surveillance facilitates patient follow-up, provides a link with oncology services and allows a more holistic approach to cancer patients that includes early access to cancer nurse specialists and smooth transition to services such as palliative care at an appropriate stage. **Level 2**
- No evidence was found with respect to the duration of surveillance.

6.5. **Recommendations**

Refer to recommendations related to this chapter which in Section 1.2 by clicking [HERE](#).

6.6. **Linking evidence to recommendations**

The GDG discussed the reasoning and strategy for surveillance of uveal melanomas at length.

With respect to the question “Should all patients should be offered surveillance”, there was consensus amongst the GDG that whilst the evidence in the literature would suggest that this practice is futile, all three ocular
oncology centres and their associated general oncologists supported the concept of conducting surveillance, with an emphasis on liver screening, particularly as there are other potential benefits for routine imaging studies. This was supported by studies demonstrating that periodic liver imaging allows the identification of liver metastases prior to the development of symptoms and/or change in blood values.

Regarding the question “Should there be a risk-adapted strategy for surveillance?”, there was no consensus in the GDG, due to the inability to agree on a definition of ‘high metastatic risk’, reflecting the varying approaches between the centres to prognostication. Whilst some centres would employ MRI with or without contrast in ‘high-risk’ uveal melanoma, others indicated that they would remain with the initial hepatic assessment using USS and only progress to other modalities when USS-detected abnormalities are seen. It was suggested that due to the insufficient evidence comparing and contrast screening modalities in uveal melanoma patients, a prospective trial for uveal melanoma surveillance is required before any change of local practice would be undertaken.

Consensus was achieved amongst the GDG for lifelong 6-monthly liver screening in all uveal melanoma patients for, despite the lack of evidence in the literature supporting this practice. This is another area that would benefit from further investigation.

The patient representatives were in favour of the uveal melanoma patients being informed of the strengths and weaknesses of differing screening methodologies, and being involved in the decision-making process of what screening method was chosen in their particular case.

### 7. Metastatic Disease

#### 7.1.1. Introduction

As discussed above, the natural history of uveal melanoma is characterised by the frequent development of metastases. Close to 50% of patients develop metastatic disease at any time from the initial diagnosis of the primary to several decades later (Kujala, Makitie et al. 2003, Diener-West, Reynolds et al. 2005). The risk of metastatic relapse for an individual can vary greatly dependent upon a number of primary tumour characteristics, including genetic alterations (see section 5 above). Outcomes are poor once metastatic disease occurs, and the median survival from the time of development of distant metastatic disease is 2 to 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 (Augsburger, Correa et al. 2009).

Metastatic disease almost always involves the liver and is rarely detectable using imaging techniques, at the time of primary tumour management (<5%). The pattern of disease is distinct from that of cutaneous melanoma. The liver may be the only metastatic site in a significant percentage of patients although lung, bone and skin metastases are also well described (Willson, Albert et al. 2001). Brain metastases are extremely uncommon.

Patients with metastatic uveal melanoma are typically managed by oncologists and palliative care teams as part of skin melanoma services and guided by skin melanoma guidelines in the absence of standards for staging investigations, metastatic biopsy and treatment.
A broad spectrum of therapies have been reported and reflect the presenting pattern of metastatic disease. Treatment may include best supportive care, systemic therapies (chemotherapy, biological therapies) or liver-directed therapies (chemotherapy, radiotherapy or surgery). Systemic chemotherapy results in an objective response rate that ranges from 5% to 15% and without any strong evidence that conventional chemotherapy prolongs survival. Access to clinical trials is limited and patients with metastatic uveal melanoma are often specifically excluded from clinical trials in skin melanoma.

In the absence of a proven standard of care or clinical trial in the UK, many patients with metastatic uveal melanoma currently receive best supportive care or dacarbazine chemotherapy for 4-6 cycles. Unlike skin melanoma, mutations in the BRAF gene are exceptionally rare and thus for these patients BRAF-directed therapies unhelpful. The anti-CTLA4 agent, Ipilimumab has National Institute for Health and Care Excellence (NICE) approval for previously treated advanced (unresectable or metastatic) melanoma based upon clinical trials in skin melanoma. [http://publications.nice.org.uk/ipilimumab-for-previously-treated-advanced-unresectable-or-metastatic-melanoma-ta268](http://publications.nice.org.uk/ipilimumab-for-previously-treated-advanced-unresectable-or-metastatic-melanoma-ta268)

The vast majority of patients with metastatic uveal melanoma have liver involvement and often as the first site of metastatic relapse. Some patients appear to relapse with liver only disease and may represent a distinct subgroup who may benefit from regional approaches to therapy. This chapter focuses on the management of all patients who present with distant metastatic recurrence irrespective of the site and aims to give guidance on:

Q1. What is the optimal method of staging?

Q2. What is the most robust prognostication (known prognostic factors for survival)?

Q3. What is the optimal management of systemic metastases?

Q4. What is the optimal management of oligometastatic disease outside the liver?

Q5. What is the optimal management of liver only metastases?

Q6. Is regional liver therapy more effective than systemic therapy?

Q7. What is the role of surveillance following metastatic treatment?

**Staging**

Staging is performed once the patient has been found to have clinical, biochemical or radiological evidence of metastatic disease. Some centres use a surveillance program, which varies depending on the predicted risk of developing metastases following the primary treatment (Marshall, Romaniuk et al. 2013). The aim of staging is to identify all sites of metastatic disease in order to determine the most appropriate treatment plan for an individual patient. For instance, if a patient has multiple lung metastases and lymph node disease within the abdomen, there is unlikely to be any survival benefit in performing a liver resection for liver metastases.

Cross sectional imaging with CT or MRI are the most commonly used imaging modalities for staging metastatic disease. MRI of the liver is more sensitive than CT in lesion detection (Niekel, Bipat et al. 2010) and the use of liver specific MRI contrast agents can increase the number of visualised liver metastases. More recently MRI diffusion-weighted imaging (DWI) has been shown to increase the detection rate of colorectal liver metastases.
(Koh, Collins et al. 2012) and (Kim, Yu et al. 2012). CT has better spatial resolution than MRI, and is more sensitive for detection of extrahepatic disease. Uveal melanoma metastases greater than 1 cm are usually seen on PET-CT, but small liver metastases are frequently missed (Orcurto, Denys et al. 2012). Despite significant improvements in cross sectional imaging, miliary and sub-capsular liver metastases, and serosal small bowel metastases are still commonly missed (Servois, Mariani et al. 2010). This supports the need for pre-operative staging laparoscopy.

**Prognostication**

Prognostic factors are critically important in the selection of patients for therapy and in guiding decision making for both patients and professionals. A number of retrospective studies have used multivariate analysis including a validated multivariate analysis in over 200 patients that allows grouping of patients into three distinct groups with differing prognosis. (Eskelin, Pyrhonen et al. 2003, Rietschel, Panageas et al. 2005).

**Management**

Systemic chemotherapy has been the standard treatment for most patients with liver metastases, with or without extrahepatic disease. Treatment protocols have often arisen from experience in cutaneous melanoma despite a lack of uveal melanoma-specific clinical trial evidence. Indeed, previous evidence base is almost entirely based upon retrospective case series and a small number of uncontrolled phase II clinical trials that are compounded by case selection. In the absence of an evidence-based standard of care, dacarbazine or temozolamide has emerged as the standard control arm in a number of recently completed and ongoing randomised clinical trials (Carvajal 2013, Sacco, Nathan et al. 2013). Progress in basic science and cancer biology has highlighted an increasing number of potential novel therapeutic targets in uveal melanoma. This has created a momentum in new clinical trials that are evaluating a wide range of targeted treatments and immunotherapy. Furthermore, and importantly, the evaluation of new therapies has been underpinned by robust clinical trial design with clear eligibility and prospective data collection in both national multicentre and international collaboration.

The delivery of systemic therapies in liver-only metastatic disease has been based on the assumption that liver resection is unlikely to offer a curative resection, as there are often more metastases within the remnant liver and occult extra-hepatic micrometastatic disease. In addition the post-operative recovery period could be a significant proportion of the patient’s remaining life. As morbidity and mortality from liver surgery has reduced, and more complex resection techniques have evolved, surgery may have a greater role to play in the future. Wedge resections and other adjunctive therapies can be used to treat small metastases in the remnant liver, either at the time of primary liver resection or at a later time.

Regional liver therapies have been extensively reported in the setting of liver-only disease; however, most of the reports are similarly flawed by the low quality of retrospective case series and uncontrolled single arm clinical trials. There is no doubt that interventional radiology has developed rapidly over the last two decades and offers potential therapeutic options for selected patients with liver-only metastatic uveal melanoma.

