Uveal Melanoma

Full guideline

Updated 2022

Original guideline published January 2015

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

Melanoma Focus is most grateful to OcuMel Uk for their donation towards the updated guidelines and corresponding patient information.

Publication Date: May 2022

Review Date: May 2027

Providing support and information for patients, carers and healthcare professionals while commissioning and funding innovative research.
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1 How to use this guideline

The Melanoma Focus guideline for Uveal Melanoma (UM) was started in 2012 and published in 2015. A review and update of that guideline was started in 2020 and completed in 2022. Sections where practice or treatment had changed to such an extent that the 2015 recommendations were out-of-date, were identified and updated. In order that the guideline be comprehensive, this document includes both the areas of the guideline which have been updated and those that remain the same as the 2015 version. The original text and recommendations are designated with [2015] and those updated with [2022].

This document contains the background information, methodology, evidence reviews and the Guideline Development Group (GDG) discussion. It supports the recommendations made regarding the management of uveal melanoma. Following the Introduction, the guideline has been divided into two sections. The first section contains the questions and reviews that have been updated or added. The second section contains the questions and reviews in the original [2015] guideline which have not been updated. For more details of the updating process see the Methodology section.

All of the further material is available here https://melanomafocus.org/for-professionals/rare-melanoma-guidelines-and-consultations/uveal-melanoma-guidelines/. This includes:

- the Executive Summary containing recommendations.
- The Care Pathway
- the Appendices with the evidence tables, search strategies and other background information from 2022 and 2015.
- information for patients
- a Power Point slideset is also available for use at clinical meetings
- the comments from consultation and the Guidline Development Group’s (GDG) replies

There is a glossary and list of abbreviations used and an additional table of all the full names of the genes at the end of this document.
2 Introduction

The first version of these guidelines published in 2015 aimed to optimise patient care by providing recommendations based on the best available scientific evidence. We ensured that the quality of evidence was assessed using a robust methodology and that the resulting guidelines reflected the strengths and weaknesses of the available evidence. We identified guidelines that were clinically impactful but which were interpreted in the light of the specific clinical context associated with each patient. The guideline development process and content met the standards required by NICE and were ultimately NICE accredited.

The guideline is reviewed in a five-year cycle, with any areas of emerging evidence that potentially impact upon the guidance being updated. We clarified with surgical ocular oncology colleagues that there have not been significant changes in the evidence instructing management of the primary tumour. There is also no new significant evidence that impacts upon surveillance for patients at risk of developing metastatic disease. However, there is a major improvement in the understanding of the genetic and molecular changes seen in uveal melanoma, and an evolving understanding of the role of currently available systemic treatment options and hepatic loco-regional therapies for advanced disease. Therefore, we have undertaken a review of evidence in these areas that has resulted in new guidance. We also have identified new evidence regarding patient experience in the UK ocular surgical centres and have taken the opportunity to revise the guidance impacting upon patient experience. Finally, the 2015 version omitted guidance regarding the role of adjuvant radiotherapy to the orbit in cases at high-risk of local tumour recurrence and the use of palliative radiotherapy to manage advanced disease; both areas are now included in this revised version.

As previously, where there is inadequate evidence to give guidance, we have where appropriate made consensus statements to aid clinical decision making. It is clear from the text which statements are evidence-based guidance and which ones are consensus statements.

We hope that the clinical community and our patients and their families find this updated guidance useful and a source of information and support. We also hope that in five years’ time at the next revision that we will have even further significant improvements to improve outcomes for our uveal melanoma patients, afflicted by this menacing disease.

2.1 Epidemiology

The age-standardized incidence of uveal melanoma (UM) in whites increases from 2 per million in southern to 8 per million to northern latitudes (1–3). These tumours are even less common in ethnic groups with darker eyes (4,5) More than 90% of UM involve the choroid, the remainder being confined to the iris and/or ciliary body. Both sexes are affected but some studies suggest a slight male preponderance (6,7). The age at presentation peaks at approximately 60 years in fair-skinned patients, except for iris melanomas, which usually present at a younger age (3,7,8). Less than 1% of all UM are described in children and young adults (<18 years) (9–11).

The most common risk factor for UM is a uveal naevus. It is estimated that at least 10 percent of UM develop from a formerly known naevus, and the life-time risk is approximately 0.2% (1:500) (12–14). Other risk factors are light-coloured irides (15,16), congenital ocular melanocytosis (17), melanocytoma (18) and neurofibromatosis (3,17). The role of sunlight is uncertain (19), although recent evidence would suggest that some iris melanomas have an ultraviolet radiation (UVR)-induced signature (20–22). Familial cases of UM are very rare but some patients may have familial atypical
mole and melanoma (FAMM) syndrome; these cases require monitoring by a dermatologist as they are also at risk of cutaneous melanoma (23). Rare families carry pathogenic variants of the Breast-Cancer-Associated-1 [BRCA1]-Associated Protein 1 (BAP1) gene on chromosome 3, which predisposes them to develop uveal melanoma, malignant mesothelioma, cutaneous melanoma, and renal cell cancer (in addition to potential other cancers) (also called the BAP1-predisposition syndrome) (24,25). Association of the breast cancer susceptibility gene, BRCA2, with UM has also been reported (26).

It is now estimated that between 20-35% of families with evidence of hereditary UM have BAP1 pathogenic variants / pro mutations (25,27–31). Although some families have BAPI pathogenic variants and cutaneous melanoma presentation, in others BAPI pathogenic variants do not include skin melanoma, suggesting that other predisposing genes (e.g., PALB2, MLH1 and MBD4) may account individually for inheritance in approximately <5% of cases (32–34). Evidence has suggested that genes involved in the DNA damage response and functioning as part of DNA repair pathways may be of particular interest, including BAPI and BRCA2 as already mentioned (26,35).

Staging for UM follows the American Joint Committee on Cancer (AJCC)/ Tumor-Node-Metastasis (TNM) staging system for eye cancer (36–39). Outcomes for patients with UM vary widely, but for patients with very small tumours are excellent, if treated early (36,40). In a cohort of 8033 patients, the 10-year metastatic rate for a 1-mm-thick UM was 5%, for a 2-mm-thick UM 10%, and that for a 6-mm-thick UM it was 30% (41). When grouping 7621 UM 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 (41). The median time from primary tumour diagnosis to metastasis detection is 2.6-3.5 years (42).

An online tool the Liverpool Uveal Melanoma Prognosticator Online (LUMPO), has been developed and is freely available (43). 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. It was externally validated by ocular oncology centres in the US and Poland (44), and more recently in a multicenter study across Europe (44,45).

A similar interactive web-based tool was developed by Vaquero-Garcia et al., in 2017 for a personalized risk estimate of developing metastases within 48 months of primary UM treatment (46).

Over the last decade significant advances have been made in the understanding of primary uveal melanoma genetics and biology, with some progress also of their metastases. In contrast to skin melanomas, posterior uveal melanomas rarely exhibit mutations in BRAF and demonstrate a low mutational burden (35,47). Instead, ~85% of them demonstrate mutations in GNAQ (guanine nucleotide-binding protein G(q) subunit alpha q) or GNA11 (Guanine nucleotide-binding protein subunit alpha-11) (48,49): they are mutually exclusive. These oncogenic mutations do not appear to be of prognostic value in primary uveal melanoma (50,51), and yet are useful for diagnostic confirmation of uveal melanoma and exclusion of cutaneous melanoma in the metastatic setting. Other rarer initiating mutations in uveal melanoma include CYSLTR2 (Cysteinyl Leukotriene Receptor 2) and PLCB4 (Phospholipase C Beta 4) (52–54). Additional cytogenetic and genetic changes, however, including monosomy 3, mutations in the BAPI tumour suppressor gene, alterations in the splicing factors SRSF2 (Serine and Arginine Rich Splicing Factor 2)/SF3B1 (spliceosome factor 3b1), and mutations in the translation initiation factor EIF1AX (Eukaryotic Translation Initiation Factor 1A X-Linked), modify the risk of metastases (35,47,55,56). These are discussed briefly below: the reader is also referred to updated reviews on the subject.
The most striking and distinctive abnormality in uveal melanoma is the complete or partial loss of chromosome 3: this was described in the early 1990’s by three independent groups (57–59). Other common genetic abnormalities of UM include loss on the short arm (p) of chromosome 1, and gains on 6p and 8q (see review, (3,60–62). 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. (35,47,63–67). Conversely, gains in chromosome 6p mainly correlate with a good prognosis, suggesting this aberration may have a functionally protective effect (35,47,61,62).

The natural history of uveal melanoma is characterised by the frequent development of hepatic metastases and patients develop metastatic disease at any time from the initial diagnosis of the primary to several decades later (68–71). The risk of metastatic relapse for an individual varies greatly dependent on primary tumour site, its morphological characteristics and the genetic alterations described above (3,43,72). It is noteworthy that most UM metastases arise from choroidal and/or ciliochoroidal melanomas, with the iridal melanomas rarely disseminating. This is the case for the majority of nodular well-circumscribed iridal melanomas; however, the rarer more diffuse iridal melanomas, with tumour cells involving the drainage channels of the anterior segment eye which lead into Schlemm’s canal and ultimately into the general circulation, are ‘high-risk’ with greater metastatic potential (73).

Outcomes for patients with metastatic uveal melanoma are currently poor once disseminated disease occurs (74–76). The median survival from the time of the development of distant metastatic disease is 2 to 12 months and 1-year survival 10-15% (3). This range reflects several prognostic factors including the burden of metastatic disease and the effect of metastatic screening programmes (77,78). Recent clinical trials using novel therapies do provide promise, albeit conservative optimism, in improving patient outcomes (74–76,79,80).

The liver is the most common site for UM 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 (3,81–83). Liver disease is usually multifocal, often in a miliary (seed-like) distribution, but some patients may develop isolated discrete and circumscribed metastases, enabling surgical removal. Our knowledge of the underlying biology and genomics of metastatic (secondary) UM has increased over the last 5 years but is not as advanced as that of primary tumours, due to the rarity of the metastatic UM samples. However, collaborative studies have enabled improved understanding of the morphological, genetic and immunological features of these tumours (47,84–92).

Liver involvement is the cause of death in most patients with metastatic UM (82). 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 hepatic nodal disease compressing the extrahepatic duct.

2.2 Strengths and limitations of the evidence

Uveal melanoma clinical and pre-clinical research has historically been hampered by the rarity of the disease. However, improvements in scientific method and organisation of clinical teams with specialist interest in UM has, over the last 5 years, resulted in a number of high-quality publications,
including randomised clinical trials. This evidence has been appraised in this updated version of the guidance.

