Uveal Melanoma National Guidelines Summary

January 2015

Authors:

Nathan P, Cohen V, Coupland S, Curtis K, Damato B, Evans J, Fenwick S, Kirkpatrick L, Li O, Marshall E, McGuirk K, Ottensmeier C, Pearce N, Salvi S, Stedman B, Szlosarek P, Turnbull N

This project is the independent work of the Uveal Melanoma Guideline Development Group

and is funded by Melanoma Focus (http://melanomafocus.com/)

Uveal Melanoma

1. Introduction

1.1. Aim of the guideline

The aim of these guidelines is to optimise patient care by providing recommendations based on the best available scientific evidence. These guidelines should assist the planning of patient care and provide an indication of the likely clinical outcomes, as well as facilitating patient counselling and informed decision-making. Where adequate evidence is lacking, the 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.

1.2. Background

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-UICC 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, Makitie et al. 2003, Diener-West, Reynolds et al. 2005, Marshall, Romaniuk et al. 2013). The risk of metastatic relapse for an individual varies greatly dependent on primary tumour characteristics and genetic alterations.

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.

1.3. Strengths and limitations of the evidence

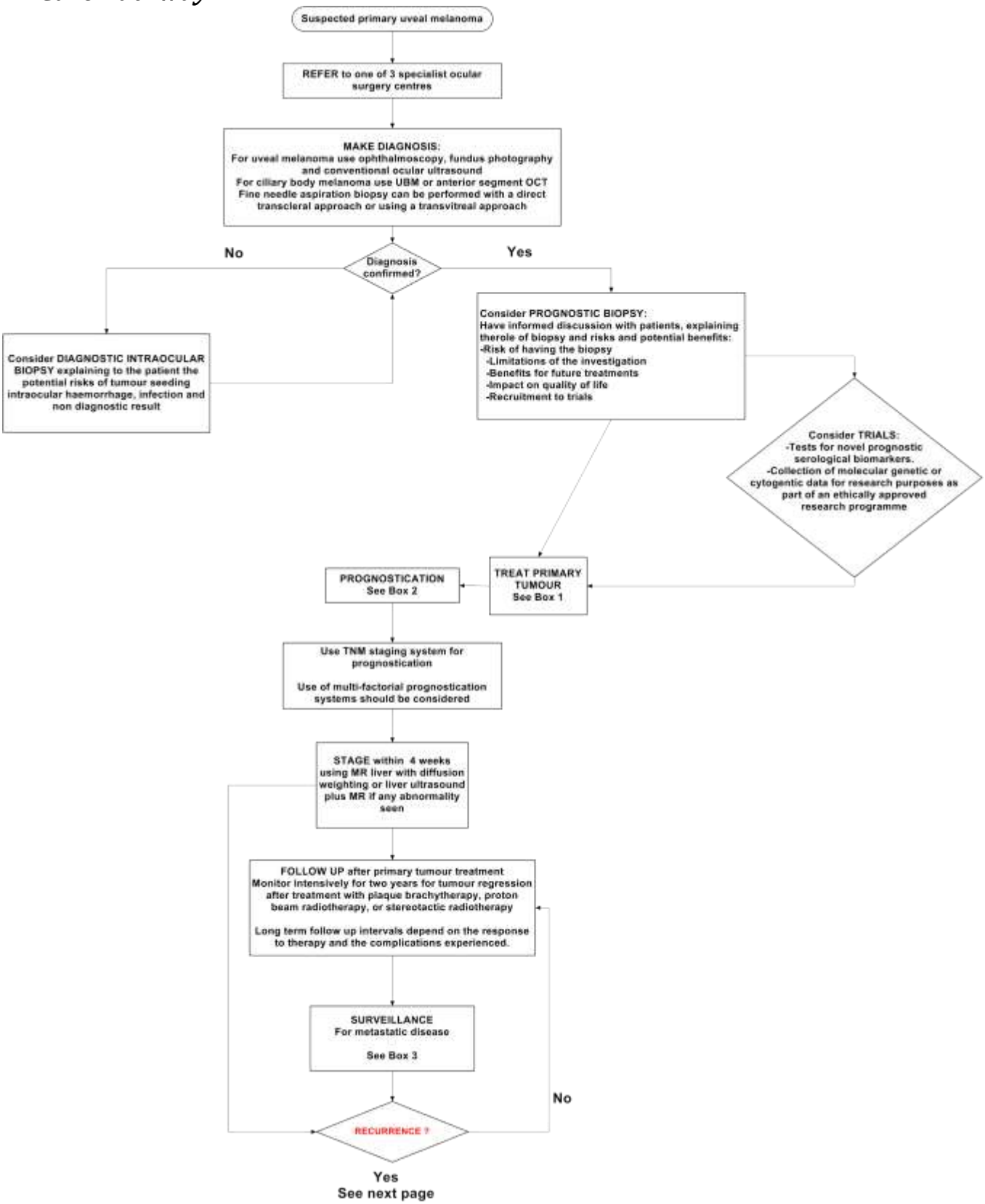
Due to the rarity of uveal melanoma and associated poor prognosis, there is limited clinical evidence guiding the optimal treatment of metastatic disease. Most reports in the literature are of small case series of ten or fewer patients. Larger non-randomised studies were scrutinised carefully for a survival bias as mortality is so high. With regard to treatment of primary tumours, each 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