Targeted treatment can be delivered to liver metastases using two different approaches: 1) Percutaneous thermal needle-based techniques include radiofrequency, laser, microwave and cryo-ablation which are all capable of treating liver metastases up to 3 cm in diameter with curative intent (Lencioni, Della Pina et al. 2005, Hamada, Yamakado et al. 2012). Recently non-thermal ablation, using irreversible electroporation, has entered
clinical practice. This technique involves passing a high voltage current between two or more needles placed around the metastasis, producing pores within the cell membrane, leading to cell death. 2) Trans-arterial treatments take advantage of the dual blood supply to the liver. The portal vein provides up to 80% of blood to the normal liver while most liver metastases, especially highly vascular tumours such as melanoma, recruit a blood supply from the hepatic artery branches. Delivering treatments through the hepatic artery will therefore treat liver metastases while sparing normal liver. Historically intra-arterial chemotherapy infusions have been used after surgical placement of a catheter within the hepatic artery (Cantore, Fiorentini et al. 1994). Clearly the benefit over systemic chemotherapy relies on the liver chemotherapy retention during the ‘first passage’ of the injected agent through the liver. A significant portion of the chemotherapy, however, will pass through the liver and reach the venous circulation.

Conventional chemoembolisation involves injecting a combination of chemotherapy and an embolic agent through a temporary catheter placed in the hepatic artery, thus slowing transit of the chemotherapy through the liver and blocking the blood/oxygen supply to the tumour. More recently, drug-eluting beads (Martin, Joshi et al. 2011) and radiolabelled beads (Van Hazel, Blackwell et al. 2004) have become available to use within the liver to treat primary and secondary liver cancers. The bead becomes trapped within the tumour microvasculature where the chemotherapy agent or β radiation, respectively, is maintained in close proximity to the tumour.

Immunooembolisation replaces the chemotherapy component with an immune modulating agent such as granulocyte macrophage colony-stimulating factor. In addition to the ischaemic effect of the embolisation, there is stimulation of antigen presenting cells leading to a possible increased systemic immunity to cancer cells (Yamamoto, Chervoneva et al. 2009).

Another arterial delivered treatment termed ‘isolated hepatic perfusion’ involves saturating the liver with high doses of chemotherapy by occluding the venous outflow from the liver for approximately 30 minutes. The drug-filled venous effluent is removed from the body and passes through an extra-corporeal filter to remove the chemotherapy before the blood is returned to the patient (Zager and Nutting 2012).

Despite more aggressive liver surgery and new interventional techniques, it is the diffuse infiltrative nature of ocular melanoma liver metastases that continues to provide the greatest challenge in disease control. The rare nature of this uveal melanoma means that most publications consist of small case series, often mixed with cutaneous melanoma liver metastases, or metastases from other primary tumours. Comparisons are often made with historical data sets.

**Surveillance**

Following any metastatic therapy imaging is performed more frequently, initially to assess treatment response and then to look for early recurrence. The modality (CT, MRI, PET) of choice will be largely guided by the pattern of metastases and need for comparison with pre-treatment assessment. The potential benefit of follow-up imaging is dependent on the availability of subsequent therapeutic options and patient wishes. Early, presymptomatic detection of relapse or progression may offer the possibility of subsequent treatment or clinical trial entry but currently there is a lack of evidence base and decisions are most appropriately made on an individual basis. Patients who have undergone a potential curative liver resection represent a highly selected subgroup with respect to ongoing surveillance. By virtue of the fact these patients have already developed liver metastases they are in a particularly high-risk group, and so imaging frequency should increase compared to the
surveillance group who have yet to develop metastases. It is not clear how long after liver treatment a patient should return to a surveillance program. As with pre-operative staging, imaging can be performed with MRI or CT, supplemented by PET-CT. Following ablation treatments the ablated area should be larger than the underlying metastasis, and should have sharply defined margins with the adjacent liver. There will be a rim of hyperaemic normal liver adjacent to the periphery of the ablation site within the first week or so, and it is important that this is not misinterpreted for residual tumour. Post ablation liver imaging at around four weeks is generally regarded as an appropriate interval to assess treated metastases.

Following intra-arterial treatments imaging assessment is more difficult as the distinction between necrotic tumour and viable tumour is not always clear. The classic Response Evaluation Criteria In Solid Tumors (RECIST) method of assessing tumour response almost always underestimates the effectiveness of treatment, as the size of the treated metastasis may not change. As ablation techniques aim to destroy a rim of normal liver at least 5mm beyond the margin of the metastasis, the RECIST assessment would regard this as progression of disease. The modified RECIST criteria (Lencioni and Llovet 2010), recently introduced to accommodate newer treatment techniques, incorporate the reduction of tumour enhancement, following intravenous contrast administration, as an indicator of response.

### 7.2. Methods

#### 7.2.1. Questions addressed

The following questions were addressed

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q. 1 What is the optimal method of staging?</td>
<td>Patients with uveal melanoma with suspected metastatic disease</td>
<td>LFT USS CT chest abdo pelvis MRI (whole body, liver, contrast enhanced) FDG PET CT Bone scan Laparoscopy</td>
<td>With each other</td>
<td>Assess the extent of disease</td>
</tr>
<tr>
<td>Q2. What is the most robust prognostication (known prognostic factors for survival)?</td>
<td>Patients with uveal melanoma with metastatic disease</td>
<td>Clinicopathological variables; Performance status CRP Platelet/lymphocyte ratio Other Treatment variables: Regional therapy Systemic therapy</td>
<td>Each other</td>
<td>Survival (hazard ratio for prognostic factors)</td>
</tr>
<tr>
<td>Q3. What is the optimal management of systemic metastases?</td>
<td>Patients with uveal melanoma with systemic +/-liver metastatic disease</td>
<td>Surgery Ablation Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Primary - Overall survival Progression free survival Disease free survival Response rate Toxicity Quality of life</td>
</tr>
<tr>
<td>Question</td>
<td>Management of Disease</td>
<td>Second line treatment</td>
<td>Notes</td>
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<tr>
<td>Q4. What is the optimal management of oligometastatic disease outside the liver?</td>
<td>Patients with uveal melanoma with oligometastatic disease outside the liver</td>
<td>Surgery, RFA, Radiotherapy</td>
<td>With each other</td>
<td>Response toxicity, QOL, PFS, Overall survival, Quality of life, Second line treatment, response rate, PFS, OS</td>
</tr>
<tr>
<td>Q5. What is the optimal management of liver only metastases?</td>
<td>Patients with uveal melanoma with liver only metastatic disease</td>
<td>Surgery, Ablation, Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Primary - Overall survival, Progression free survival, Disease free survival, Response rate, Toxicity, Quality of life</td>
</tr>
<tr>
<td>Q6. Is regional liver therapy more effective than systemic therapy?</td>
<td>Patients with uveal melanoma with liver +/- systemic metastatic disease</td>
<td>Surgery, Ablation, Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above</td>
<td>With each other</td>
<td>Primary - Overall survival, Progression free survival, Disease free survival, Response rate, Toxicity, Quality of life</td>
</tr>
<tr>
<td>Q7. What is the role of surveillance following metastatic treatment?</td>
<td>Patients with uveal melanoma following resection or regional treatment</td>
<td>USS, CT, MRI</td>
<td>Each other</td>
<td>Survival, Ability to identify disease recurrence or new metastatic disease</td>
</tr>
</tbody>
</table>

### 7.2.2. Inclusion and exclusion criteria for selecting evidence

Included were all human, adult only, Phase I/II/III studies. All study types were included except for case reports. Studies relating to prognostic factors in advanced disease and imaging for advanced disease were included. Studies relating to in vitro cytogenetic markers and cell line studies were excluded.
7.2.3. Appraisal and extraction

Information from each of the studies was extracted and presented to the GDG for discussion, with an update of the evidence presented after the update search. For full details of each of the included studies, see the evidence tables in Appendix B.

All references were sifted first by a GDG member with expertise in the topic. The primary reasons for excluding papers were that they did not address the question.

The reviewers appraised and reviewed the included papers, and the quality of the studies was assessed using the SIGN checklists as a guide. Most of the studies were case series and because SIGN does not have a quality checklist for this study type, the guideline developers used additional criteria to assign an overall quality rating to these studies. The quality rating was as follows: those with a larger number of subjects and where subjects were recruited from more than one centre, were considered as being of better quality.

7.3. Evidence summary

7.3.1. Question 1. What is the optimal method of staging?

Systemic: There are no randomised controlled trials evaluating staging investigations in metastatic uveal melanoma. Most reports consist of small patient numbers from institutional series only and often based upon retrospective review.

The prevalence and location of metastases from uveal melanoma was reported in 110 patients at the MD Anderson Cancer Centre (Lorigan, Wallace et al. 1991). In 55% of patients, the liver was the only organ affected. Extrahepatic metastases included lung, bone, skin and lymph nodes were noted but were rare in the absence of liver involvement (8%). Brain and adrenal metastases were seen in <5% of cases.