2.3 Acknowledgements

Melanoma Focus would like to thank the Guideline Development Group members for giving of their valuable time to develop this guideline. Further, the Guideline Development Group would like to thank Melanoma Focus and OcuMel UK for funding this work. Both Camille Gerard and Jack Broadfoot helped with the reviews and the writing of chapters.

Particular thanks go to the associations and individuals listed below who took the time to read the draft and comment on it. The guideline has been improved by their efforts. All comments and the replies from GDG members can be viewed on the Melanoma Focus website https://melanomafocus.org/wp-content/uploads/2022/05/full-comments-table.pdf.

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OcuMel UK
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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. Therefore, these guidelines should be neither 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 main aim of the 2022 Update was to identify the areas where there has been new evidence published leading to revision requirements of the recommendations, to review this evidence and to alter the recommendations, as necessary.

2.4.2 Clinical areas covered by the updated guideline

The areas from the 2015 guideline which have been reviewed and updated are:
- Patient support and information
- Prognostication (title changed to Genetic and molecular features to inform prognostication) including tissue-based pathology, Cytology, Chromosome analysis and Genotyping / mutational analysis.
- Metastatic disease – Hepatic loco-regional and systemic therapy
- Patient information and support
  - The following topics not in the 2015 guideline which have been added in 2022
    - Adjuvant systemic therapy
    - Adjuvant radiation therapy
    - Palliative radiation therapy for local orbital recurrence at site
    - Radiation therapy for local recurrence

2.4.3 Clinical areas which will NOT be covered by the updated guideline

The areas where there were no significant changes in the evidence or practice are:
- Management of the primary tumour
- Surveillance

2.4.4 Target population and 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.
The full scope including the clinical questions the guideline aimed to address can be found in 2022 Appendix B in a separate document.

3 Methodology

The guideline was convened by Melanoma Focus, which is a national charity with a professional core membership undertaking patient support as well as research and education in the field of melanomas and skin cancers. Dr Paul Nathan, who chaired the 2015 guideline undertook the chairing of the update and was responsible for selecting the Guideline Development Group (GDG) members following a call for applications. He was also responsible for finalising the scope, leading the GDG discussions and signing off the guideline.

In July 2019, a systematic search of the literature from 2014 (the date of the last search) to the present was undertaken; it was reviewed by the chairman to identify areas that required updating. The members of the 2015 development group were contacted in November 2019 asking for their opinion on which areas should be updated and inviting them to apply to be on the new development group.

The two main areas where it was agreed that there were no significant changes in the evidence or practice were management of the primary tumour and liver surveillance. Hence, these two chapters were not updated. The text, references and format remain in the same as the original 2015 guideline. Where there was ambiguity in the wording of the recommendations or circumstances had changed (e.g.; service configuration), the wording was clarified. However, no evidence reviews were undertaken and, therefore, recommendations were not updated in light of new evidence.

Following the publication of the original 2015 guideline, Melanoma Focus applied and gained NICE accreditation for their guidelines process. To do so, the Methods Manual was revised and updated https://melanomafocus.org/wp-content/uploads/2020/10/Melanoma-Focus-Methods-Manual-V4.4.pdf. The revised methods were used in the Melanoma Focus guidelines published since 2015 including Mucosal melanoma (Ano-rectal, Vulva-vaginal and Penile) and Head and neck mucosal melanoma. The revised methods have been used for this update.

The general methods used for the recruitment of the GDG, scoping, searching, selecting and reviewing evidence, and developing recommendations and consulting on the draft are described in the above-mentioned methods manual. A description of the development of this guideline is given below.

3.1 Recruitment of GDG

The guideline development was advertised on the Melanoma Focus website. In addition, a letter was sent out to the members of the previous GDG and to several specialists in the uveal melanoma field telling them of the planned development and giving details of how to apply. They were asked to cascade the letter to colleagues who might be interested.

The GDG comprised the following membership professions. A list of the actual members is found at the beginning of this document and their declarations of interests are detailed in the separate Appendix.

1 - Patient representative
1 – Pathologist with a special interest in ocular tumours and genetics
1 – Scientist with a special interest in ocular tumours
4 – Medical Oncologists including the chairman
1 – Clinical Oncologist
1 – Interventional Radiologist
1 – Trainee medical oncologist who assisted with reviews

The Project Manager attended all meetings to take notes. A representative of Melanoma Focus and of OcuMel UK attended as observers but did not participate in the meetings.

3.2 Scoping

The areas identified for updating were agreed based on the evidence search and the clinical opinions of the 2015 GDG and the 2020 GDG. At the first meeting of the GDG in March 2020, it was decided that radiation therapy, both adjuvant and for recurrence at site, should be added to the guideline and a clinical oncologist was recruited to the group. It was also agreed at that meeting that an interventional radiologist was needed to assist with the review of metastatic disease of the liver, and therefore one was recruited on to the group.

3.3 Search, sifting and selection and evidence review

The information scientists at the National Guidelines Centre (NGC) (https://www.rcplondon.ac.uk/about-us/what-we-do/national-guideline-centre-ngc) conducted the searches and the initial sifting of the literature for duplicates and items which did not fit the specification. The first search took place in July 2019 covering publications from 2014 until July 2019. An update search was carried out 1 year later because of the delay in progress of the guideline due to the COVID-19 pandemic outbreak. A final search will be carried out prior to final publication 21st September 2021. The searches are detailed in the separate Appendix.

The methods of the evidence reviews are detailed in the methodology manual referred to above. Within each clinical chapter for each question, the PICO question (Population, Intervention/Investigation, Comparator and Outcomes) is given along with the selection strategy. The content experts on the GDG carried out the selection of evidence and the reviews which were presented and discussed at virtual group meetings, and evidence statements and recommendations were drafted.

3.4 Meetings

The first meeting of the group was held in March 2020 at the British Association of Dermatologists headquarters in London. There was then a six-month delay, due to the COVID-19 pandemic outbreak. The second meeting was held as a video-conference in October 2020. There were 8 further video meetings held.

3.5 Consultation

The GDG identified organisations and individuals who had an interest in the condition. These potential consultees were contacted in August 2021 informing them of the upcoming consultation on
the guideline and inviting them to act as reviewers. The draft full guideline and executive summary, along with instructions, was sent out on 30th August 2021 to 15 organisations (see separate 2022 Appendix) and 29 individuals. Notice of the consultation was also posted on the Melanoma Focus website and emailed to their mailing list inviting comments. Four organisations (see separate Appendix) and 26 individuals (1 individual responded both as a former GDG member and as a representative for an organisation), including former GDG members, returned comments. Declarations of interest were requested and returned by most consultees. These are available on request. The organisations and individuals are also acknowledged in section 3.

All comments and the GDG’s responses to these contents are published on the Melanoma Focus website https://melanomafocus.org/wp-content/uploads/2022/05/full-comments-table.pdf.

3.6 Funding of Guideline

The development of the guideline was funded by Melanoma Focus (https://melanomafocus.org/) with a donation from OcuMel UK (https://www.ocumeluk.org/).
4 2022 Reviews

4.1 Patient information and support [2022]¹

4.1.1 Introduction

A diagnosis of uveal melanoma (UM) is devastating to patients, their families and friends. Much of the information available is non-specific and usually relates to (skin) melanoma in general. Uveal melanoma can be life-changing, particularly if it results in blindness and/or the loss of an eye. There is also the worry of local recurrence or liver metastasis.

Although there is no actual cure for metastatic UM, treatment can now be effective in some cases, which means people are living longer with these conditions.

Depression and anxiety are common but can be alleviated by timely information and support. Support is needed at all stages including at diagnosis, during treatment and following treatment.

The patient representative on the group carried out a small survey of the information and support needs of people with UM which is reported below.

4.1.2 Review question: What information and support should patients receive at each stage?

Table 1: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with a confirmed diagnosis of UM</th>
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<tr>
<td>Intervention</td>
<td>Before and after diagnosis and at various stages of journey including surveillance</td>
</tr>
<tr>
<td>Comparison</td>
<td>-</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Quality of life (QOL), anxiety, depression, regret, worry</td>
</tr>
<tr>
<td>Study design</td>
<td>Surveys, questionnaires, interview</td>
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Only studies in which the subject all had UM were included. Case reports were excluded.

4.1.3 Clinical Evidence

Eleven studies were included (93,94,103,95–102); 2 were systematic reviews (93,101), 2 were cross sectional studies and the remainder were cohort or cases series. Most used were questionnaires to gather information: e.g., HADS (Hospital Anxiety and Depression Scale), EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire and Ophthalmic Oncology module and SF36 (Medical Outcomes Study short form with 36 elements divided into domains). The studies are summarised in Table 2 with full details of the included and excluded studies in Appendix A1 in the separate document entitled Appendix 2022.

The aim of most of the studies was to measure QOL and/or social, physical and emotional functioning, including worry about recurring disease and distress at different time points or with different treatments. (93,95–99,101–103)

¹ The information for this chapter was reviewed, presented and drafted by Audrey Woraker & Nancy Turnbull
Barker (95) reported severe worry about recurrence in nearly 50% of patients at diagnosis at Sloan Kettering in New York. Ocular irritation and visual impairment were also reported. A Liverpool study (96) administered questionnaires at 6, 12 and 24 months after treatment. Ocular irritation, headache, and functional problems as well as worry about recurrent disease at 6 months were predictors of anxiety and depression at 24 months. They suggest that these patients be monitored for anxiety and depression and given reassurance that symptoms do not mean there will be future disease. A retrospective review of case-notes over a four-year period, again at Liverpool, (98) of patients with UM who had accepted a routine appointment with a health psychologist during initial treatment compared the health psychologist’s assessment to screening with the Hospital Anxiety and Depression Scale (HADS) questionnaire. The health psychologist identified about half of the 261 patients were in ‘psychological need’ with anxiety or depression whereas less than one-third were identified by the HAD questionnaire. The assessments were misaligned on about 30% of patients. The view of the paper is that much of the emotional distress identified by HADS is normal given the circumstances and does not require a psychological intervention and that dialogue with the patient is important in identifying psychological need which requires intervention.

4.1.3.1 By treatment

A recent systematic review by Anchouche et al reported on 18 studies of 4285 patients comparing different treatment regimens for QOL and physical, social and emotional functioning (104). Overall, there were no differences in QOL after a year between treatments regardless of tumour size. Patients who underwent enucleation reported poor emotional well-being, social functioning and vitality at 3 months showed a recovery by one year. The systematic review by Miniati et al (101) reviewed on 18 studies over 25 years including those of the Collaborative Ocular Melanoma Study (COMS) among others. Overall, there were no significant differences in QoL or depression and anxiety between patients undergoing radiotherapy and those undergoing enucleation.