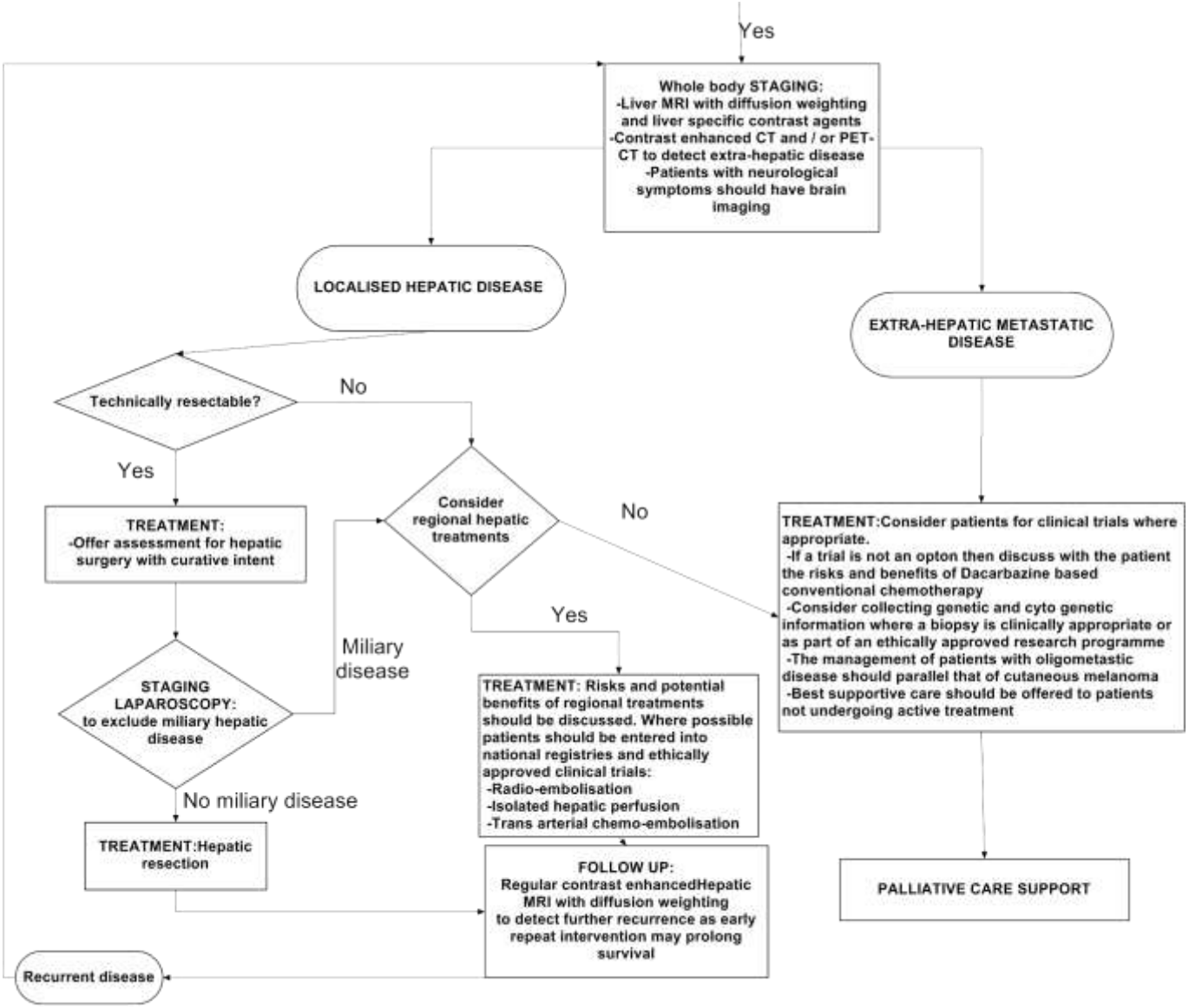
are no randomised comparative trials (RCT) from the UK. The COMS study (Collaborative Ocular Melanoma Study (http://www.jhu.edu/wctb/coms/) in the US has provided a valuable source of data; however, overall, the limitations of the evidence base in the literature are considerable. The COMS study is discussed in more detail in section 4.