Patel et al (Patel, Winston et al. 2011) reported on the CT characteristics in biopsy-proven liver metastases from uveal melanoma. Seventy-six patients were identified over an 11-year review period. Radiographic evidence of extrahepatic metastases was evident in 53% of cases that represented advanced malignancy with high liver tumour burden. In this cohort, overall survival correlated with tumour volume, hepatomegaly and ascites.

Liver: Several small case series (Servois, Mariani et al. 2010, Orcurto, Denys et al. 2012) report that PET-CT is not able to detect metastases less than 12mm. MRI is able to detect the majority of liver metastases even as small as 5mm. Contrast-enhanced MRI was compared with PET CT in the preoperative stage of known liver metastases in 15 uveal melanoma patients (Servois, Mariani et al. 2010). All patients proceeded to laparotomy. MRI was superior to PET CT for staging liver metastases. MRI was also more sensitive for detecting small liver metastases in a second small study (Orcurto, Denys et al. 2012).

While the available evidence for optimal staging of uveal melanoma liver metastases is small, the findings are consistent with the much larger experience with colorectal liver metastases where MRI with liver specific contrast is the most sensitive imaging modality for pre-operative staging. This concordance fits with what we already know about the sensitivity of PET CT. Similarly the false positive rate of PET CT for extrahepatic disease is as much a problem in ocular melanoma staging (Finger, Kurli et al. 2005) as it is with more common tumour groups such as colorectal cancer.
On balance, uveal melanoma liver metastases are best staged with liver specific contrast-enhanced MRI (Servois, Mariani et al. 2010, Orcurto, Denys et al. 2012) and extrahepatic disease with PET CT (Kurli, Reddy et al. 2005). As sub centimetre extrahepatic metastases can be missed on PET CT and some metastases can be PET-negative (Strobel, Bode et al. 2009), a contrast enhanced CT scan, either in addition or as part of PET CT, may increase the identification of small extrahepatic metastases.

One study (Strobel, Bode et al. 2009) showed that 50% of liver metastases were FDG PET negative. It also showed that if the liver metastases were PET negative, then so were the extrahepatic metastases. This would suggest that patients with PET-negative liver metastases need whole body CT for complete staging.

No studies were identified concerning the role of biopsy and histological confirmation in suspected metastatic uveal melanoma.

7.3.2. Question 2. Is there a preferred prognostic method for a patient with metastatic disease

Many of the published therapeutic studies incorporate prognostic factor evaluation using univariate and/or multivariate analysis. This most often represented institutional case series. Factors identified included tumour burden (maximum diameter of largest tumour, percentage of liver involvement, tumour volume, hepatomegaly, ascites), performance status, LFTs (e.g. ALP, LDH), gender, pattern of metastases and surgical resection outcome (R0 resection).

Several institutional series report on variates of survival and potential prognostic indices. (Eskelin, Pyrhonen et al. 2003) defined a potential prognostic model in 91 consecutive patients combining performance status, tumour diameter and ALP. A validated multivariate analysis reported by Eskelin 2007 may represent the most robust prognostication currently available. (Eskelin, Piperno-Neumann et al. 2007)

Retrospective review of 119 patients managed over a 10-year period at Memorial Sloan Kettering Cancer Centre identified five variates of survival: age < 60 years, long disease-free interval from initial diagnosis to metastatic disease, treatment with surgery or intrahepatic therapy, lung/soft tissue as the only site of disease and female gender (Rietschel, Panageas et al. 2005).

None of the putative prognostic factors have been formally evaluated or validated in prospective randomised controlled trials.

Four papers (Kodjikian, Grange et al. 2005, Shields, Ganguly et al. 2007, Frenkel, Nir et al. 2009, Patel, Winston et al. 2011) (Eskelin, Pyrhonen et al. 2003) looking at prognostic factors in patients with metastatic liver disease, all found a correlation between liver metastatic burden and survival. Each paper measured the disease burden in different ways: greater than 10 metastases in one paper (Kodjikian, Grange et al. 2005), and a volume greater than 100cm$^3$ of the largest metastasis in another (Patel, Winston et al. 2011) and found that both of these measures were poor prognostic indicators for survival. In addition to these, two other studies (Kodjikian, Grange et al. 2005, Patel, Winston et al. 2011) showed that involvement of the ciliary body at the time of primary diagnosis and the presence of ascites and hepatomegaly were independent negative prognostic factors. It was not stated whether the ascites was malignant or related to liver failure.
7.3.2.1. Following surgery
A clear resection margin has a significant impact on survival. The overall median survival in one study (Mariani, Piperno-Neumann et al. 2009) was 14 months following liver resection, but in the R0 group median survival was 68 months. Similarly, the median survival in another study (Frenkel, Nir et al. 2009) rose from 16.6 months to 65.6 months, when comparing R1/R2 with R0 resections, respectively.

Interestingly, the presence of extrahepatic disease was not found to correlate with a worse survival in one of the studies (Patel, Winston et al. 2011).

7.3.2.2. Following non-surgical liver treatment
Three studies (Gupta, Bedikian et al. 2010, Huppert, Fierlbeck et al. 2010, Heusner, Antoch et al. 2011) found that tumour burden (>9 metastases, >75 % liver replacement and >25% liver replacement respectively) was a poor prognostic factor in patients who underwent transarterial chemoembolization (TACE) (Gupta, Bedikian et al. 2010, Huppert, Fierlbeck et al. 2010) and isolated hepatic perfusion (IHP) (Heusner, Antoch et al. 2011). The baseline LDH level was also a negative prognostic factor in one of the TACE studies (Gupta, Bedikian et al. 2010).

The angiographic appearances of the liver metastases seen at the time of TACE have been shown to correlate with both the primary tumour location and with survival (Dayani, Gould et al. 2009). Compared to a nodular pattern of contrast distribution at angiography, an infiltrative pattern tends to be seen with primary tumours involving the ciliary body or those with extra-scleral spread (p=0.01). The nodular appearance is also significantly associated with improved survival following TACE (12.7 months) compared to the infiltrative pattern (3.7 months).

7.3.3. Question 3. What is the optimal management of systematic metastases?
7.3.3.1. Systemic Therapy
The evidence base reviewed consists of a heterogeneous collection of reports including single arm prospective clinical trials, retrospective single institution case series and subset analysis in unselected metastatic melanoma trials. Two of the larger uveal-specific trials included 48 patients (Becker, Terheyden et al. 2002, Schmittel, Schmidt-Hieber et al. 2006). The majority of studies evaluated conventional chemotherapy with a smaller number of reports including biological therapies, including immunotherapy.

Schmittel et al reported a progression-free benefit in the first and only published randomised phase II trial evaluating treosulfan versus gemcitabine and treosulfan in 48 patients (Schmittel, Schmidt-Hieber et al. 2006). No overall survival data were presented.

The objective response rate to systemic therapy was very low with stable disease most often reported. Despite this low response rate, single case responders were not uncommon irrespective of the therapy under evaluation. Progression-free and overall survival was not consistently reported with a range of PFS (1.5-3months) and OS (6-12months) reflecting heterogeneity of cases. The largest published case series of 201 uveal melanoma patients represents retrospective data from a single institutional experience and reported 1% response rate to systemic chemotherapy (Bedikian, Legha et al. 1995). Only 1 published randomised phase III trials evaluating systemic therapy against regional therapies or surgery was identified (Levyraz, Piperno-Neumann et al. 2014).
7.3.3.2. Emerging therapies

Two randomised clinical trials in patients with metastatic uveal melanoma confined to the liver have been completed although only one has been published following peer review. A randomised trial comparing percutaneous hepatic perfusion (PHP) of melphalan compared to best active care (BAC) (including systemic therapy) reported at the annual meeting of the American Society for Clinical Oncology (ASCO), patients in the PHP arm had a median PFS of 6.1 months compared with just 1.6 months with BAC (P≤0.001) (Pingpank, Hughes et al. 2010). Improvement in PFS did not appear to extend to overall survival (OS), which at 12 months was 26% with BAC and 29% with PHP although OS was confounded by crossover between the study arms. Median survival was 9.9 months versus 11.4 months respectively.

The EORTC 18021 trial is the largest prospective clinical trial completed to date in metastatic uveal melanoma and compared intrahepatic chemotherapy versus intravenous treatment (Leyvraz, Piperno-Neumann et al. 2014). Between February 2005 and February 2011, 171 patients were randomized (Hepatic intra-arterial (HIA): 86, Intravenous (IV): 85). Due to poor accrual, an interim analysis was performed after 134 deaths in order to test futility (power=79%). Intra-arterial chemotherapy led to a higher overall response rate (ORR) (12% versus 2%) and longer PFS (HR=0.62; 6-month rate 41% versus 27%; 1-year rate: 19% versus 8%) compared to IV administration but did not translate into an improvement in OS (median ~ 13.5 months).