Damato (97) compared enucleation with radiation therapy (plaque and proton beam) in 1154 patients with choroidal melanoma. Patients who underwent enucleation were more worried about metastasis whereas patients who had radiotherapy were more concerned about the possibility of local tumour recurrence. Poor wellbeing was found in a small minority of patients and was mostly caused by factors unrelated to type of ocular treatment, such as poor general health, poor social support and unemployment.

4.1.3.2 Screening for future distress

Another Liverpool study (96) carried out a prospective survey of 261 UM patients who returned data at all at 6, 12 and 24 months after diagnosis. Their conclusions were that symptoms and functional problems at 6/12 months may predict, or contribute to, future anxiety and depression or poor QoL and that early psychological intervention may be preventative. This could be an early intervention e.g., 6-week structured group intervention soon after initial diagnosis and therapy or consultation with a health psychologist (98). In further work in Liverpool, Brown (105), using multi-variate analysis with patient reported outcomes, reports that elevated depression scores at 6 months post diagnosis were an increased mortality risk thus further confirming early psychological intervention.

Cai (106) investigated marital status as a prognosticator of survival in a Chinese population. Older, widowed males had poorer survival when compared with married patients. Widowed males had a poorer survival than females; however, widowed females also had lower overall survival. The authors suggest that widowed patients may need more physical and psychological care.

Klingenstein (99) surveyed 106 patients using the National Comprehensive Cancer Network (NCCN) Stress Thermometer after primary diagnosis which could be integrated into clinical routine as it
proved to be a rapid and sensible screening tool for emotional and physical distress in patients with uveal melanoma. In a follow-up paper (107) she further validates the distress thermometer as a rapid assessment for patients requiring psychological intervention.

The Nshimiyimana study (102) was a conference abstract reporting a pilot study. However as it was the only included study that addressed patients with metastatic cancer, it is included here. Patients were sent the HADS and the World Health Organization Quality of Life-BREF questionnaires over a 3-month period. In total, 65/70 (93%) responded: 30.8% (n=20) had at least borderline anxiety; 13.8% (n=9) had at least borderline depression; and 32.3% (n=21) had a decrease in global QoL. Patients under 60 years had higher anxiety scores and lower QOL scores in environmental health. Those with a shorter duration of illness since metastasis had higher anxiety scores and higher QoL scores in physical. There were no differences by gender or time to metastatic disease.

4.1.3.3 Genetic testing

Three studies reported on the psychological impact of genetic testing (100,101,108)

A prospective German study identified patients who were eligible for genetic testing. Those who consented to genetic testing comprised the intervention group and those who did not formed the observational group. Patients were assessed before and after surgery, and at 6–12 weeks, 6 and 12 months after initial admission. Patients usually received genetic test results at 6–12 weeks. The results of this study were reported on in 2020 (100). The Miniati et al systematic review (101), also reports that psychological status did not vary based on cytogenetic test results. A 2016 study is included (108) supporting this finding and also showing that genetic testing was found not to be associated with poorer subsequent psychological well-being. Also reported in this review is the 2016 study from Liverpool (109) which investigated differences by treatment, age and genetic status at 6 months, and 1 and 2 years. Patients diagnosed with monosomy-3 UM “more depressed” than others at each time point, and this did not decrease with time.

4.1.3.4 Patient Satisfaction

One study reported on a patient satisfaction survey of patients across the United States. (94) It was an online study undertaken in 2015 and had 312 respondents: about half through direct email contact and half through Facebook. Although much of this is more relevant to the United States, it reports a strong desire for more information and counselling from the respondents with women being more interested in the impact of their disease on activities and quality of life when compared to men. Over 50% of respondents reported dissatisfaction with:

- Psychological counselling and accepting cancer diagnosis
- Counselling on treatment and other measures aimed at preventing liver tumours
- Counselling on genetic tests
- Prognostication predicting chances of future health
- Counselling on treatment of metastatic disease

The authors have developed twenty ‘Tentative standards of care specific to ocular melanoma’ many of which are relevant to the UK and could be adapted for inclusion in this guideline.
Table 2: Summary of studies included in the review

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Title</th>
<th>Study topic</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchouche</td>
<td>2020</td>
<td>Quality-of-life considerations in patients with uveal melanoma: a systematic review</td>
<td>Comparison of QoL, anxiety by treatment</td>
<td>No difference by treatment</td>
</tr>
<tr>
<td>Afshar</td>
<td>2018</td>
<td>The Patient’s Experience of Ocular Melanoma in the US: A Survey of the Ocular Melanoma Foundation</td>
<td>Patient satisfaction in the US</td>
<td>Dissatisfaction with much of information giving. Lists standards for a good service many of which are relevant to the UK.</td>
</tr>
<tr>
<td>Barker</td>
<td>2020</td>
<td>Quality of Life Concerns in Patients with Uveal Melanoma after Initial Diagnosis</td>
<td>Questionnaire at initial diagnosis</td>
<td>About half the patients were severely worried about recurrence.</td>
</tr>
<tr>
<td>Brown</td>
<td>2018</td>
<td>Predictors of anxiety and depression 2 years following treatment in uveal melanoma survivors</td>
<td>Patients followed up by questionnaire for 2 years following diagnosis</td>
<td>Long term (&gt; 2years) anxiety and depression could be predicted by 6 months following diagnosis.</td>
</tr>
<tr>
<td>Brown</td>
<td>2021</td>
<td>Predictors of long-term anxiety and depression in uveal melanoma survivors: A cross-lagged five-year analysis</td>
<td>Multi-variate analysis of predictors of mortality</td>
<td>Depression at 6 months post diagnosis is a predictor of increased mortality.</td>
</tr>
<tr>
<td>Cai</td>
<td>2020</td>
<td>The Influence of Marital Status on the Survival of Patients with Uveal Melanoma</td>
<td>Data from SEER</td>
<td>Older, widowed patients, particularly male have a poorer overall survival</td>
</tr>
<tr>
<td>Damato</td>
<td>2019</td>
<td>Patient-Reported Outcomes and Quality of Life after Treatment for Choroidal Melanoma</td>
<td>Comparison of enucleation with plaque and PBT</td>
<td>Wellbeing after enucleation was similar to that after radiotherapy when other factors were taken into account.</td>
</tr>
<tr>
<td>Hope-Stone</td>
<td>2018</td>
<td>Reflections on a Health Psychology Service for Patients with Uveal Melanoma: The Challenge of Psychological Screening and Intervention When Distress is “Normal.”</td>
<td>Anxiety and depression at diagnosis and identification of psychological need</td>
<td>Difference between a face-to-face assessment was superior to a screening questionnaire</td>
</tr>
<tr>
<td>Klingenstein</td>
<td>2020</td>
<td>The national comprehensive cancer network distress thermometer as a screening tool for the evaluation of quality of life in uveal melanoma patients</td>
<td>Testing the use of the NCCN distress thermometer</td>
<td>This very short questionnaire was useful in identifying patients with high distress levels.</td>
</tr>
</tbody>
</table>
### Table 2: Summary of studies included in the review

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
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<th>Study topic</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klingenstein</td>
<td>2020</td>
<td>Screening for Predictive Parameters Requiring Psycho-Oncological Intervention via the National Comprehensive Cancer Network Distress Thermometer in the Follow-Up of Uveal Melanoma Patients</td>
<td>Testing the use of the NCCN distress thermometer</td>
<td>Further validation of its efficacy.</td>
</tr>
<tr>
<td>Lieb</td>
<td>2020</td>
<td>Psychosocial impact of prognostic genetic testing in uveal melanoma patients: a controlled prospective clinical observational study</td>
<td>Impact the genetic testing</td>
<td>Genetic testing did not result in greater anxiety and distress.</td>
</tr>
<tr>
<td>Miniati</td>
<td>2018</td>
<td>Quality of Life, Depression, and Anxiety in Patients with Uveal Melanoma: A Review.</td>
<td>Systematic review of use of mainly questionnaires to identify anxiety and depression.</td>
<td>Genetic testing did not result in greater anxiety and distress.</td>
</tr>
<tr>
<td>Nshimiyimana</td>
<td>2018</td>
<td>Pilot study of anxiety, depression, and quality of life in patients with the diagnosis of metastatic uveal melanoma</td>
<td>Anxiety, depression and QoL in patients with metastatic disease</td>
<td>Patients under 60 reported higher levels of anxiety and depression than older patients.</td>
</tr>
<tr>
<td>Scannell</td>
<td>2020</td>
<td>Melanoma Patients in Ireland: A Single-Centre Survey. Ocul Oncol Pathol</td>
<td>Comparison of QoL between treatments of brachytherapy and enucleation.</td>
<td>No difference between treatment groups.</td>
</tr>
</tbody>
</table>

### 4.1.4 Patient Survey

Audrey Woraker, the patient representative on the GDG, carried out two surveys of the experience of patients at different centres in England and Scotland. She advertised the survey via OcuMel UK and had 107 responses from the first survey and 42 responses to the second.

The first survey *Wish List 2* was devised to find out what information each person was given at diagnosis to assess the patient satisfaction with the aim of supplying the GDG the findings to encourage hospitals to provide a standardised information leaflet/booklet. The introduction to the survey made it very clear that ‘this is not a survey to see “which hospital is best” but to pick the best aspects ... so a more standard approach [can be made].’ The survey asked practical questions such as ‘in what format were you given your information.’
The results of the first survey found that there was a disparity in how the patients are informed of their diagnosis, treatment and any future complications. The general response was that consistency between the hospitals was key; where the high quality (both physical and content) of literature that hospitals provide to patients would be set as standard.

The second survey (Does Counselling help?) is a follow up to the first survey but looked at the emotional well-being of the participants and was only open to those who had previously responded to Wish List 2.

The results of the second survey found that there was a disparity in the offer of counselling following UM diagnosis. The survey found only 35% of participants took up the offer of counselling when offered but 100% said that it helps ‘to know support is available’. Of those who were not offered support, 69% have since needed some type of emotional support. The survey suggests that hospitals should provide the offer of support (and it being available at any stage). The support can be by provided by the hospital or through an agreement between hospital and an outside party such as a charity who can provide counselling or via the patients GP. Participants suggested hospitals should provide both counselling and signposting to other resources such as Maggies and OcuMel UK for temporary emotional support.