1.4. Risks versus benefits

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

1.1 Care Pathway




Yes
Whole body STAGING:
-Liver MRI with diffusion weighting and liver specific contrast agents
-Contrast enhanced CT and / or PET-CT to detect extra-hepatic disease
-Patients with neurological symptoms should have brain imaging
LOCALISED HEPATIC DISEASE
EXTRA-HEPATIC METASTATIC DISEASE
Technically resectable?
No
Yes
TREATMENT:
-Offer assessment for hepatic surgery with curative intent
Consider regional hepatic treatments
No
Yes
TREATMENT:Consider patients for clinical trials where appropriate.
-If a trial is not an opton then discuss with the patient the risks and benefits of Dacarbazine based conventional chemotherapy
-Consider collecting genetic and cyto genetic information where a biopsy is clinically appropriate or as part of an ethically approved research programme
-The management of patients with oligometastic disease should parallel that of cutaneous melanoma
-Best supportive care should be offered to patients not undergoing active treatment
STAGING LAPAROSCOPY:
to exclude miliary hepatic disease
Miliary disease
TREATMENT: Risks and potential benefits of regional treatments should be discussed. Where possible patients should be entered into national registries and ethically approved clinical trials:
-Radio-embolisation
-Isolated hepatic perfusion
-Trans arterial chemo-embolisation
No miliary disease
TREATMENT:Hepatic resection
FOLLOW UP:
Regular contrast enhancedHepatic MRI with diffusion weighting to detect further recurrence as early repeat intervention may prolong survival
PALLIATIVE CARE SUPPORT
Recurrent disease

BOX 1 TREATMENT OPTIONS

Treatment	Used for	Outcomes	Complications	Comments
RADIOTHERAPY				
Brachytherapy Ruthenium 106 Iodine 125	Small/Medium /Large uveal melanoma <20mm in basal diameter	Good local tumour control	Loss of vision Tumour recurrence	Dose and position of plaque can be adjusted to limit the loss of vision
Proton Beam radiotherapy	Medium to Large uveal melanoma which can not be treated with brachytherapy or resection	Good local tumour control	Loss of vision Loss of the eye from neovascular glaucoma Tumour recurrence	Not available in all ocular oncology units
Stereotactic radiosurgery	Juxta papillary uveal melanoma ; patients unsuitable for ruthenium plaque or unfit for surgery	Good local tumour control	Loss of vision Radiation related complications. Tumour recurrence	Not available in all ocular oncology units
PHOTOTHERAPY				
Transpupillary thermotherapy	Local recurrence and of adjuvant therapy of uveal melanoma	Improves local tumour control	Loss of vision Extraocular tumour recurrence	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
Photodynamic therapy	Small melanoma	Uncertain	Tumour recurrence	Avoids radiotherapy complications New treatment option not widely used for uveal melanoma. This is an experimental treatment.
SURGERY				
Exoresection +/- plaque	Medium to large melanoma with a narrow basal diameter	Variable	Retinal detachment Loss of vision Loss of the eye Tumour recurrence Risk of orbital dissemination of tumour	Only performed in limited centres. Always performed with brachytherapy to reduce the risk of recurrence.
Endoresection +/- radiotherapy	Medium-sized uvela melanoma. Toxic tumour syndrome post PBR	Variable	Transient intraocular haemorrhage; Rarely tumour seeding	Only performed in limited centres in the UK
Enucleation	Large uveal melanoma Melanoma associated with neovascular glaucoma +/- extensive retinal detachment	100% local tumour control if completely excised	Socket related complications. Orbital recurrence	Cosmetic results are reasonably good with an orbital implant and artificial eye
Exenteteration	Large extra-ocular extension after uveal melanoma	100% local tumour control if completely excised	Orbital recurrence	Rarely performed in the UK.