Data from the SUAVE trial, a randomised study comparing sunitinib with dacarbazine in 74 patients, showed no significant difference in PFS or OS. Results were presented at ASCO 2013 (Sacco, Nathan et al. 2013).

7.3.3.3. Biological Therapies

Uveal melanoma is a unique clinical and molecular subtype of melanoma that has no known effective therapy in the metastatic setting. The increasing understanding of the underlying biology of uveal melanoma has led to the identification of a number of novel and promising therapeutic strategies that warrant investigation. Currently, an increasing number of novel agents are under evaluation in well-designed prospective and uveal-specific phase II clinical trials. A randomised phase II study in 98 patients compared selumetinib versus temozolamide has reported improved response rate and doubling of PFS (15.9 versus 7 weeks) (Carvajal 2013).

A number of case series have now reported on the activity of ipilimumab in patients with metastatic uveal melanoma. Luke et al (Luke, Callahan et al. 2013) reported 2 out of 34 patients having a radiological response with a median overall survival of 9.6 months. Maio et al (Maio, Danielli et al. 2013) also reported a 5% response rate in 84 patients with a median overall survival of 6 months, and Kelderman et al (Kelderman, van der Kooij et al. 2013) 1 patient out of 22 having a radiological response and a median overall survival of 5.2 months.

7.3.4. Question 4. What is the optimal treatment for oligometastatic disease outside the liver

In a single retrospective series of 12 patients with oligometastatic disease, two patients with lung metastases and one patient with a brain metastasis underwent metastatectomy. The remaining 9 patients had either liver only or liver plus extra-hepatic metastases (Aoyama, Mastrangelo et al. 2000). Median recurrence-free and overall 5-year survival was 15.6% and 53.3%, respectively for the whole series. A single case report of a solitary pulmonary metastatectomy was also identified (Komatsu, Sowa et al. 2013). The surgical cases were characterised by a long interval from initial diagnosis (median 8 years) and incidental detection in asymptomatic patients.
7.3.5. Question 5. What is the optimal management of liver only metastases?

**Intra-arterial treatments (chemotherapy infusion, chemoembolization, immunoembolisation).**

There is one randomised controlled trial evaluating optimal management with intra-arterial treatments. Studies are mostly small case series (Egerer, Lehnert et al. 2001), (Farolfi, Ridolfi et al. 2011), some comparing response rates with escalating doses of chemotherapy (Agarwala, Panikkar et al. 2004), others using different sorts of chemotherapy (Gupta, Bedikian et al. 2010) or combination chemotherapy (Melichar, Voboril et al. 2009). All case series made comparison with historical data sets. These studies provide preliminary support for the concept that regional therapy produces a higher response rate than systemic chemotherapy. The largest multi-centre case series (Peters, Voelter et al. 2006) of 101 patients receiving repeated intra-arterial fotemustine administrations, showed a median survival of 15 months and 2-year survival of 29%. In a small study (Fiorentini, Aliberti et al. 2009) assessing a series of 10 patients, irinotecan drug-eluting beads showed a response rate in up to 80% of patients, with a similar number experiencing an improvement in quality of life. Response rates were measured using modified RECIST. The results of another study (Yamamoto, Chervoneva et al. 2009) suggest that immunoembolisation may increase PFS of extrahepatic sites but the numbers are small.

7.3.5.1. Radioembolisation (selective internal radiation therapy)

No randomised controlled trials have been conducted for this relatively new technique. Two papers reported on radioembolisation, one a single-centre case series (Gonsalves, Eschelman et al. 2011), the other a multi-centre retrospective case series (Kennedy, Nutting et al. 2009). Both studies showed a response or stabilisation of disease in 63-100% of patients. This included heavily pre-treated patients (chemoembolization, immunoembolisation) in the larger study (32 patients) (Kennedy, Nutting et al. 2009, Gonsalves, Eschelman et al. 2011). The overall median survival was 10 months (PFS of hepatic metastases 4.7 months). A smaller pre-treatment liver tumour volume (<25%) improved survival (10.5 months) compared to patients who had >25% liver replacement (3.9 months). When compared to historical data sets, extrahepatic disease progression was a more prominent feature in this series of patients, presumably due to slowing of disease progression in the liver. The smaller study (Kennedy, Nutting et al. 2009) showed a high response rate (1 complete response, 6 partial responses, 1 stable disease, 1 progressive disease) at 3 months, with 80% survival at 1 year.

7.3.5.2. Percutaneous Isolated Hepatic Perfusion

There have been several technical papers reporting the development of isolated hepatic perfusion (IHP) to treat a variety of secondary liver tumours including uveal melanoma liver metastases (Alexander, Libutti et al. 2003, van Etten, de Wilt et al. 2009, Alexander 2012, Lindner, Rizell et al. 2012, Zager and Nutting 2012). Registry data from Sweden (Olofsson, Cahlin et al. 2014), which included 34 patients with uveal melanoma liver metastases who were treated with IHP, showed a median overall survival of 27 months, a 14 month improvement over historical patients not treated with IHP.

A randomised controlled cross-over trial (Alexander 2012) of 93 patients with ocular or cutaneous melanoma liver metastases comparing IHP with BAC demonstrated a median hepatic progression free-survival of 8.0 months with IHP melphalan versus 1.6 months with BAC. Up to 6 treatments were given every 4-8 weeks. The cross over design of the study meant that 57% of the BAC patients were also treated with IHP, which made survival benefit difficult to evaluate.
7.3.5.3. Surgery

Seven case series (Hsueh, Essner et al. 2004, Pawlik, Zorzi et al. 2006, Herman, Machado et al. 2007, Frenkel, Nir et al. 2009, Mariani, Piperno-Neumann et al. 2009, Caralt, Marti et al. 2011), mostly retrospective single centre studies, showed that in a highly selective patient group there is a survival benefit with surgery. The selection criteria include the absence of extra-hepatic disease after evaluation with CT/MRI and FDG-PET scans; disease-free interval longer than 24 months after the resection of the primary melanoma; presumed completely resectable lesions; low tumour burden; absence of clinical co-morbidities. One study (Pawlik, Zorzi et al. 2006), in 16 patients, showed that patients eligible for liver surgery based on performance status, no extrahepatic disease, and a favourable liver disease distribution had a significantly longer PFS and median overall survival (9 months and 29 months respectively). Many of the studies, however, included patients who received adjuvant chemotherapy.

Another study (Mariani, Piperno-Neumann et al. 2009) demonstrated that at >24 months from the primary resection, an R0 resection, < 5 metastases and absence of miliary disease were consistently found to be good prognostic factors. Some studies identified more extensive liver disease or unexpected extrahepatic disease in up to 44% at the time of surgery (Herman, Machado et al. 2007). Accurate staging is therefore vitally important to try to exclude these inoperable cases. In a large single centre surgical series 255 patients (Mariani, Piperno-Neumann et al. 2009), the R2 resection rate was 62%, which probably accounted for the post resection overall median survival being only 14 months. In the same study, the median survival of the R0 resections rose to 27 months. There is currently no evidence of survival benefit to support hepatic de-bulking surgery. This could be reconsidered should an effective hepatic regional or systemic therapy be shown to be of greater benefit in patients with small volume disease, in which case surgical de-bulking may prove to be an adjunct to these therapies. This would need to be investigated as part of a well-designed clinical trial.

7.3.6. Question 6. Is regional liver therapy more effective than systemic therapy

The question of optimal therapy for liver-only disease remains unanswered but of great relevance to both patients and clinicians. Whilst many studies combined systemic therapy with liver surgery or targeted liver intervention there were only a few papers that directly compared systemic treatment with liver treatment for patients with liver only metastatic disease. Two small randomised trials (Pingpank, Hughes et al. 2010, Leyvraz, Piperno-Neumann et al. 2014) have been completed and have been described above. Neither study was able to identify a survival advantage despite improved response rate and PFS. Furthermore, no data on quality of life is available from these studies.