4.1.5 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Information should be offered throughout the patient pathway in an individualised manner and provided as needed. Ideally this should adhere to these quality standards (<a href="https://pifonline.org.uk/pif-tick/">https://pifonline.org.uk/pif-tick/</a>). [2022]</td>
</tr>
<tr>
<td>2. Patients should be encouraged to record their consultations with the knowledge of the clinician. [2022]</td>
</tr>
</tbody>
</table>
| 3. Patients should be given the time and opportunity to discuss their condition and treatment on each visit. This should include:  
  - risks and benefits of investigations, procedures and treatments  
  - the treatment options available locally and at other centres  
  - the pros and cons of prognostication including the role of biopsy  
  - timely information on the roles of other teams in their care  
  - signposting to other high-quality resources, for example Melanoma Focus, OcuMel UK, Cancer Research UK, MacMillan, Maggie’s. [2022] |
<p>| 4. Each patient should have a named keyworker, with contact details including telephone and email address, who is responsible for communication between the different cancer centre teams caring for the patient and between the cancer centre and primary and secondary care. Ideally this should be a Clinical Nurse Specialist. [2022] |
| 5. Patients should be given scan results as early as possible to mitigate anxiety. [2022] |</p>
<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Standard care available to all patients nationwide should include:</td>
</tr>
<tr>
<td>• information on the side effects of local or systemic treatment</td>
</tr>
<tr>
<td>• advice for patients and families regarding signs and symptoms that may indicate that the cancer has recurred</td>
</tr>
<tr>
<td>• the offer of psychological support</td>
</tr>
<tr>
<td>• easy access to out-patient review or remote consultation</td>
</tr>
<tr>
<td>• the opportunity to have family member with them at consultations. This may be done remotely if necessary.</td>
</tr>
<tr>
<td>• the offer of early referral to services, for example, enhanced supportive care, palliative care support services and support groups [2022]</td>
</tr>
</tbody>
</table>
4.2 Genetic and molecular features [2022] 

4.2.1 Introduction

As outlined in the Introduction (Section 2.1), uveal melanoma (UM) can arise in the iris, ciliary body and the choroid, with the latter being the most common site (3). Despite successful treatment of the primary tumours in most cases, approximately 40%-50% of patients will develop disseminated disease, predominantly in the liver, but also in the lungs, bone and other organs. Early surgical removal of metastases has improved patient survival in some cases (110–113); however, in general, the prognosis of UM patients with metastatic disease is currently poor, with a median overall survival (OS) of between 10-22 months (114,115) because of a paucity of effective systemic agents for most patients (74–76,79). The longer-term OS of UM patients with metastatic disease is associated with previous partial response to immune checkpoint blockade (ICB) and presence of extrahepatic disease (78).

Several parameters associated with the primary UM have been identified in the literature, which have prognostic significance with varying degrees of strength that predict metastasis onset and, therefore, UM patient survival. 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 (116). Others have undergone extensive analysis using large data sets, either as part of a one-centre or multicentre analysis, 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, update according to the numerous recent advances since the original UM Guidelines in 2015; and specifically, to address whether the new knowledge of underlying genetics has influenced the design of molecular prognostic tools, and if these in turn better help define metastatic risk.

4.2.1.1 Established Prognostic Parameters in Uveal melanoma

Clinical, histomorphological, immunohistochemical, genetic, and ‘combined’ methods have all been applied to determine the prognosis of UM patients. The majority of these features are well established, and their importance and value remain the same as indicated in the first UM Guideline 2015.

Clinical factors that have been consistently demonstrated in the literature to have strong statistical significance when predicting the risk of UM metastasis include:


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2The information for this chapter was reviewed, presented and drafted by Prof Sarah Coupland and Dr Karen Sisley
3. Tumour height (3,36,41,123–129)
4. Tumour basal diameter (3,36,38,118,120,124,127,128,130)
5. Tumour location – i.e., ciliary body involvement (3,36,132,38,119,123–127,131)

All parameters have been included in the 8th Edition of the AJCC TNM staging system.

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

2. Mitotic count (on haematoxylin and eosin staining only) (62,120,137–139).
3. Mean diameter of ten largest nucleoli. (140–142)
4. Presence of extravascular matrix patterns, particularly ‘closed connective tissue loops’ (62,120,143).
5. Microvascular density (144–148).

**Immunohistochemical parameters** described to be of prognostic significance in UM include:

1. Tumour cell proliferation markers (Ki-67, PCNA/PC-10, Ser10/PHH3). (140,149–152)
2. Tumour cell nuclear expression for BAP1 using immunohistochemistry has been recently demonstrated by several groups to represent a close surrogate for the BAP1 gene status, in most cases (153,154,163,155–162).
3. Density and type of tumour-infiltrating macrophages (90,120,164–168).

**Genetic tumour biomarkers** are quite distinctive in UM and enable stratification of patients into metastatic risk subgroups. These cytogenetic and molecular genetic features are outlined below.

**Cytogenetic features** of the tumour cells have been demonstrated to have strong prognostication value in UM. The most striking abnormality in posterior UM is the complete or partial loss of chromosome 3 (57–59). Other common genetic abnormalities of UM include loss on 1p, 6q, 8, and 9p as well as gain on 1q, 6p, and 8q (3,61,62,175).

Chromosome 3 loss is associated with a reduction of the 5-year survival probability of UM patients from approximately 100% to about 50% (2,62,183–185,139,176–182). Similarly, chromosome 8 gains and loss of chromosome 1p significantly correlate with reduced survival (35,62,66,67,186). The presence of both monosomy 3 and polysomy 8q in UM cells highlights a particularly high-risk tumour, usually associated with a poor survival outcome (35,65,66,187,188). Unsurprisingly, most UM hepatic metastases show similar alterations when analysed (88,91,189).

Both chromosome 3 loss and polysomy 8q are also associated with other poor prognostic factors, including increasing tumour basal diameter, ciliary body involvement, presence of epithelioid cells,
high mitotic count, and closed connective tissue loops (62,66,139,190). Conversely, gains in chromosome 6p may correlate with a good prognosis, suggesting this aberration has a functionally protective effect (62,139,191).

**Mutational Features:** As described in the Introduction (Section 2.1), mutational features of UM cells have been revealed over the last 5-10 years through multicentre collaborative studies and by applying advanced molecular technologies, enabling a better understanding of the underlying tumour biology and how they relate to prognosis.

Of particular interest in UM is its low mutational burden compared to other tumours (192). These findings are potentially attributable to how UM cells repair DNA damage and implicate an emerging role for DNA repair genes in UM (35,193,194).

As outlined in the Introduction (Section 2.1), the most prevalent changes in UM are the mutually exclusive mutations of \textit{GNAQ} and \textit{GNA11}, and less frequently other genes in the same pathway (3,48,49,195,196). As they are present in over 95% of UM, these mutations have no prognostic significance, but are useful for confirmation of metastatic UM in unclear lesions and the exclusion of cutaneous melanoma.

The somatic mutations in UM cells that have been most attributed with prognostic significance are those of \textit{BAP1}, \textit{SF3B1}, and \textit{EIF1AX} (3,35,187). Mutations of BRCA1-associated protein-1 (\textit{BAP1}), located at 3p21, are found characteristically in UM with monosomy 3, whilst the mutually exclusive mutations of \textit{SF3B1} (197) and \textit{EIF1AX} (198) usually segregate UM with disomy 3 (199). Hence, UM can essentially be divided into 4 biological subgroups of clinical prognostic relevance (35,47):

- **Subgroup 1:** Disomy 3, disomy 8q, \textit{EIF1AX} mutant
- **Subgroup 2:** Disomy 3, polysomy 8q*, \textit{SF3B1} mutant
- **Subgroup 3:** Monosomy 3, polysomy 8q*, \textit{BAP1} mutant
- **Subgroup 4:** Monosomy 3, polysomy 8q*, \textit{BAP1} mutant

(*Distinguishing subgroups 2, 3 and 4 are the numbers of copies of chromosome 8q, with subgroup 4 having the greatest number (47)).

These changes can serve to further stratify posterior UM into low, intermediate and high metastatic risk groups, as does the expression of PRAME (‘preferentially expressed antigen in melanoma’) by the tumour cells (200,201), which is independent of other genetic changes.

Another characteristic feature of UM is its relative homogeneity of copy number variations (CNVs) and mutations across the tumour. However, emerging evidence has suggested that the gene, \textit{MBD4} (Methyl-CpG Binding Domain 4, DNA Glycosylase), may be associated with increased instability (and potential heterogeneity) in a very small subset of UM patients (<5%), and that this hypermutator phenotype may offer therapeutic options in the metastatic setting (202–204). However, this is the subject of future multicentre research (34); the search for hypermutated UM might lead to the stratification of patients for treatment with checkpoint inhibitors.

**Iris melanoma:** Compared to the posterior UM, less is known about the genetic changes of anterior UM - i.e., iris melanoma. This is due to their rarity (approx. 1-2% of all intraocular melanomas) as well as the difficulty in accessing samples, which represent pure iris tumours (i.e., without involvement of the immediately adjacent ciliary body).
The literature regarding iris melanomas was quite contradictory regarding the genetic features of iris melanomas, perhaps because of the relatively small numbers- and types of samples examined (205,206); however, increasing evidence suggests that these discrepancies in results may be intrinsic to the iris melanoma cells themselves. That is, although they can share some of the classic genetic changes of posterior UM, some at least have a greater similarity to cutaneous melanoma, with a more hyper-mutated and UV radiation-related signature (20,21,207,208). In general, iris melanomas tend to have a greater frequency of \textit{SF3B1} mutations and rarely display \textit{BAP1} mutations, perhaps explaining their indolent clinical course in most cases (209). It should be noted most indolent iris melanomas are well-circumscribed and nodular, whilst those associated with an aggressive course are most often diffuse with tumour cell involvement of the drainage angle of the anterior chamber(210). Genetic alterations in iris melanoma have yet to be shown to act as prognostic biomarkers, but future studies should probably take these growth patterns into account.

4.2.1.2 Prognostic methods (laboratory-based).

Different methods (i.e., techniques or ‘tools’) can be applied to assess the genetic alterations of UM, and segregate into those looking for cytogenetic or molecular indicators. These can be performed on varying-sized tissue samples, ranging from small intraocular tumour biopsies to local tumour or endoresections, to the larger enucleations or orbital exenterations.

Increasingly, there is demand for the techniques to produce reliable results on intraocular tumour biopsies; hence, this has resulted in specialist centres performing these biopsies and their subsequent analyses, which includes confirmatory (cyto)morphological review before any molecular testing. The safety and efficacy of a performing prognostic biopsies will not be discussed here, as this review was performed in the last Guidelines. However, the ‘pros and cons’ of intraocular biopsy for UM is summarised below in Table 6. The advantages and disadvantages of undertaking a UM biopsy.