BOX 2 PROGNOSTICATION

The following features should be recorded:

- Age
- Gender
- Tumour location
- Tumour height
- Tumour Largest basal diameter
- Ciliary body involvement
- Extraocular 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 used within

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 the full guideline) 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.

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 (MDT), 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 of 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.

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.

2. Recommendations

The grading of the recommendations is detailed in the Methodology.

2.1.1. 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]**

2.1.2. 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]**

2.1.3. 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]**

2.1.4. 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**

Treatment	Used for	Outcomes	Complications	Comments	Grade of recommendations
RADIOTHERAPY					
Brachytherapy Ruthenium 106 Iodine 125	Small/Medium /Large uveal melanoma* <20mm in basal diameter	Good local tumour control	Loss of vision Tumour recurrence	Dose and position of plaque can be adjusted to limit the loss of vision	Grade A
Proton Beam radiotherapy	Medium to Large uveal melanoma which cannot be treated with brachytherapy or resection	Good local tumour control	Loss of vision Loss of the eye from neovascular glaucoma Tumour recurrence	Not available in all ocular oncology units	Grade C
Stereotactic radiosurgery	Juxta-papillary uveal melanoma ; patients unsuitable for ruthenium plaque or unfit for surgery	Good local tumour control	Loss of vision Radiation related complications Tumour recurrence	Not available in all ocular oncology units	Grade C
PHOTOTHERAPY					
Transpupillary thermotherapy	Local recurrence and of adjuvant therapy of uveal melanoma	Improves local tumour control	Loss of vision Extraocular tumour recurrence	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.	Grade C
Photodynamic therapy	Small melanoma	Uncertain	Tumour recurrence	Avoids radiotherapy complications New treatment option not widely used for uveal melanoma. This is an experimental treatment.	Grade D
SURGERY					

Exoresection +/- plaque	Medium to large melanoma with a narrow basal diameter	Variable	Retinal detachment Loss of vision Loss of the eye Tumour recurrence Risk of orbital dissemination of tumour	Rarely performed in the UK. Only performed in limited centres. Always performed with brachytherapy to reduce the risk of recurrence	Grade C
Endoresection +/- radiotherapy	Medium-sized uveal melanoma. Toxic tumour syndrome post PBR	Variable	Transient intraocular haemorrhage; Rarely tumour seeding	Only performed in limited centres in the UK	Grade D
Enucleation	Large uveal melanoma Melanoma associated with NVG +/- extensive retinal detachment	100% local tumour control if completely excised	Socket related complications Orbital recurrence	Cosmetic results are reasonably good with an orbital implant and artificial eye	Grade A
Exenteteration	Large extra-ocular extension after uveal melanoma	100% local tumour control if completely excised	Orbital recurrence	Rarely performed in the UK.	Grade D

* = 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 of the response of the tumour to brachytherapy and the radiotherapy complications experienced. [GPP]

2.1.5. 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**

2.1.6. 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** Error! Reference source not found.**) of developing etastases 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**

2.1.7. 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. **Loco-regional treatment for the management of oligometastatic disease (i.e. when metastases are limited to a single or limited number of organs) should be considered. This may include surgery, stereotactic treatment or other forms of ablation. [GPP]**

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]**

3. Using and implementing the guideline

3.1. 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 (eg 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.

3.2. Audit criteria

Audit standard	**Guidance reference**	**Exceptions**	**Comments**
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		Patient consent withheld	
All patients referred for an initial diagnosis within two weeks		None	
All patients with a diagnosis or a suspected diagnosis of ocular melanoma are referred to one of the three specialist centres		Documented patient refusal	
Documentation of a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks including: – 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		None	
The following features are 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)		None	

– 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.		Documented patient refusal	
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.		No appropriate trial available, but consideration documented	Document type of trial entered (surgical, cytotoxic agent, targeted therapy, immune therapy, other biological)

4. Review and updates

The guideline was published 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 in *Uveal Melanoma Guideline Development Methodology* (Link), which also contains further details of the update methods.