7.3.7. Question 7. What is the role of surveillance following liver metastases treatment?

Despite improved overall survival following liver metastatectomy, the majority of patients will relapse a second time; thus patients who undergo R0 resection remain at high risk of further hepatic and extrahepatic relapse. No published studies were found addressing the question of continued surveillance in this highly selected population.
7.4. **Evidence Statements**

7.4.1. **Staging**

- Contrast enhanced MRI is superior to PET in staging liver disease. **Level 2+**
- AJCC/UICC TNM 7th edition includes simple staging by dividing M1 in M1a-M1c. **Level 3**
- Intrahepatic metastases less than 12 mm are often not detected on PET CT. **Level 3**
- Extrahepatic metastases less than 10 mm are often not detected on PET CT. **Level 3**
- Liver metastases can be PET-negative in up to 50% of patients. **Level 3**
- When liver metastases are PET-negative then so are the extrahepatic metastases. **Level 3**
- Small subcapsular or miliary liver metastases may not be detected on MRI. **Level 3**
- PET/CT can identify extra hepatic disease. **Level 3**
- No evidence was found that the FDG component of PET was useful in adding increased sensitivity for staging. **Level 3**
- There is insufficient evidence that any imaging technique is superior to any other in identifying extra-hepatic disease. **Level 3**

7.4.2. **Preferred prognostic method**

- Metastatic Tumour Burden (volume, diameter and number), LDH, ALP, gender, age, performance status, DFS have been shown to be prognostic factors. **Level 3**
- The validated Eskelin model may represent the most robust prognostication but the reported factors that have not been sufficiently investigated. **Level 2**
- The absence of liver disease (soft tissue metastasis) appears favourable to outcome. **Level 3**
- Post-treatment survival (surgical and non-surgical) is worse in patients with a greater liver tumour burden. **Level 3**
- Liver disease presenting <24 months after primary diagnosis has a worse prognosis. **Level 3**

**Following treatment**

- The presence of ascites at the time of surgery is associated with a worse prognosis. **Level 3**
- R0 resection achieves a significantly better prognosis than R1 or R2 resections. **Level 3**
- Post treatment survival (surgical and non-surgical) is worse in patients with a greater liver tumour burden. **Level 3**
- Ciliary body involvement is associated with a worse post resection prognosis. **Level 3**
- High pre-operative LDH levels are associated with a worse post resection prognosis. **Level 3**
- Defined tumours have a better prognosis than miliary tumours. **Level 3**

7.4.3. **Management of systemic disease**

- Response rates to chemotherapy are very low. **Level 3**
- No high quality evidence was found showing improved survival or quality of life following systemic therapies.
- A small subset of patients may have prolonged stable disease irrespective of the therapy delivered. **Level 3**
• There is no evidence that one chemotherapy regimen is superior to another in terms of outcome or quality of life. **Level 3**
• MEK inhibitors are an area requiring further evaluation. **Level 1+**
• Occasional patients appear to have benefit from treatment with ipilimumab. **Level 3**

### 7.4.4. Management of oligometastatic-extrahepatic metastatic disease
- Highly selected patients presenting with oligometastatic disease having had a significant disease-free interval may benefit from resection of metastasis. **Level 3**

### 7.4.5. Management of liver disease
- No evidence was identified for ablative techniques.
- In selected patients, curative liver resection is associated with longer survival in case series. **Level 3**
- There is no evidence of survival benefit to support hepatic de-bulking surgery. **Level 3**
- All the regional non-surgical techniques can reduce measurable tumour burden, but there is inadequate evidence to demonstrate an overall improvement in survival. **Level 1-**
- The data does not enable a differentiation that one intervention is superior to another in terms of outcomes. **Level 3**

### 7.4.6. Systemic versus targeted liver treatment
- There is no evidence that liver targeted treatment produces a better overall survival than systemic therapies.

### 7.4.7. Surveillance following liver treatment
- No evidence was found.

### 7.5. Recommendations
Refer to recommendations related to this chapter, which are in Section 1.2 by clicking [HERE](#).

### 7.6. Linking evidence to recommendations

#### 7.6.1. Staging
There was insufficient evidence to compare and contrast staging modalities in advanced uveal melanoma patients. In the absence of evidence, the view of the GDG was that the pattern of relapse in uveal melanoma metastatic disease should include imaging of the chest, abdomen and pelvis. Because of the low incidence of CNS metastases, the GDG were of the opinion that that routine brain imaging in the absence of symptoms was not justified. As bone metastases occur in a minority of patients the GDG thought that routine imaging with bone scan was not required in the absence of progressive symptoms.

There was evidence that PET CT can detect uveal melanoma metastases but as there was no strong evidence that this influences management or adds additional information above and beyond CT, the GDG did not recommend this. Whilst PET CT can detect metastases at all sites within the body it has a relatively high false negative rate due to either lesion size (<12 mm) or lack of FDG-avidity. Contrast-enhanced CT, which is also more widely available than PET CT, should be able to detect metastases below 10 mm in diameter at all sites imaged.
Liver surgery should only be considered when there is no evidence of extrahepatic disease, so accurate staging with imaging and pre-operative laparoscopy is vitally important. MRI for liver staging in other cancer groups is generally accepted to be the most accurate imaging modality. From the low volume of evidence available for the detection of uveal melanoma liver metastases, the GDG were of the opinion that contrast-enhanced MRI with the addition of DWI offers the best available non-user dependent imaging modality at present.

Overall the GDG felt that the combination of contrast enhanced MR liver and contrast-enhanced CT of the chest, abdomen and pelvis is the best and most easily available, at present, to stage a patient thought to have metastatic uveal melanoma.

7.6.2. Preferred prognostic method

No evidence was found to define a single validated prognostic tool for advanced uveal melanoma. A number of putative factors have been described but require validation in future prospective trials. In the absence of evidence, the view of the GDG was that prospective collection of these factors is recommended. Outside clinical trials, specialist centres should collaborate with the aim of developing a common central database that incorporates primary tumour details, staging information, treatment and outcomes, in order to collect data for future research to improve care.

Prognosis is likely to be related to a combination of factors: tumour biology, host immune response, disease volume, achievement of clear resection margins. Recognised poor prognostic indicators in patients with ocular melanoma liver metastases—e.g. tumour volume, ascites, early (<24 months) liver involvement following primary diagnosis and ciliary body involvement—are all apparent at the time of surgical assessment. They should be viewed as contraindications to liver surgery.

Liver resection, in carefully selected patients, gives the best chance of prolonged survival. R0 resection, however, is only determined following pathological review of the resected liver specimen. In the reviewed surgical studies, R0 resection was highly significant and the main determinant for prolonged survival.

7.6.3. Management

There was no evidence that current therapies impact on survival or quality of life for most patients with advanced uveal melanoma. Because of the current absence of evidence, the GDG were of the opinion that emphasis should be placed on developing and conducting well-designed clinical trials as a priority for all patients, particularly as there are a number of emerging novel therapies that hold promise but that require further validation before these can be considered as standards. Outside the clinical trial setting, conventional chemotherapy delivered according to local protocol or best supportive care remain valid options for selected patients following a full discussion with the patient of their own potential to benefit.

As in all studies, there was evidence that a small subset of patients may achieve protracted stable disease irrespective of the therapy; in the view of the GDG conventional chemotherapy should be reserved for patients with good performance status (PS 0-2) who may benefit. Good performance status patients should be managed in specialist centres with appropriate oncology expertise in uveal melanoma and that collaborate with hepatobiliary and interventional radiology services.
Liver surgery offers the best chance for long-term survival, but patient selection is vitally important to avoid R2 resections. Pre-operative laparoscopy may detect additional disease and should be performed in all patients. There is no evidence at present that de-bulking liver resection offers any survival benefit.

Whilst there is a trend towards improved survival with non-surgical treatments, the evidence is poor quality and low in volume. If the patient understands the palliative intent of the selected treatment, and is fully informed about the potential side effects, then liver targeted treatments could be considered. The available options have varying degrees of invasiveness, side effects, cost and need for repeated treatments. The choice of treatments offered varies between and across countries. Published studies are mostly based on case series with their inherent biases. Despite the fact that two small RCTs have failed to show a survival benefit for regional therapies over systemic therapy, in the absence of firmer evidence the GDG regarded regional therapy as a viable option to be considered for patients with liver predominant disease.

The GDG thought that, as a minimum, all patients treated with surgical or liver targeted interventions should be entered on a registry with an accompanying minimum data set. Ideally every patient should become part of a well-constructed clinical trial. All patients should be discussed at a specialist multidisciplinary team meeting and treatment should take place at recognised centres.

7.6.4. Surveillance following liver treatment

No evidence was identified to demonstrate whether a surveillance programme is useful following treatment for uveal melanoma metastases. It would seem reasonable to perform cross-sectional imaging soon after a surgical or non-surgical liver procedure (4–6 weeks) to assess treatment response. Thereafter, appropriate post-treatment imaging should be performed to identify disease recurrence at an early stage, which may be suitable for further intervention. It is recommended that the same imaging modality is used each time to aid the assessment of treatment response; contrast-enhanced MRI with DWI is thought to be the optimal choice.

8. Using and implementing the guideline

8.1. Potential organisational and financial barriers in applying its recommendation

The GDG recognises that the lack of evidence base is a significant challenge in defining standards in the context of a rare cancer. The GDG strongly supports the concept of greater specialisation to facilitate research and prospective audit and collaboration. Against this background, few barriers to implementation are anticipated amongst those who specialise in this condition. Where patients choose to receive local care, it is possible that individual trusts may view some aspects of follow up (e.g. surveillance) as an added resource pressure. The GDG considers this a potential barrier to implementation but are aware of the emerging consensus concerning follow-up imaging in high risk cutaneous melanoma, the very low incidence of uveal melanoma and the opportunity to support an element of centralised follow up in specialist centres.