The most 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 (175,211). The latter technique divides UM into two ‘classes’ based on an mRNA expression signature: class 1 (A and B), and class 2 (151,178). Essentially, ‘Class 1A’ UM often show 6p gain and disomy 8. ‘Class 2’ UM tend to demonstrate more aneuploidy with 1p loss, 3 loss, 8p loss, and polysomy 8q. Class 2 UM are also strongly associated with inactivating mutations of \textit{BAP1}, located at 3p21 (212). The GEP-based test has been patented and is commercially available.

As above, the use of new sequencing technologies in examining primary UM over the last 5-7 years has increased our knowledge significantly (20,35,47,207), and in turn has led to improvements in the molecular tools applied for prognostication. Hence, the analysis of specific genes has also been included in laboratory prognostication methods.

Neither \textit{GNAQ} nor \textit{GNA11} status in UM is considered to be of prognostic relevance in most cases, but mutations of \textit{BAP1}, \textit{SF3B1} and \textit{EIF1AX} can provide additive information. These can be analysed using conventional or next generation sequencing (NGS) platforms. The latter have enabled bespoke-designed NGS prognostic assays for UM, incorporating analyses of relevant CNVs and mutations (175,213–215), as well as those that have incorporated epigenetic changes (200).

Furthermore, it has become clear that the status of some genes can be assessed using an immunohistochemical surrogate marker, e.g., nuclear \textit{BAP1} (nBAP1) in the UM cells. Loss of nBAP1 expression equates with somatic mutation of the \textit{BAP1} gene in most cases, whilst its presence within the cells’ nuclei is usually consistent with the wild type status of the gene. This has been demonstrated independently by several groups (153–160,216), and a single centre study found that nBAP1 immunoexpression helped define prognostic subgroups within monosomy 3 UM (159). Such
immunostaining could be of value as a low-cost test, where genetic testing is not available. Indeed, the application of artificial intelligence and deep learning models to simple hematoxylin-and-eosin slides has been shown to predict nBAP1 expression, and thereby the BAP1 status in UM (163).

To date, there has been a paucity of studies that directly compare each of the differing prognostic techniques in UM (217). Only limited comparative analyses have been performed (176,181,183,217–219), each with their respective flaws. Therefore, no statement can be made here regarding superiority of a particular genomic technique over another.

Multiparameter prognostic algorithms.

The TNM/AJCC staging system is a purely anatomically-based system and is useful when no molecular genetic data are available. Preliminary findings from single centres suggest that it may be improved upon, when other significant prognostic parameters are included (220) since combining prognostic parameters in UM achieves greater accuracy – e.g., – combining the TNM/AJCC staging of UM with cytogenetic or molecular genetic alterations of the tumour cells (66,126,216,221). Another example is combining the AJCC/TNM stage of the tumour with CNV- and with epigenetic profiles of the tumour cells, leading to prognostic groups (222). It has recently been proposed that the TNM/AJCC staging system could be superseded by The Cancer Genome Atlas classification system of UM (223,224); however, this requires a multicentre and multiparametric study for verification.

Combined multiparameter prognostic models have been designed and validated by some ocular oncology centres (43,225–227). The prognostic models consider a number of the stronger prognostic parameters in UM, 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 datasets, 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. The Liverpool Uveal Melanoma Prognosticator Online (LUMPO) has been validated externally via a multicentre study (44), and has been used in clinical care for ~8 years. It is being used for patient counselling and to determine liver screening frequency and the ultimate modality for screening (e.g., MRI versus ultrasound) applied. A similar interactive web-based tool was developed by Vaquero-Garcia et al., in 2017 for a personalized risk estimate of developing metastases within 48 months of primary UM treatment (46).

4.2.1.3 Tumour Heterogeneity of UM

Although there are a relatively small number of mutations and CNVs in primary UM compared to other cancers, concerns were raised regarding intraocular UM biopsies as being representative of the whole tumour – i.e., whether potential tumour heterogeneity within the tumours could lead to sampling errors. Earlier FISH analyses performed on paraffin sections did reveal some heterogeneity of monosomy 3 in UM (228–231). This question was also examined using MLPA using formalin-fixed enucleated globes; however, in the latter study it was found in most primary UM 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 whole tumour (139,232). Indeed, data demonstrate a very high concordance rate between MLPA and MSA results of intraocular biopsies of UM that were subsequently enucleated and re-examined using these techniques (233). Some rare cases are exceptions to the rule (233). To date, there are few reports examining primary UM for heterogeneity and how it may impact on other prognostication techniques, e.g., gene expression profiling (234,235).

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. For example, a report suggests that carcinoma metastases to the choroid
generate variable gene expression profile results (236–238). Furthermore, Disomy 3 or Class IA results are to be interpreted with caution if the sample has not been examined for cellular content or cell type: inflammatory infiltrates within the choroid can also generate such findings.

Finally, it is evident that metastatic UM, like other cancers, continue to evolve as they become established and grow within their hepatic niche. Studies have demonstrated subclonal genomic complexity and transcriptional states in metastatic, possibly influenced the tumour microenvironment (88,239).

4.2.1.4 Emerging areas

A potential driver of heterogeneity for a subset of posterior UM may have an impact on the interpretation of biopsies. Mutations of *MBD4* are found in a small subset (~5%) of UM and correlate with increased instability. As these mutations may identify tumours susceptible to certain therapies a better understanding of the timing of these events and their concordance throughout UM is required (240). Another area that requires further study is the suggestion that *SF3B1* mutations render UM more susceptible to immunotherapy(241,241)).

**Liquid (serological) biopsy**

Some serological markers have been proposed to be associated with poorer prognosis and ‘high-risk’ UM: these include MIA-1 (242–245); S-100B, osteopontin; TPS (244) ; GDF-15 (246)B2-microglobulin (247); and circulating tumour cells, cell free DNA and UM-related exosomes (248–255).

Most of these serological biomarkers are being investigated as a research tool; however, to date, are not being used to influence clinical management. There is indeed potential to incorporate one or more of these serological markers into the above prognostic algorithms, to identify UM patients who could benefit from adjuvant therapies in the future.

4.2.2 Review question: Does the recent evidence of molecular pathology inform a change or add to the prognostic tool?

Table 3: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with diagnosed primary uveal melanoma with and without clinical evidence of metastatic disease</th>
</tr>
</thead>
</table>
| Interventions | Clinical variables  
Histomorphological features  
Immunohistochemical features  
Genetic data  
Serological markers |
| Comparison(s) | Each other |
| Outcomes | Survival (hazard ratio for prognostic factors) |
| Study design | |
4.2.2.1 Clinical evidence

The studies are summarised in Table 4 with full details of the included and excluded studies in Appendix A2 in the separate document entitled Appendix 2022. The accumulation of new data with respect to the underlying molecular biology of UM cells over the last decade has indeed led to new designs and refinement of molecular diagnostic and prognostic tools. These can be applied as an adjunct to other prognostication parameters in this tumour. That is, instead of looking at Copy Number Variants (CNVs) such as monosomy 3 only in UM cells, novel bespoke platforms have been designed for UM to assess both CNVs as well as the most relevant mutations in UM or to assess the epigenetic profiles of UM subgroups (as outlined above). Furthermore, these molecular tools employing new technologies have the potential of being applied to diminishingly smaller amounts of tumour tissue, as the techniques improve their specificities and sensitivities.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakhoum</td>
<td>2019</td>
<td>Molecular Characteristics of Uveal Melanoma: Insights from the Cancer Genome Atlas (TCGA) Project</td>
</tr>
<tr>
<td>Caines</td>
<td>2015</td>
<td>Cluster analysis of multiplex ligation-dependent probe amplification data in choroidal melanoma</td>
</tr>
<tr>
<td>Dogrusöz</td>
<td>2017</td>
<td>The Prognostic Value of AJCC Staging in Uveal Melanoma Is Enhanced by Adding Chromosome 3 and 8q Status</td>
</tr>
<tr>
<td>Farquhar</td>
<td>2018</td>
<td>Patterns of BAP1 protein expression provide insights into prognostic significance and the biology of uveal melanoma.</td>
</tr>
<tr>
<td>Field</td>
<td>2016</td>
<td>PRAME as an Independent Biomarker for Metastasis in Uveal Melanoma</td>
</tr>
<tr>
<td>Glasgow</td>
<td>2018</td>
<td>Correlation of Immunocytochemistry of BRCA1-associated Protein-1 (BAP1) With Other Prognostic Markers in Uveal Melanoma.</td>
</tr>
<tr>
<td>Kalirai</td>
<td>2014</td>
<td>Lack of BAP1 protein expression in uveal melanoma is associated with increased metastatic risk and has utility in routine prognostic testing.</td>
</tr>
<tr>
<td>Koopmans</td>
<td>2014</td>
<td>Clinical significance of immunohistochemistry for detection of BAP1 mutations in uveal melanoma</td>
</tr>
<tr>
<td>Patrone</td>
<td>2018</td>
<td>Prognostic value of chromosomal imbalances, gene mutations, and BAP1 expression in uveal melanoma.</td>
</tr>
<tr>
<td>Robertson</td>
<td>2017</td>
<td>Integrative Analysis Identifies Four Molecular and Clinical Subsets in Uveal Melanoma</td>
</tr>
<tr>
<td>Royer-Bertrand</td>
<td>2016</td>
<td>Comprehensive Genetic Landscape of Uveal Melanoma by Whole-Genome Sequencing.</td>
</tr>
<tr>
<td>See</td>
<td>2020</td>
<td>BAP1 Immunoreactivity Correlates with Gene Expression Class in Uveal Melanoma.</td>
</tr>
<tr>
<td>Shah</td>
<td>2013</td>
<td>BAP1 protein loss by immunohistochemistry: a potentially useful tool for prognostic prediction in patients with uveal melanoma</td>
</tr>
<tr>
<td>van de Nes</td>
<td>2016</td>
<td>Comparing the Prognostic Value of BAP1 Mutation Pattern, Chromosome 3 Status, and BAP1 Immunohistochemistry in Uveal Melanoma.</td>
</tr>
<tr>
<td>van Essen</td>
<td>2014</td>
<td>Prognostic parameters in uveal melanoma and their association with BAP1 expression.</td>
</tr>
</tbody>
</table>

Table 4 Summary of key studies included in the review

However, it must be noted that, whilst these new technologies are very exciting and promising with some of them already having been introduced into clinical care, (35,47,65,66,187,200) they: a)
require validation on larger multicentre cohorts, and on a variety of tumour samples (fresh versus formalin-fixed; biopsy versus resection specimen); and b) do not replace previously well-validated methods, including simple morphological and immunohistological prognostic parameters. That is, the latter should not be considered superseded by the molecular information; rather that the molecular tools provide additional information, which when combined into multiparameter prognostic algorithms, enhance and refine UM patient stratification into metastatic risk groups (66).