5. 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

Augsburger, J. J., Z. M. Correa and A. H. Shaikh (2009). "Effectiveness of Treatments for Metastatic Uveal Melanoma." American journal of ophthalmology 148(1): 119-127.

Cheung, M., J. Talarchek, K. Schindeler, E. Saraiva, L. S. Penney, M. Ludman and J. R. Testa (2013). "Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma." Cancer Genet 206(5): 206-210.

Coupland, S. E., S. L. Lake, M. Zeschnigk and B. E. Damato (2013). "Molecular pathology of uveal melanoma." Eye (Lond) 27(2): 230-242.

Damato, B., A. Eleuteri, A. F. Taktak and S. E. Coupland (2011). "Estimating prognosis for survival after treatment of choroidal melanoma." Prog Retin Eye Res 30(5): 285-295.

Damato, E. M. and B. E. Damato (2012). "Detection and time to treatment of uveal melanoma in the United Kingdom: an evaluation of 2,384 patients." Ophthalmology 119(8): 1582-1589.

Diener-West, M., S. M. Reynolds, D. J. Agugliaro, R. Caldwell, K. Cumming, J. D. Earle, B. S. Hawkins, J. A. Hayman, I. Jaiyesimi, L. M. Jampol, J. M. Kirkwood, W. J. Koh, D. M. Robertson, J. M. Shaw, B. R. Straatsma, J. Thoma and G. Collaborative Ocular Melanoma Study (2005). "Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26." Arch Ophthalmol 123(12): 1639-1643.

Finger, P. T. and The 7th Edition AJCC-UICC Ophthalmic Oncology Task Force (2009). "The 7th edition AJCC staging system for eye cancer: an international language for ophthalmic oncology." Arch Pathol Lab Med 133(8): 1197-1198.

Kujala, E., B. Damato, S. E. Coupland, L. Desjardins, N. E. Bechrakis, J. D. Grange and T. Kivela (2013). "Staging of ciliary body and choroidal melanomas based on anatomic extent." J Clin Oncol 31(22): 2825-2831.

Kujala, E., T. Makitie and T. Kivela (2003). "Very long-term prognosis of patients with malignant uveal melanoma." Invest Ophthalmol Vis Sci 44(11): 4651-4659.

Lorigan, J. G., S. Wallace and G. M. Mavligit (1991). "The prevalence and location of metastases from ocular melanoma: imaging study in 110 patients." AJR Am J Roentgenol 157(6): 1279-1281.

Marshall, E., C. Romaniuk, P. Ghaneh, H. Wong, M. McKay, M. Chopra, S. E. Coupland and B. E. Damato (2013). "MRI in the detection of hepatic metastases from high-risk uveal melanoma: A prospective study in 188 patients." British Journal of Ophthalmology 97(2): 159-163.

McLaughlin, C. C., X. C. Wu, A. Jemal, H. J. Martin, L. M. Roche and V. W. Chen (2005). "Incidence of noncutaneous melanomas in the U.S." Cancer 103(5): 1000-1007.

Patel, K. A., N. D. Edmondson, F. Talbot, M. A. Parsons, I. G. Rennie and K. Sisley (2001). "Prediction of prognosis in patients with uveal melanoma using fluorescence in situ hybridisation." Br J Ophthalmol 85(12): 1440-1444.

Reidy, J. J., D. J. Apple, R. L. Steinmetz, J. M. Craythorn, K. Loftfield, S. C. Gieser and S. E. Brady (1985). "Melanocytoma: nomenclature, pathogenesis, natural history and treatment." Surv Ophthalmol 29(5): 319-327.

Saornil, M. A. (2004). "Iris colour and uveal melanoma." Can J Ophthalmol 39(4): 448-452.

Shields, C. L., M. Furuta, E. Berman, J. Zahler, D. Hoberman, D. Dinh, A. Mashayekhi and J. A. Shields (2009). "Choroidal nevus transformation into melanoma: Analysis of 2514 consecutive cases." Archives of Ophthalmology 127(8): 981-987.

Shields, C. L., M. Furuta, A. Thangappan, S. Nagori, A. Mashayekhi, D. R. Lally, C. C. Kelly, D. S. Rudich, A. V. Nagori, O. A. Wakade, S. Mehta, L. Forte, A. Long, E. F. Dellacava, B. Kaplan and J. A. Shields (2009). "Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes." Arch Ophthalmol 127(8): 989-998.