The delivery of highly specialist regional therapies merits specific comment. The GDG does not consider the potential of curative liver surgery to be a barrier given existing resources and standards of care within NHS specialist hepatobiliary surgical teams. This is not the case with respect to the availability of regional
interventional therapies, which are considered options within the guideline. At present there is no nationally agreed funding stream within the NHS specialist commissioning for this aspect of care resulting in a lack of equity of access or agreed standards. The GDG recognise the critical importance of collaboration amongst specialist centres to facilitate research and evidence base in this area.

The NHS England Commissioning through Evaluation programme provides one platform to commission novel therapies and the GDG encourage all specialist uveal melanoma centres to engage and develop opportunities within this framework.
### 8.2. Audit criteria

<table>
<thead>
<tr>
<th>Audit standard</th>
<th>Guidance reference</th>
<th>Exceptions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with a diagnosis of melanoma enrolled on a national uveal melanoma register, based on a standardised minimum data set, with follow-up data collected at least annually</td>
<td></td>
<td>Patient consent withheld</td>
<td></td>
</tr>
<tr>
<td>All patients referred for an initial diagnosis within two weeks</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>All patients with a diagnosis or a suspected diagnosis of ocular melanoma are referred to one of the three specialist centres</td>
<td></td>
<td>Documented patient refusal</td>
<td></td>
</tr>
<tr>
<td>Documentation of a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks including:</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>- Risk of having the biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Limitations of the investigation</td>
<td></td>
<td></td>
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<tr>
<td>- Benefits for future treatments (including possible recruitment to trials)</td>
<td></td>
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<tr>
<td>- Impact on quality of life</td>
<td></td>
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<tr>
<td>- Recruitment to trials</td>
<td></td>
<td></td>
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<tr>
<td>The following features are recorded:</td>
<td></td>
<td>None</td>
<td></td>
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<tr>
<td>- Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gender</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Tumour location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tumour height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tumour Largest basal diameter</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Ciliary body involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Extraocular melanoma growth (macroscopic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The following features should be recorded if tissue is available:</td>
<td></td>
<td></td>
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<tr>
<td>- Cell type (modified Callender system)</td>
<td></td>
<td></td>
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<tr>
<td>- Mitotic count (number/40 high power fields in H&amp;E stained sections)</td>
<td></td>
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</tr>
</tbody>
</table>
- Presence of extravascular matrix patterns (particularly closed connective tissue loops).
- Presence of extraocular melanoma growth (size, presence of encapsulation or not).

Any local recurrences of the primary uveal melanoma are reported to a surgical ocular oncology centre.

All patients with technically resectable liver disease offered assessment for curative intent hepatic resection.

This minimum data set collected for all patients with systemic disease (Stage IV):
- Metastatic Tumour Burden (site, volume, diameter and number)
- LDH
- ALP
- GGT
- Bilirubin
- Presence or absence of ascites
- Gender
- Age
- Performance status,
- DFS following definitive primary therapy

All patients with systemic disease with or without liver involvement having whole staging (chest, abdomen and pelvis) with CT scan or PET CT

Patients with systemic disease should be considered for clinical trials and informed of available trial options at other centres.

<p>| | | |</p>
<table>
<thead>
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</table>

Documented patient refusal

No appropriate trial available, but consideration documented

Document type of trial entered (surgical, cytotoxic agent, targeted therapy, immune therapy, other biological)
9. Review and updates
The guideline was published on 13 January 2015 and a full copy of the guideline and appendices is available on http://melanomafocus.com/activities-2/um-guidelines-resources/. Melanoma Focus will take administrative and the chairman, or someone designated by the chairman, will take clinical responsibility for maintaining the guideline. GDG members will be asked to notify the chairman at any time, if new evidence makes any aspect of the Guideline unsafe. Annually, the chairman or designate will write to the GDG members and the consultees, who comprise many of the leaders in the field, asking if there has been any new evidence which would change the recommendations. At three year intervals, there will be a full search of the literature from the date of the last search to identify any new evidence which would change a recommendation. This will be reviewed by the chairman, or designate, and experts from the each of the four GDG sub-groups (Primary treatment, Prognostication, Surveillance and Metastatic disease). For any section of the Guideline which needs updating, the members of that subgroup will meet to review the evidence and agree changes. The re-drafted sections of the Guideline will be sent to the full GDG for agreement before publication. Only if there are several sections that need updating will the full GDG meet. Updates of the guideline should follow the methodology detailed in Uveal Melanoma Guideline Development Methodology (Link), which also contains further details of the update methods.

10. Research recommendations
- Linking the primary tumour genetics to metastatic genetics
- Establishment of a register to study the disease
- The sensitivity and specificity of liver ultrasound compared to MRI for screening for metastatic disease as part of primary treatment
- Role of a prognostic biopsy - does it identify the right group of patients to follow up the more intensively? There is a need to identify the risk at each stage, and then quantify the benefit.

Research/trials into systemic treatment options for metastatic disease

References


slow-release irinotecan-eluting beads. Early results of a phase II clinical study." In Vivo 23(1): 131-137.


Niekel, M. C., S. Bipat and J. Stoker (2010). "Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment." Radiology 257(3): 674-684.


Appendices

A – Extraction tables of Evidence (separate document)