With time and further knowledge about UM biology, it can only be hoped that newer molecular tools/information may enable UM patient stratification into predictive groups, i.e., identifying those who would respond to pharmaceutical agents in the metastatic setting.

4.2.3 Review question: Do the new prognostic markers help better define risk?

Table 5: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with diagnosed primary uveal melanoma with and without clinical evidence of metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Clinical variables</td>
</tr>
<tr>
<td></td>
<td>Histomorphological features</td>
</tr>
<tr>
<td></td>
<td>Immunohistochemical features</td>
</tr>
<tr>
<td></td>
<td>Genetic data</td>
</tr>
<tr>
<td></td>
<td>Serological markers</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Each other</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Survival (hazard ratio for prognostic factors)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
</tr>
</tbody>
</table>

Information for each of the above questions was extracted from an updated list of references compiled from references published after the first guidelines, and generated by an extensive literature search until the date of January 2021. All papers regarding prognostic parameters – apart from clinical parameters - predicting survival outcome described for primary UM were included for review. Preclinical and animal studies, in vitro cytogenetic markers and cell line studies, single centre unvalidated series and single case reports were excluded.

4.2.3.1 Clinical Evidence

The studies are summarised in

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakhoum</td>
<td>2019</td>
<td>Molecular Characteristics of Uveal Melanoma: Insights from the Cancer Genome Atlas (TCGA) Project</td>
</tr>
<tr>
<td>Caines</td>
<td>2015</td>
<td>Cluster analysis of multiplex ligation-dependent probe amplification data in choroidal melanoma</td>
</tr>
<tr>
<td>Dogrusöz</td>
<td>2017</td>
<td>The Prognostic Value of AJCC Staging in Uveal Melanoma Is Enhanced by Adding Chromosome 3 and 8q Status</td>
</tr>
<tr>
<td>Farquhar</td>
<td>2018</td>
<td>Patterns of BAP1 protein expression provide insights into prognostic significance and the biology of uveal melanoma.</td>
</tr>
</tbody>
</table>
Table 4 with full details of the included and excluded studies in Appendix A2 in the separate document entitled Appendix 2022. Recent evidence in the literature would suggest that the new molecular prognostic markers in UM (e.g., BAP1 immunohistochemistry, the NGS panels assessing both CNV and most relevant mutations in UM as well as the TCGA UM subgroupings) do help better define metastatic risk in UM \((35,47,160–162,187,200,65,66,153–157,159)\). However, to date, the data is restricted and requires additional assessment on larger multicentre cohorts.

4.2.4 Evidence Statements

**Does the recent evidence of molecular pathology inform a change (or add to) prognostic tools?**

- Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological, immunohistochemical and genetic features.
- There are several different cytogenetic and updated molecular techniques for evaluating genetic changes in primary uveal melanoma, which help define metastatic risk.
- There is insufficient comparative data of the differing laboratory methods. No evidence was found that demonstrated one technique was superior to another but could be an area of future collaborative research.
- Incorporation of prognostic parameters into robust algorithms improves risk stratification of patients.

**Do the new prognostic markers help better define risk?**

- Updated molecular techniques and their targets, in combination with established copy number changes can stratify UM into genetic subgroups.
- There is insufficient comparative and longitudinal studies to demonstrate that the new prognostic markers better define risk. The genetic stratification suggests there is a basis, but
future and collaborative research is required to confirm if this translates to improved definition of risk level

**Prognostic tumour biopsy**

- Biopsy provides powerful prognostic information and aids patient stratification with respect to metastatic development; however, whilst preliminary data would suggest that treatment of a high-risk primary tumour when small could improve patient outcome, there is as yet inadequate evidence to demonstrate that changing management as a result of this genetic information affects survival in patients with larger tumours. (See Table 6)

### 4.2.5 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognostic factors/tool</strong></td>
</tr>
<tr>
<td>28. Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological and genetic features. The following features should be recorded:</td>
</tr>
<tr>
<td>• Patient age</td>
</tr>
<tr>
<td>• Patient sex</td>
</tr>
<tr>
<td>• Tumour location</td>
</tr>
<tr>
<td>• Tumour height</td>
</tr>
<tr>
<td>• Tumour Largest basal diameter</td>
</tr>
<tr>
<td>• Ciliary body involvement</td>
</tr>
<tr>
<td>• Extraocular melanoma growth (macroscopic and microscopic)</td>
</tr>
<tr>
<td>The following features should be recorded if tissue is available:</td>
</tr>
<tr>
<td>• Cell type (modified Callender system)</td>
</tr>
<tr>
<td>• Mitotic count (number/40 high power fields in H&amp;E stained sections)</td>
</tr>
<tr>
<td>• Presence of extravascular matrix patterns (particularly ‘closed loops’).</td>
</tr>
<tr>
<td>• Presence of extraocular melanoma growth (size in mm; presence/absence of encapsulation; relation to surgical margin).</td>
</tr>
<tr>
<td>• Positive or negative expression of nuclear BAP1 protein in the tumour cells. [2022]</td>
</tr>
</tbody>
</table>

29. The following features should be recorded if cytology of tumour is available:

- Confirmation of melanoma cells (i.e., exclude differential diagnoses, particularly metastatic carcinoma) – immunocytology may be required for this, but is not always necessary.
<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cell type (modified Callender system), if possible. [2022]</td>
</tr>
</tbody>
</table>

**Prognostic biopsy**

*See Table 6 The advantages and disadvantages of undertaking a UM biopsy*

30. There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
- Enabling prognostication and allow tailored follow-up
- Allowing recruitment into adjuvant trials
- Risks of having the biopsy
- Limitations of the investigation
- Effects of prognostication information on quality of life [2022]

31. The minimum dataset for UM from the Royal College of Pathology (or national official equivalents) should be recorded in the pathology reports. See: https://www.rcpath.org/profession/publications/cancer-datasets.html [2022]

32. Use the most up-to-date edition of the TNM staging system for prognostication and include in pathology/clinical reports. [2022]

33. Collect 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. [2022]

34. The use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features should be considered. [2022]

35. Where available the results of state-of-the-art molecular analysis should be combined with clinical features and standard anatomical and pathological staging for prognostication [2022]

36. Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programmes. [2022]
1. Comparative studies between panels and between molecular tools with a view to further refinement should be undertaken.

2. Genetic studies are required to examine the differences between indolent nodular and aggressive diffuse iris melanomas.

3. Comparative studies of prognostic algorithms should be carried out.

4. Supporting precision medicine and clinical trial design by validating tumour-related biomarkers.

5. Investigation of blood-borne biomarkers in a research or clinical trial setting would be of value.

An extensive review of the UM literature since the previous UM guidelines assessing morphological, immunohistochemical and genomic parameters in UM was undertaken, and presented to the UM Guideline writing committee over several sessions. The most relevant data in each of these differing areas were distilled and discussed in detail.

With respect to the potential blood-borne markers in UM, it was considered that there was insufficient evidence at the time of writing for these to be recommended to be included in routine clinical care. Instead, they were considered to be important for continued assessment in the domains of clinical trials and translational research.

### Table 6 The advantages and disadvantages of undertaking a UM biopsy

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of diagnosis in very small melanomas (differential diagnosis, naevus)</td>
<td>Currently no influence on treatment of metastatic disease</td>
</tr>
<tr>
<td>Resolving uncertainty about metastatic risk</td>
<td>Low potential of vision threatening complications</td>
</tr>
<tr>
<td>Patients’ preference</td>
<td>Rare risk of tumour cell seeding</td>
</tr>
<tr>
<td>Psychological impact: ‘Forewarned is forearmed’</td>
<td>Possibility of ‘negative’ biopsies – i.e., result not obtained in 5-10% of cases – e.g., small or necrotic tumours.</td>
</tr>
<tr>
<td>Justifying screening examinations in patients with small tumours and high-risk characteristics</td>
<td></td>
</tr>
<tr>
<td>Possible screening exclusion of patients with low-risk characteristics</td>
<td></td>
</tr>
<tr>
<td>Inclusion into future trials of adjuvant treatment to prevent metastatic disease</td>
<td></td>
</tr>
<tr>
<td>Influence on treatment in selected cases</td>
<td></td>
</tr>
</tbody>
</table>
- Test results not 100% predictive when 'standalone' – incorporation with other prognostic parameters required

- Psychological impact: high-risk result can be devastating for some patients; support required.
4.3 **Adjuvant therapy**

4.3.1 **Adjuvant systemic therapy** [2022]

4.3.1.1 **Introduction**

As above, around half of all patients with uveal melanoma subsequently develop metastases despite successful management of the primary. There remains no standard of care for metastatic uveal melanoma and at present it appears unlikely that any such treatment would be curative. An effective adjuvant treatment would have a significant impact in decreasing the proportion of patients developing metastases and thus on long term survival. In addition, well validated methods for prognostication have been developed (see section 4.2) which allow for the selection of patients most likely to develop metastases and which potentially allow targeting of adjuvant therapy at patients at high-risk only. Adjuvant therapy was not addressed in the previous edition of the guidelines due to a paucity of clinical trials. However, the recent presentation of a randomised study as well as other clinical studies, and the potential benefits of this approach supported a review of the area in the current edition.

4.3.1.2 **Review question: Is there a role for adjuvant systemic therapy after surgery?**

**Table 7: PICO characteristics of review question**

<table>
<thead>
<tr>
<th>Population</th>
<th>People with a diagnosis of uveal melanoma who have undergone primary treatment with curative intent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>Any adjuvant systemic anti-cancer therapy</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Observation alone, or alternative adjuvant therapy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Overall survival, melanoma specific survival, metastases free survival and/or recurrence free survival</td>
</tr>
<tr>
<td>Study design</td>
<td>Any, with the exception of case studies (n of 1)</td>
</tr>
</tbody>
</table>

The search was from 2015 onwards, hence studies were included from that date, any previous randomised studies identified from reviews and references were screened. There were no case studies identified in the search.

4.3.1.3 **Clinical evidence**

A systematic review of the literature was performed. Eleven studies which reported on adjuvant therapy were identified and all were included in the review; (256,257,266,258–265) of which 5 were randomised trials, 4 non-randomised trials and 2 case series.

The studies are listed in Table 8 below with full details of the included and excluded studies in Appendix A3 in the separate document entitled Appendix 2022.