Shields, C. L., J. A. Shields, M. Materin, E. Gershenbaum, A. D. Singh and A. Smith (2001). "Iris melanoma: risk factors for metastasis in 169 consecutive patients." Ophthalmology 108(1): 172-178.

Singh, A. D., P. De Potter, B. A. Fijal, C. L. Shields, J. A. Shields and R. C. Elston (1998). "Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis." Ophthalmology 105(1): 195-198.

Singh, A. D., I. G. Rennie, S. Seregard, M. Giblin and J. McKenzie (2004). "Sunlight exposure and pathogenesis of uveal melanoma." Surv Ophthalmol 49(4): 419-428.

Sisley, K., M. A. Parsons, J. Garnham, A. M. Potter, D. Curtis, R. C. Rees and I. G. Rennie (2000). "Association of specific chromosome alterations with tumour phenotype in posterior uveal melanoma." Br J Cancer 82(2): 330-338.

Smith, J. H., L. Padnick-Silver, A. Newlin, K. Rhodes and W. S. Rubinstein (2007). "Genetic study of familial uveal melanoma: association of uveal and cutaneous melanoma with cutaneous and ocular nevi." Ophthalmology 114(4): 774-779.

Virgili, G., G. Gatta, L. Ciccolallo, R. Capocaccia, A. Biggeri, E. Crocetti, J. M. Lutz, E. Paci and E. W. Group (2008). "Survival in patients with uveal melanoma in Europe." Arch Ophthalmol 126(10): 1413-1418.

Willson, J. K. V., D. M. Albert, W. M. Diener, L. McCaffrey, C. S. Mo, R. E. Scully, N. Robinson and M. Zimbric (2001). "Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the collaborative ocular melanoma study coms report no. 15." Archives of Ophthalmology 119: 670-676.

Appendices

A - Glossary and Acronyms

Anti-angiogenic	Inhibiting the formation and differentiation of blood vessels.
Ascites	Accumulation of fluid in the spaces between tissues and organs in the abdomen
Brachytherapy	Targeted radiotherapy when the radiation is placed in or near to the tumour.
Choroid	A vascular membrane between the retina and the sclera of the eye containing large branched pigment cells.
Choroidectomy	Removal of choroidal melanomas.
Ciliary body	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.
Computed Tomography (CT)	A method to use X-rays to give a high resolution pictures of the inside of the body.
CyberKnife	A particular brand of equipment to deliver stereotactic radiosurgery (SRS).

Cyclectomy	Removal of small, ciliary body tumours.
Debulking	Removal of most or all of the tumour, thus reducing the size.
Embolisation	Introduction of pellets into the circulatory system in order to occlude blood vessels supplying the tumour.
Endoresection	The surgical removal of part of an organ or tumour from within.
Enucleation	Removal of the eye.
Exoresection	Removal of the tumour 'en bloc' through a large sclera opening.
Extrahepatic	Outside of the liver (commonly used for metastasis outside of the liver).
Exudative retinopathy	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.
Fractionate	Splitting of a whole into different parts.
Fractionated stereotactic radiation treatments/therapy	Treatments of moderately high doses of radiation usually given over three to eight sessions (fractions).
Fundus of the eye	The interior surface of the eye, opposite the lens. It includes the retina, optic disc, macula and fovea, and posterior pole.
GammaKnife	A particular brand of equipment to deliver stereotactic radiosurgery (SRS).
Hepatomegaly	Enlargement of the liver.
Hypofractionated radiotherapy treatment	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.
Intraocular	Located within the eye.
Intraocular haemorrhage	Bleeding within the eye.
Iridectomy	Removal of the iris or parts of the iris to treat iris melanoma.
Iris	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.
Ischaemia	A reduction of blood supply resulting from the blocking of an artery.
Laproscopy	Looking inside of the abdomen using a laparoscope.
Magentic Resonance Imaging (MRI)	A non-invasive diagnostic technique that produces computerized images of internal body tissues. It uses magnetic signals rather than X rays.
Miliary spread of melanoma	A large number of small nodules of melanoma that resemble grains of small seeds (of millet).
Monosomy 3	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.
Neovascular glaucoma	The abnormal production of new blood vessels causing increased pressure in the eye.
Oedema	Swelling caused by fluid accumulating particularly in the abdomen.
Ophthalmoscopy	A visual examination with an instrument to look inside of the eye. The instrument is called an ophtalmoscope. Usually an uveal melanoma can be seen by ophthalmoscopy.
Parenchyma	The functional part of an organ such as the liver.
Pars plana	Translates as 'flat part' – the outer ring of the ciliary body.
Pars plana vitrectomy	Surgical removal of vitreous body from the eye, with introduction of the instruments via the pars plana of the ciliary body.
Percutaneous	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 "open" approach where inner organs or tissue are exposed (typically with the use of a scalpel).
Percutaneous ablative techniques	Removal or destruction of metastases using a percutaneous approach. This is usually the case for microwave and radiofrequency ablation or cryothearapy.
Plaque therapy	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.
Porta hepatis	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).
Proton beam therapy	A type of radiation treatment. Beams of particles, called protons, are aimed at the cancer bearing part of the eye.
R0 resection	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.
R1 resection	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.
R2 resection	After surgery visible residual tumour following is left behind.
Radiogenic retinopathy	Long term damage of the retina caused as a side effect of radiation treatment.
Resectable	When surgical removal of the tumour is possible.
Retina	The light-sensitive layer of tissue, lining the inner surface of the eye.
Retinopexy	A procedure to seal the retina to the surface beneath to stop it detaching.
Retinotomy	A surgical incision through the retina.
Sclera	The tough white outer layer of the eyeball.
Stereotactic	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.
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 hel absolutely still during the treatment.
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).
Uvea	The middle layer of the eye including the iris and ciliary body as well as the choroid.
Vitreous body	The clear jelly-like structure that fills the posterior part of the eyeball.
Vitreous haemorrhage	Bleeding into the vitreous body.