B - Glossary and Acronyms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-angiogenic</td>
<td>Inhibiting the formation and differentiation of blood vessels.</td>
</tr>
<tr>
<td>Ascites</td>
<td>Accumulation of fluid in the spaces between tissues and organs in the abdomen</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Targeted radiotherapy when the radiation is placed in or near to the tumour.</td>
</tr>
<tr>
<td>Choroid</td>
<td>A vascular membrane between the retina and the sclera of the eye containing large branched pigment cells.</td>
</tr>
<tr>
<td>Choroidectomy</td>
<td>Removal of choroidal melanomas.</td>
</tr>
<tr>
<td>Ciliary body</td>
<td>A ring of made up mainly of muscle on the inner surface of the front wall of the eye. Consists of the ciliary body and ciliary processes, and is responsible for providing the fluid that nourishes the the lens and cornea of the eye.</td>
</tr>
<tr>
<td>Computed Tomography (CT)</td>
<td>A method to use X-rays to give a high resolution pictures of the inside of the body.</td>
</tr>
<tr>
<td>CyberKnife</td>
<td>A particular brand of equipment to deliver stereotactic radiosurgery (SRS).</td>
</tr>
<tr>
<td>Cyclectomy</td>
<td>Removal of small, ciliary body tumours.</td>
</tr>
<tr>
<td>Debulking</td>
<td>Removal of most or all of the tumour, thus reducing the size.</td>
</tr>
<tr>
<td>Embolisation</td>
<td>Introduction of pellets into the circulatory system in order to occlude blood vessels supplying the tumour.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Endoresection</td>
<td>The surgical removal of part of an organ or tumour from within.</td>
</tr>
<tr>
<td>Enucleation</td>
<td>Removal of the eye.</td>
</tr>
<tr>
<td>Exoresection</td>
<td>Removal of the tumour ‘en bloc’ through a large sclera opening.</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>Outside of the liver (commonly used for metastasis outside of the liver).</td>
</tr>
<tr>
<td>Exudative retinopathy</td>
<td>Damage to the retina caused by serum, fibrin (involved in blood clotting), and white blood cells leaked from blood vessels into the retina. Fibrin is an insoluble protein in response to bleeding and is the major component in a blood clot.</td>
</tr>
<tr>
<td>Fractionate</td>
<td>Splitting of a whole into different parts.</td>
</tr>
<tr>
<td>Fractionated stereotactic radiation treatments/therapy</td>
<td>Treatments of moderately high doses of radiation usually given over three to eight sessions (fractions).</td>
</tr>
<tr>
<td>Fundus of the eye</td>
<td>The interior surface of the eye, opposite the lens. It includes the retina, optic disc, macula and fovea, and posterior pole.</td>
</tr>
<tr>
<td>GammaKnife</td>
<td>A particular brand of equipment to deliver stereotactic radiosurgery (SRS).</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Enlargement of the liver.</td>
</tr>
<tr>
<td>Hypofractionated radiotherapy treatment</td>
<td>Radiation treatment split into large doses per timepoint (fraction) but giving less treatment doses (fractions) than with standard fractionation. A particular way to improve efficacy of radiation treatment.</td>
</tr>
<tr>
<td>Intraocular</td>
<td>Located within the eye.</td>
</tr>
<tr>
<td>Intraocular haemorrhage</td>
<td>Bleeding within the eye.</td>
</tr>
<tr>
<td>Iridectomy</td>
<td>Removal of the iris or parts of the iris to treat iris melanoma.</td>
</tr>
<tr>
<td>Iris</td>
<td>A thin, circular structure in the eye, responsible for controlling the diameter and size of the pupil and thus the amount of light reaching the retina.</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>A reduction of blood supply resulting from the blocking of an artery.</td>
</tr>
<tr>
<td>Laproscopy</td>
<td>Looking inside of the abdomen using a laparoscope.</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging (MRI)</td>
<td>A non-invasive diagnostic technique that produces computerized images of internal body tissues. It uses magnetic signals rather than X rays.</td>
</tr>
<tr>
<td>Miliary spread of melanoma</td>
<td>A large number of small nodules of melanoma that resemble grains of small seeds (of millet).</td>
</tr>
<tr>
<td>Monosomy 3</td>
<td>Loss of part of or of the whole of one of the two chromosomes three in cancer cells. Monosomy 3 is present in some uveal melanomas and then is linked with development of metastases and an increased risk of dying from uveal melanoma.</td>
</tr>
<tr>
<td>Neovascular glaucoma</td>
<td>The abnormal production of new blood vessels causing increased pressure in the eye.</td>
</tr>
<tr>
<td>Oedema</td>
<td>Swelling caused by fluid accumulating particularly in the abdomen.</td>
</tr>
<tr>
<td>Ophthalmoscopy</td>
<td>A visual examination with an instrument to look inside of the eye. The instrument is called an ophthalmoscope. Usually an uveal melanoma can be seen by ophthalmoscopy.</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>The functional part of an organ such as the liver.</td>
</tr>
<tr>
<td>Pars plana</td>
<td>Translates as ‘flat part’ – the outer ring of the ciliary body.</td>
</tr>
<tr>
<td>Pars plana vitrectomy</td>
<td>Surgical removal of vitreous body from the eye, with introduction of the instruments via the pars plana of the ciliary body.</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>Translates literally as ‘through the skin’. Used to describe a medical procedure where inner organs are accessed by needle-puncture of the skin, rather than by using an &quot;open&quot; approach where inner organs or tissue are exposed (typically with the use of a scalpel).</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Percutaneous ablative techniques</td>
<td>Removal or destruction of metastases using a percutaneous approach. This is usually the case for microwave and radiofrequency ablation or cryoablation.</td>
</tr>
<tr>
<td>Plaque therapy</td>
<td>A form of radiation therapy where a radioactive patch (plaque) is placed on or near the tumour from the outside of the eye for a period of time.</td>
</tr>
<tr>
<td>Porta hepatis</td>
<td>Also called the transverse fissure of the liver. It is a short fissure that extends across the under surface of the left portion of the right lobe of the liver. It contains a number of important structures of the liver (hepatic portal vein, hepatic artery proper, Common hepatic duct).</td>
</tr>
<tr>
<td>Proton beam therapy</td>
<td>A type of radiation treatment. Beams of particles, called protons, are aimed at the cancer bearing part of the eye.</td>
</tr>
<tr>
<td>R0 resection</td>
<td>Surgery at which a primary tumour or metastasis this is removed completely. No tumor is found at the edges (margins) of the removed tissue when examining the tissue under the microscope.</td>
</tr>
<tr>
<td>R1 resection</td>
<td>Surgery at which a primary tumour or metastasis this is removed as far as the eye can see. Under the microscope the tumour reaches the edges (margins) of the removed tissue.</td>
</tr>
<tr>
<td>R2 resection</td>
<td>After surgery visible residual tumour following is left behind.</td>
</tr>
<tr>
<td>Radiogenic retinopathy</td>
<td>Long term damage of the retina caused as a side effect of radiation treatment.</td>
</tr>
<tr>
<td>Resectable</td>
<td>When surgical removal of the tumour is possible.</td>
</tr>
<tr>
<td>Retina</td>
<td>The light-sensitive layer of tissue, lining the inner surface of the eye.</td>
</tr>
<tr>
<td>Retinopexy</td>
<td>A procedure to seal the retina to the surface beneath to stop it detaching.</td>
</tr>
<tr>
<td>Retinotomy</td>
<td>A surgical incision through the retina.</td>
</tr>
<tr>
<td>Sclera</td>
<td>The tough white outer layer of the eyeball.</td>
</tr>
<tr>
<td>Stereotactic</td>
<td>A technique for precisely directing the tip of a delicate instrument (as a needle) or multiple beams of radiation in three dimensions at a tumour or other lesion.</td>
</tr>
</tbody>
</table>
| Stereotactic Radiosurgery     | A one-session of high dose radiation using stereotactic methods. Like all radiotherapy is works by reducing or destroying the ability to the tumour to grow. There are three types
  - Particle beam (proton)
  - Cobalt-60 based (photon) e.g. Gamma Knife
  - Linear accelerator based (linac) e.g Cyber Knife
  It can be used to treat parts of the body that can remain or be held absolutely still during the treatment. |
<p>| Stereotactic resection        | The removal of the tumour using microsurgery with the aid of the stereotactic techniques. |
| Surgical Ocular Oncology Centre | One of three treatment centres in the UK that have nationally recognised expertise for the treatment of eye cancer including uveal melanoma. They are centrally funded through government. |
| Thermotherapy                 | The use of heat to treat a tumour. |
| Transcatheter arterial chemoembolization / Transarterial Chemoembolization (TACE) | Injection of small particles coated with chemotherapeutic drugs directly into an artery supplying a tumour. This restricts the tumour’s arterial blood supply and delivers chemotherapy directly to the target tissue. |
| Tumour seeding                | Spreading of cancer cells from the place the cancer started (primary) to another part to other parts of the body. This can be close to the primary (for example, in the eye) or distant (for example, the liver). |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uvea</td>
<td>The middle layer of the eye including the iris and ciliary body as well as the choroid.</td>
</tr>
<tr>
<td>Vitreous body</td>
<td>The clear jelly-like structure that fills the posterior part of the eyeball.</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>Bleeding into the vitreous body.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>BAC</td>
<td>Best Available Care</td>
</tr>
<tr>
<td>BCNU</td>
<td>Carmustine (bis-chloroethylnitrosourea)</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CGE</td>
<td>Cobalt Gray Equivalent</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease free survival</td>
</tr>
<tr>
<td>DTIC</td>
<td>Trade name for Dacarbazine</td>
</tr>
<tr>
<td>DWI</td>
<td>Density weighted imaging</td>
</tr>
<tr>
<td>ELND</td>
<td>Elective Lymph Node Dissection</td>
</tr>
<tr>
<td>FNAB</td>
<td>Fine Needle Aspiration Biopsy</td>
</tr>
<tr>
<td>FSRT</td>
<td>Fractionated Stereotactic Radiation Therapy</td>
</tr>
<tr>
<td>IE or CE</td>
<td>Immunoembolization/Chemoembolization</td>
</tr>
<tr>
<td>IFN or INF</td>
<td>Interferon Alfa-2b</td>
</tr>
<tr>
<td>IHIP</td>
<td>Isolated Hepatic Perfusion</td>
</tr>
<tr>
<td>IL-2</td>
<td>Interleukin-2</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>Intron-A</td>
<td>Interferon Alfa-2b</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver Function Test</td>
</tr>
<tr>
<td>MFS</td>
<td>Metastatic Free Survival</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NED</td>
<td>No Evidence of Disease</td>
</tr>
<tr>
<td>NVG</td>
<td>Neovascular Glaucoma</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PBR</td>
<td>Proton Beam Radiotherapy</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised control trials</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency Ablation</td>
</tr>
<tr>
<td>SIRT</td>
<td>Selective Internal Radiation Therapy</td>
</tr>
<tr>
<td>SLN</td>
<td>Sentinel Lymph Node</td>
</tr>
<tr>
<td>SNB or SLNB</td>
<td>Sentinel Node Biopsy/Sentinel Lymph Node Biopsy</td>
</tr>
<tr>
<td>SRS</td>
<td>Stereotactic Radiosurgery</td>
</tr>
<tr>
<td>TACE</td>
<td>Transcatheter Arterial Chemoembolization/ Transarterial Chemoembolization</td>
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<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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<tr>
<td>TNM</td>
<td>Tumor Node Metastasis staging system</td>
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<tr>
<td>UBM</td>
<td>Ultrasound Biomicroscopy</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
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<tr>
<td>WLE</td>
<td>Wide Local Excision</td>
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</table>
### C - Lists of Guideline Development Group members