---

3 The information for this section was reviewed, presented and drafted by Drs. Joe Sacco & Sukaina Rashid
Table 8 Summary of key studies included in the review

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binkley</td>
<td>2020</td>
<td>A prospective trial of adjuvant therapy for high-risk uveal melanoma: assessing 5-year survival outcomes</td>
</tr>
<tr>
<td>Desjardins</td>
<td>1998</td>
<td>Randomized study of adjuvant therapy by DTIC in choroidal melanoma</td>
</tr>
<tr>
<td>Fountain</td>
<td>2019</td>
<td>Adjuvant Ipilimumab in High-Risk Uveal Melanoma.</td>
</tr>
<tr>
<td>Lane</td>
<td>2009</td>
<td>Adjuvant Interferon Therapy for Patients with Uveal Melanoma at High-risk of Metastasis.</td>
</tr>
<tr>
<td>Lawson</td>
<td>2015</td>
<td>Randomized, placebo-controlled, phase III trial of yeast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) versus peptide vaccination versus GM-CSF plus peptide vaccination versus placebo in patients with no evidence of disease after comp</td>
</tr>
<tr>
<td>McLean</td>
<td>1990</td>
<td>A randomized study of methanol-extraction residue of bacille Calmette-Guerin as postsurgical adjuvant therapy of uveal melanoma</td>
</tr>
<tr>
<td>Piperno-Neumann</td>
<td>2017</td>
<td>A randomized multicenter phase 3 trial of adjuvant fotemustine versus surveillance in high-risk uveal melanoma (UM) patients (FOTEADJ)</td>
</tr>
<tr>
<td>Sato</td>
<td>2020</td>
<td>A randomized phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma.</td>
</tr>
<tr>
<td>Valsecchi</td>
<td>2018</td>
<td>Adjuvant Sunitinib in High-Risk Patients with Uveal Melanoma: Comparison with Institutional Controls.</td>
</tr>
<tr>
<td>Voelter</td>
<td>2008</td>
<td>Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients.</td>
</tr>
</tbody>
</table>

Randomised studies

Four randomised studies were identified; however, one of these only included 11 uveal melanoma patients (260). This was a study investigating GM-CSF, peptide vaccination, both or placebo in melanoma (predominately cutaneous). The study was negative, showing no evidence for benefit for any of the interventions. No further conclusions could be drawn on the uveal melanoma subpopulation.

Most recently, Piperno-Neumann et al (263) presented results from a randomised phase III study which compared adjuvant fotemustine and surveillance alone. The study was well designed and recruited 244 patients from two countries, before terminating early following evidence of futility. The primary endpoint was 5-year metastasis free survival (MFS). With a median follow-up of 3 years, the 3-year MFS is 60.3% in the chemo group and 60.7% in the surveillance group (HR 0.97 [0.64-1.47]). The 3-year OS is 79.4% [73.2-85.7], with no difference between the 2 groups of patients. Publication of full results is awaited, however the results presented to date strongly suggest adjuvant fotemustine is ineffective. However, the study does provide a template for future adjuvant studies, while highlighting the difficulties in recruiting to adjuvant studies in uveal melanoma and underpinning the need for multinational collaboration in this field.
A further randomised study (257) investigated the activity of adjuvant dacarbazine against observation alone. This study predated the use of molecular prognostication, which reduces the overall power. However, the study was negative showing no evidence of improvement in outcome with dacarbazine.

McLean et al (262) investigated methanol-extracted residue of bacille Calmette-Guerin (BCG) as adjuvant treatment for posterior uveal melanoma. The study was randomised against no treatment, with 34 receiving the treatment and 79 having no treatment. There was a significant potential for bias as a proportion of patients who were randomized to intervention did not receive it and were included in control arm. While the study showed no evidence of benefit from the intervention, it was underpowered and predated the routine use of genetic prognostication.

A randomized non-comparative study of sunitinib and valproic acid is ongoing (264) and is discussed in the section below.

**Non-randomised studies**

Binkley et al (256) investigated adjuvant therapy with dacarbazine and interferon-α-2b. The study included 33 patients with a further 29 patients with high-risk disease were included in the control group (non-randomised). Following adjustment for risk factors, there were no significant differences in outcome (metastasis free survival and overall survival). A single arm study of adjuvant intra-arterial hepatic fotemustine (266) recruited 22 patients with 66 matched controls. While there was a numerical difference in overall survival (9 years versus 7.4 months in controls) this was not statistically significant and is subject to selection bias as there was no randomisation. A larger study investigated adjuvant interferon study in comparison to historical controls. A total of 121 patients were treated (55 of whom completed treatment) with 242 controls. In multivariate Cox regression, interferon had no significant influence on melanoma specific mortality or all-cause mortality.

The activity of adjuvant sunitinib has been investigated in two studies. In the first, sunitinib was used off label (265) in 54 patients and compared to 74 historical controls in a retrospective analysis. In univariate analysis, the sunitinib group had longer overall survival (hazard ratio, 0.53; 95% confidence interval, 0.29-0.99; P=0.041) while in multivariate Cox regression analysis, the following variables were statistically associated with prediction of overall survival: cytogenetic/molecular status (P =0.015), T-size category (P = 0.022), gender (P =0.040), and adjuvant sunitinib in patients aged <60 yrs (p=0.0004). However, as a retrospective non-randomised study with relatively small numbers, it is subject to significant confounders which limits the ability to draw conclusions. The results however supported the set-up of a prospective randomised study in patients with high-risk uveal melanoma (264) which is ongoing. The study, although randomising between sunitinib and valproic acid, is not powered to allow comparison between the arms. An initial abstract reports outcomes on 90 patients randomised (46 in the sunitinib arm and 44 in VPA arm). The 2-year OS rates of the sunitinib and VPA group were 95.6% (90% CI 86.5-98.6) and 90.7% (90% CI 80.1 - 95.8), respectively. In view of the numerically better outcome for the sunitinib arm, a further cohort has been opened to investigate this further.

A single study investigating the activity of immune checkpoint inhibitors in the adjuvant setting has been published (258). The study only recruited 10 patients out of a planned 89, and discontinued early. Due to the small numbers, no conclusions can be made on activity in this setting. Finally, a retrospective cohort study of adjuvant therapy at a cancer centre in China (261) has been presented. This included patients on observation only (n = 39), interferon (n = 15), chemotherapy (n = 13), and dendritic cell vaccination (n = 2). This is available in abstract only and with low numbers and few details on risk stratification, it is impossible to draw further conclusions.
Ongoing studies

A number of other studies were identified on clinicaltrials.gov (23) with most having completed recruitment. These include a randomized, open-label phase III study to evaluate the adjuvant vaccination with tumour RNA-loaded autologous dendritic cells versus observation of patients with resected monosomy 3 uveal melanoma; results of which are not currently available.

Studies on crizotinib, and iplimumab and nivolumab are ongoing as well as the previously discussed study of sunitinib and valproic acid.

4.3.1.4 Economic evidence

No economic evidence was found.

4.3.1.5 Evidence statements

- There is currently insufficient evidence to support the use of adjuvant systemic therapy outside of clinical trials.
- While some single arm studies have shown a potential signal for benefit, these require further validation which may include randomized studies, independent cohorts and/or use of well matched, large synthetic control arms.
- The availability of well validated prognostic markers that correlate strongly with survival, provides a means to identify patients who would benefit from active adjuvant agents and further trials in this area are urgently needed.

4.3.1.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>37. The availability of prognostic tools that allow identification of high-risk primary disease and the poor outcomes for metastatic uveal melanoma support an adjuvant approach. In the absence of proven therapy, adjuvant systemic therapy should only be given within a well-designed clinical trial. [2022]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Linking evidence to recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The view of the GDG was that, although some of the trials looked promising, the absence of randomisation hampers interpretation. Selection bias and confounding factors are difficult to counter for in single arm studies and would likely require very large contemporary matched control arms with pre-planned rigorous statistical designs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. High quality clinical trials of adjuvant treatment with associated bio-banking for translational research are required</td>
</tr>
</tbody>
</table>
4.3.2 Adjuvant radiation therapy\textsuperscript{4} [2022]

4.3.2.1 Introduction

Extra-ocular extension is defined as tumour expansion past the corneo-scleral envelope and occurs in 2-6\% of all cases, and approximately 13\% of cases undergoing enucleation (132). The presence of extra-ocular extension (particularly if unencapsulated) is associated with an increased risk of developing metastases, poorer survival and increased risk of local recurrence. The 8th edition of the American Joint Committee on Cancer (130) includes extra ocular extension within the staging system, with extra ocular extension >5mm conferring a worse prognosis.

There is a paucity of data demonstrating whether adjuvant external beam radiation therapy to the orbit after enucleation improves local control or overall survival. It is postulated that in high-risk cases, adjuvant external beam radiation therapy will increase local control and reduce the incidence of metastatic disease. However, radiation therapy does cause local side effects including socket contracture and wound breakdown.

4.3.2.2 Question: What is the role of radiation therapy as adjuvant treatment to the orbit?

Table 9: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with uveal melanoma who have undergone surgery with curative intent (enucleation or exenteration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>External beam radiation therapy</td>
</tr>
<tr>
<td>Comparison</td>
<td>Observation (No adjuvant radiation therapy)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Local control rate, overall survival, toxicity from radiation therapy</td>
</tr>
<tr>
<td>Study design</td>
<td>Any</td>
</tr>
</tbody>
</table>

4.3.2.3 Clinical evidence

A literature review did not identify any randomised controlled trials conducted comparing the effectiveness of adjuvant radiation therapy against no radiation therapy for patients with uveal melanoma. Two single centre observational studies from the same centre (267,268) were identified one which was published in 1990 and one in 2020. The studies are listed in Table 10 below with full details of the included and excluded studies in Appendix A4 in the separate document entitled Appendix 2022.

The first paper is a case series of 17 patients with extra-scleral extension who had adjuvant external beam radiation therapy to the orbit. The extra-scleral extension was encapsulated in 5 patients, non-encapsulated in two patients and transected at enucleation in 10 patients. External beam radiation therapy was delivered with cobalt-60, caesium-137 or megavoltage electrons. The average dose

\textsuperscript{4} The information for this section was reviewed, presented and drafted by Dr. Rachel Lewis
delivered was 50Gy/22 fractions. The dose per fraction >2Gy is used, as melanoma cells are radioresistant and have a high intrinsic capacity to repair sublethal DNA damage by radiation. They have a low α/β ratio and are therefore more sensitive to dose per fraction2.