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

B - Guideline Development Group members

Dr	Paul	Nathan		Consultant Medical Oncologist Mount Vernon Cancer Centre Northwood, Middlesex
Miss	Victoria	Cohen		Consultant Ocular Oncologist Lead Clinician Ocular Oncology Service St Bartholomew's and Moorfields Eye Hospital London
Prof	Sarah	Coupland		George Holt Chair of Pathology and Deputy Head of Department Molecular and Clinical Cancer Medicine Honorary Consultant in Pathology University of Liverpool
Ms	Kathryn	Curtis		Patient Representative OcuMel UK*
Prof	Bertil	Damato	Moved to USA and did not attend meetings after May 2013, but contributed to the guideline electronically.	Hon. Professor of Ophthalmology Royal Liverpool University Hospital' Liverpool
Dr	Jonathan	Evans		Consultant Interventional Radiologist The Royal Liverpool University Hospital Liverpool
Mr	Stephen	Fenwick		Consultant Hepatobiliary Surgeon University Hospital Aintree, Liverpool.
Dr	Ji-Peng Olivia	Li		Ophthalmic Specialist Trainee, Moorfields Eye Hospital, London
Dr	Lesley	Kirkpatrick		Patient Representative
Dr	Ernie	Marshall		Macmillan Consultant in Medical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool
Mr	Kieran	McGuirk		Patient Representative, Chair, OcuMel UK*
Mr	Bruce	Oliver	Resigned October 2012	Patient Representative
Prof	Christian	Ottensmeier		Professor in Experimental Cancer Medicine Consultant in Medical Oncology Southampton University Hospitals and University of Southampton
Mr	Neil	Pearce		Consultant Hepatobiliary and Pancreatic Surgeon, University

			Hospital Southampton, Southampton
Dr	Brian	Stedman	Consultant Interventional Radiologist Southampton University Hospitals NHS Trust, Southampton
Mr	Sachin	Salvi	Consultant Ophthalmologist , Royal Hallamshire Hospital, Sheffield
Dr	Peter	Szlosarek	Consultant in Medical Oncology, St Bartholomew's Hospital, Clinical Senior Lecturer, Barts Cancer Institute, Queen Mary, University of London London
Ms	Nancy	Turnbull	Project Manager; London

* 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.

The following appendices are posted separately on the website of Melanoma Focus http://melanomafocus.com/activities-2/um-guidelines-resources/.

Full guideline containing detailed evidence reviews and references, declaration of interests and reviewers

Extraction Tables of Evidence

Ocular Melanoma Guideline Development Methodology

Patient information

Table of consultation comments and GDG responses

PowerPoint Presentations of evidence from meetings

Powerpoint presentation of the key points of the guideline for use by clinicians

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