<table>
<thead>
<tr>
<th>Dr/Patient Representative</th>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Paul</td>
<td>Nathan</td>
<td>Consultant Medical Oncologist</td>
<td>Mount Vernon Cancer Centre Northwood, Middlesex</td>
</tr>
<tr>
<td>Miss Victoria</td>
<td>Cohen</td>
<td>Consultant Ocular Oncologist Lead Clinician Ocular Oncology Service St Bartholomew’s and Moorfields Eye Hospital London</td>
<td></td>
</tr>
<tr>
<td>Prof Sarah</td>
<td>Coupland</td>
<td>George Holt Chair of Pathology and Deputy Head of Department Molecular and Clinical Cancer Medicine Honorary Consultant in Pathology University of Liverpool</td>
<td></td>
</tr>
<tr>
<td>Ms Kathryn</td>
<td>Curtis</td>
<td>Patient Representative OcuMel UK*</td>
<td></td>
</tr>
<tr>
<td>Prof Bertil</td>
<td>Damato</td>
<td>Moved to USA and did not attend meetings after May 2013, but contributed to the guideline electronically.</td>
<td>Hon. Professor of Ophthalmology Royal Liverpool University Hospital Liverpool</td>
</tr>
<tr>
<td>Dr Jonathan</td>
<td>Evans</td>
<td>Consultant Interventional Radiologist</td>
<td>The Royal Liverpool University Hospital Liverpool</td>
</tr>
<tr>
<td>Mr Stephen</td>
<td>Fenwick</td>
<td>Consultant Hepatobiliary Surgeon University Hospital Aintree, Liverpool</td>
<td></td>
</tr>
<tr>
<td>Dr Ji-Peng Olivia</td>
<td>Li</td>
<td>Ophthalmic Specialist Trainee, Moorfields Eye Hospital, London</td>
<td></td>
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<tr>
<td>Dr Lesley</td>
<td>Kirkpatrick</td>
<td>Patient Representative</td>
<td></td>
</tr>
<tr>
<td>Dr Ernie</td>
<td>Marshall</td>
<td>Macmillan Consultant in Medical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool</td>
<td></td>
</tr>
<tr>
<td>Mr Kieran</td>
<td>McGuirk</td>
<td>Patient Representative, Chair, OcuMel UK*</td>
<td></td>
</tr>
<tr>
<td>Mr Bruce</td>
<td>Oliver Resigned 2012</td>
<td>Patient Representative</td>
<td></td>
</tr>
<tr>
<td>Prof Christian</td>
<td>Ottensmeier</td>
<td>Professor in Experimental Cancer Medicine Consultant in Medical Oncology Southampton University Hospitals and University of Southampton</td>
<td></td>
</tr>
<tr>
<td>Mr Neil</td>
<td>Pearce</td>
<td>Consultant Hepatobiliary and Pancreatic Surgeon, University</td>
<td></td>
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</tbody>
</table>
* Ms Curtis and Mr McGuirk shared attendance at GDG meeting. When neither could attend Mr Rob Cheek, another member of OcuMel board, attended. Sadly, Kieran died in September 2014.
### D- GDG Declarations of Interest tables

<table>
<thead>
<tr>
<th>First Name</th>
<th>Last Name</th>
<th>DOI last updated</th>
<th>Personal Pecuniary</th>
<th>Non-personal pecuniary</th>
<th>National body</th>
<th>Stated personal opinion</th>
<th>Editorial</th>
<th>Patents</th>
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</thead>
<tbody>
<tr>
<td>Paul</td>
<td>Nathan</td>
<td>12/10/2014</td>
<td>Member of advisory committees for pharmaceutical companies with drugs in development for melanoma (GSK, Roche, Astra Zeneca and BMS) -Reported at meeting 1</td>
<td>Chief UK investigator on the SUMIT study</td>
<td>Melanoma Focus Trustee Member of NCRI Melanoma Clinical Studies Group Ex-secretary melanoma study group</td>
<td>-</td>
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<tr>
<td>Victoria</td>
<td>Cohen</td>
<td>10/07/2013</td>
<td>-</td>
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<tr>
<td>Sarah</td>
<td>Coupland</td>
<td>10/07/2013</td>
<td>-</td>
<td>CRUK sponsorship for collection of clinical samples collected during the ITEM and SUAVE studies (Novartis and Pfizer) Reported at meeting 1</td>
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<tr>
<td>Kathryn</td>
<td>Curtis</td>
<td>10/07/2013</td>
<td>-</td>
<td>-</td>
<td>Chair of trustees of OcuMel</td>
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<tr>
<td>Bertil</td>
<td>Damato</td>
<td>02/04/2012</td>
<td>-</td>
<td>Have received support from Bebig (manufacturing plaques), Ellex (manufacturing ocular ultrasound machines) and Optos (manufacturing cameras).</td>
<td>See PubMed articles Receive royalties for textbooks or chapters relating to uveal tumours.</td>
<td>-</td>
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<tr>
<td>Jonathan</td>
<td>Evans</td>
<td>07/08/2013</td>
<td>Involvement in the Delcath system Reported at meeting 1</td>
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<tr>
<td>Stephen</td>
<td>Fenwick</td>
<td>10/07/2013</td>
<td>-</td>
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<tr>
<td>Lesley</td>
<td>Kirkpatrick</td>
<td>10/07/2013</td>
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<tr>
<td>Olivia</td>
<td>Li</td>
<td>01/03/2012</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ernie</td>
<td>Marshall</td>
<td>10/07/2013</td>
<td>-</td>
<td>Pharmaceutical company sponsored drug trials - ITEM and SUAVE</td>
<td>NCRI, Melanoma CGG</td>
<td>Screening, psychology and treatment</td>
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<tr>
<td>Kieran</td>
<td>McGuirk</td>
<td>10/07/2013</td>
<td>-</td>
<td>-</td>
<td>Chair of trustees of OcuMel</td>
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<tr>
<td>Bruce</td>
<td>Oliver</td>
<td>04/03/2012</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Christian</td>
<td>Ottensmeier</td>
<td>10/07/2013</td>
<td>Consulting for Bristol Myers Squibb and Novatis</td>
<td>Research funding for a clinical trial for Ipilimumab for lung cancer</td>
<td>-</td>
<td>Strong opinion that immunology plays a role. (Reported at meeting 1)</td>
<td>-</td>
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<tr>
<td>Neil</td>
<td>Pearce</td>
<td>03/01/2012</td>
<td>-</td>
<td>-</td>
<td>I have written patient advice for the OcuMelUK website / patient forum on surgical aspects of management of metastatic uveal melanoma</td>
<td>See above re OcuMelUK,</td>
<td>-</td>
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<tr>
<td>Brian</td>
<td>Stedman</td>
<td>27/04/2012</td>
<td>Sponsorship from radiology providers. ‘Temmis’ - Manufacturers, DP beamis/TACE, Medical Advisor for and sponsorship from SIRTX</td>
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<td>Sachin</td>
<td>Salvi</td>
<td>10/07/2013</td>
<td>-</td>
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<td>National Ocular Oncology Group</td>
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<tr>
<td>Peter</td>
<td>Szlosarek</td>
<td>15/6/14</td>
<td>Sponsored by BMI to attend ASCO conference 2014</td>
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<tr>
<td>Nancy</td>
<td>Turnbull</td>
<td>01/07/2013</td>
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</table>
E - Guideline Reviewers

Individuals and organisations involved in the care of patients with uveal melanoma were invited to review the draft guideline. The invitation to review the guideline was also posted on the Melanoma Focus website. The GDG are grateful to the organisations and colleagues who took the not inconsiderable time to read the guideline and provide comments. These were:

Organisations

- British Society of Interventional Radiology
- British Oculoplastic Surgery Society
- EORTC Ocular Group
- International society of ocular oncology
- International Eye Cancer website
- Melanoma Focus
- OcuMel
- The Royal College of Radiologists

Individuals

| Dr Ruth Board | Consultant medical oncologist | Lancashire teaching hospital. |
| Dr Richard Carvajal | | Memorial Sloan-Kettering Cancer Center New York USA |
| Dr Pippa Corrie | Consultant and Associate Lecturer in Medical Oncology | Cambridge University Hospitals NHS Foundation Trust (Addenbrooke’s Hospital) |
| Dr Sarah Danson | Medical Oncologist | Royal Hallamshire Hospital, Sheffield |
| Ms Sheena Dryden | Nurse specialist | NHS Lothian, Scotland |
| Ms Rhona Jacques | Nurse specialis | Royal Hallamshire Hospital, Sheffield |
| Dr Nasir Khan | Interventional Radiologist | Royal Marsden, London |
| Prof Tero Kivela | Professor and Chair, Department of Ophthalmology | Helsinki University Central Hospital Helsinki, Finland |
| Mr Ali Majeed | Liver Surgeon | Royal Hallamshire Hospital, Sheffield |
| Dr Hardeep Singh Mudhar | Consultant Ophthalmic Histopathologist, | Royal Hallamshire Hospital, Sheffield |
| Mr Bruce Oliver | Patient | Yorkshire |
The following appendices are posted separately on the website of Melanoma Focus

- Guideline Development Methodology
- Summary of Information (for patients, carers and public)
- Consultation Comments & GDG Responses
- Presentations of Evidence Used at GDG Meetings
- PowerPoint Presentation of Key Points (for use in training)

In addition the NICE accreditation application and report are publically available from NICE.