The actuarial overall survival rate was 51% at 5 years, 44% at 10 years and 33% at 15 years. There was no significant difference in survival of patients in patients who had transected versus non-transected extraocular spread, or the size of extraocular spread. One patient developed orbital recurrence within 3 weeks of completing radiation therapy. No significant toxicity was reported other than slight loss of eyebrow hair and thinning of the eyelashes.

The second paper is an observational study of a cohort of 51 patients with extra-ocular extension treated over a 22-year period in the same centre. 22 of these patients had adjuvant post-enucleation radiation therapy. These were patients who had more extensive extra-ocular extension (5.1mm vs 2.6mm) or incomplete surgical resection. No local recurrence was noted in either those irradiated or those not irradiated. The 5- and 10-year overall survival rates were 56% and 12% respectively with no difference in all-cause mortality between those receiving radiation therapy and those who didn’t. Patients received 50Gy/20 fractions with MV photons on the linear accelerator. 14 of the 22 patients developed side effects – 4 developed socket contractures, 8 developed persistent inflammation of the eyelids and socket, 1 had implant exposure and 1 had discomfort necessitating removal of the implant.

In view of the paucity of evidence, a survey was conducted of practice in different centres in the UK. This varies between no radiation therapy, radiation therapy for all patients with extra-ocular extension or radiation therapy for those patients with >5mm extra-ocular extension. All agreed that data collection should be shared and a multicentre randomised controlled study assessing the role of external beam radiation therapy in patients with extensive extra-ocular extension should be carried out.

Table 10: Summary of key studies included in the review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Intervention and comparison</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hykin</td>
<td>1990</td>
<td>Postenucleation orbital radiotherapy for the treatment of malignant melanoma of the choroid with extrascleral extension.</td>
<td>Observation, no control 17 patients receiving adjuvant external beam radiotherapy.</td>
<td>Patients had extra-ocular extension. 12 male 5 female.</td>
<td>1 local relapse. OS 51% at 5 years, 44% at 10 years, 33% at 15 years. No significant side effects noted.</td>
</tr>
<tr>
<td>Roelofs</td>
<td>2020</td>
<td>Adjuvant External Beam Radiotherapy Following Enucleation of Eyes With Extraocular Extension</td>
<td>Observational cohort study 51 patients, 22 of which received adjuvant external beam radiotherapy.</td>
<td>59% male, mean age 67. 22 patients had external beam radiotherapy Patients who received EBRT had larger extra-ocular extension (5.1mm vs 2.6mm)</td>
<td>5-year survival 56%, 10 year survival 12%. No difference in all cause mortality between those receiving radiotherapy and those who didn’t. No cases orbital recurrence. Local</td>
</tr>
</tbody>
</table>
4.3.2.4 Economic evidence

No economic evidence was found.

4.3.2.5 Evidence statements

There are no published randomised controlled data to support

4.3.2.6 Recommendations and link to evidence

| Recommendations |
|-----------------|---------------------------------------------------------------|
| 38. | There is very limited evidence for adjuvant radiation therapy to the orbit after definitive surgical treatment of primary disease. It is an option that can be considered for patients deemed to be at high risk of local relapse (e.g., greater than 5mm tumour extra-ocular extension in enucleation samples). Toxicity should be balanced against lack of evidence for efficacy and patients should be counselled on the benefits and risks of radiation therapy. [2022] |
| 39. | When radiation therapy is indicated, due to the relative radio resistance of melanoma, doses greater than 2Gy per fraction are recommended with a total does of 45-50Gy/20#. [2022] |

<table>
<thead>
<tr>
<th>Research recommendation</th>
<th>8. In the absence of a prospective trial, audit of all patients with pathological evidence of extra-ocular extension is recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion of the evidence to recommendations</td>
<td>• There are no randomised controlled trials looking at the benefit of adjuvant radiation therapy to the orbit for patients who have had an enucleation for high-risk ocular melanoma with extra-ocular extension • The theory is that adjuvant radiation therapy may reduce the risk of local recurrence • Case series have demonstrated that external beam radiation therapy can cause long term side effects, for example socket contracture • The committee has recommended that radiation therapy should be considered in patients with a high-risk of recurrence (with extra-ocular extension &gt;5mm) but that a national study should be carried out to support this going forward.</td>
</tr>
</tbody>
</table>
4.4 Treatment options for macroscopic orbital recurrence [2022]

4.4.1 Introduction

There is currently no evidence-based consensus on the optimal way to treat macroscopic orbital recurrence with treatment being on a case-by-case basis. Consequently, it was added as a question to the revision of the guideline in order to look for recent evidence.

4.4.2 Review question: What are the treatment options for macroscopic orbital recurrence

Table 11: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients diagnosed with a macroscopic orbital recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>Radiation therapy, surgery</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Each other or usual care</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Reduction in tumour size</td>
</tr>
<tr>
<td>Study design</td>
<td>Any</td>
</tr>
</tbody>
</table>

4.4.3 Clinical evidence

No evidence was found.

4.4.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>45. For local macroscopic recurrence in the orbit, there should be a discussion at MDT to discuss surgical and radiation therapy options. [2022]</td>
</tr>
<tr>
<td>46. When radiation therapy is indicated, due to the relative radio resistance of melanoma, doses greater than 2Gy per fraction are recommended with a total does of 45-50Gy/20#.</td>
</tr>
</tbody>
</table>

Discussion of the evidence to recommendations

The GDG discussed the situation when there is local recurrence of tumour in the orbit with no distant metastases. The committee agreed that each patient situation is different as this may occur after surgery, plaque brachytherapy or proton beam therapy and the patient may have had an enucleation/exenteration or may have the globe in situ. Each situation should be considered on a case-by-case basis and as such there are no data to support any intervention. Options include surgery, external beam radiotherapy with photons, proton beam radiotherapy and stereotactic radiotherapy and treatment intent may be radical or palliative.

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5 The information for this section was reviewed, presented and drafted by Dr Rachel Lewis
4.5 Metastatic disease

4.5.1 Systemic treatment [2022]6

4.5.1.1 Introduction

The management of metastatic disease remains an area of unmet need. When the previous iteration of these guidelines was published in 2015 there were few randomised controlled trials (RCTs), no standard of care and no therapies that had been shown to improve survival. After this, there have been several studies presented or published, particularly of targeted agents and immunotherapy-based treatments, including an RCT confirming a survival benefit (80) There is therefore a need to update the guidelines on this aspect of UM management.

4.5.1.2 Review question: What are the best available systemic options for the management of metastatic uveal melanoma?

Table 12: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients diagnosed with metastatic uveal melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>Chemotherapy, selumetinib, sunitinib, sorafenib, cabozantinib, ipilimumab, nivolumab, pembrolizumab, adoptive T cell therapy, tebentafusp, other systemic agents</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>With each other, with placebo, with nothing</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Overall survival, progression-free survival, objective response rate</td>
</tr>
<tr>
<td>Study design</td>
<td>Meta-analysis, Systematic reviews, RCT, Non-randomised trials, Case Series</td>
</tr>
</tbody>
</table>

Case series with n<10 were excluded. Papers not addressing uveal melanoma (e.g., cutaneous melanoma, mucosal melanoma and conjunctival papers) were excluded. Pre-clinical papers were excluded.

4.5.1.3 Clinical evidence

Description of studies

Sixty-one studies were included in the review. This included:

- Systematic reviews & Meta-analyses (n=5) (115,269–272)
- Randomised trials (n=12) (80,273,282–284,274–281)
- Non-randomized trials (n=19) (285,286,295–301,287–294)

The studies are listed in Table 13 below with full details of the included and excluded studies in Appendix A5 in the separate document entitled Appendix 2022.

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66 The information for this section was reviewed, presented and drafted by Drs Matthew Wheater, Joe Sacco and Jack Broadfoot
**Table 13: Summary of key studies included in the review**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itchins</td>
<td>2017</td>
<td>A multireferral centre retrospective cohort analysis on the experience in treatment of metastatic uveal melanoma and utilization of sequential liver-directed treatment and immunotherapy</td>
</tr>
<tr>
<td>Jochems</td>
<td>2019</td>
<td>Metastatic Uveal Melanoma: Treatment Strategies and Survival-Results from the Dutch Melanoma Treatment Registry</td>
</tr>
<tr>
<td>Khoja</td>
<td>2019</td>
<td>Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study</td>
</tr>
<tr>
<td>Lane</td>
<td>2018</td>
<td>Survival rates in patients after treatment for metastasis from uveal melanoma</td>
</tr>
<tr>
<td>Moser</td>
<td>2015</td>
<td>The Mayo Clinic experience with the use of kinase inhibitors, ipilimumab, bevacizumab, and local therapies in the treatment of metastatic uveal melanoma</td>
</tr>
<tr>
<td>Nicholas</td>
<td>2018</td>
<td>Prognostic factors for first-line therapy and overall survival of metastatic uveal melanoma: The Princess Margaret Cancer Centre experience</td>
</tr>
<tr>
<td>Rantala</td>
<td>2019</td>
<td>Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis</td>
</tr>
<tr>
<td>Rodriguez-Vidal C</td>
<td>2021</td>
<td>Treatment of Metastatic Uveal Melanoma: Systematic Review</td>
</tr>
<tr>
<td>Seedor</td>
<td>2020</td>
<td>An Outcome Assessment of a Single Institution’s Longitudinal Experience with Uveal Melanoma Patients with Liver Metastasis</td>
</tr>
</tbody>
</table>

**Chemotherapy**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee</td>
<td>2015</td>
<td>Results of a Phase II Study to Evaluate the Efficacy of Docetaxel and Carboplatin in Metastatic Malignant Melanoma Patients Who Failed First-Line Therapy Containing Dacarbazine</td>
</tr>
<tr>
<td>Peuker</td>
<td>2018</td>
<td>Retrospective analysis of the treatment of metastatic uveal melanoma comparing systemic chemotherapy and transarterial chemoembolization</td>
</tr>
<tr>
<td>Sacco,</td>
<td>2013</td>
<td>Sunitinib versus dacarbazine as first-line treatment in patients with metastatic uveal melanoma (review of published abstract and unpublished manuscript provided by author)</td>
</tr>
<tr>
<td>Schinzari</td>
<td>2017</td>
<td>Cisplatin, dacarbazine and vinblastine as first line chemotherapy for liver metastatic uveal melanoma in the era of immunotherapy: a single institution phase II study</td>
</tr>
</tbody>
</table>

**Targeted treatment**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caravajal</td>
<td>2014</td>
<td>Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial</td>
</tr>
<tr>
<td>Luke</td>
<td>2020</td>
<td>Randomized Phase II Trial and Tumor Mutational Spectrum Analysis from Cabozantinib versus Chemotherapy in Metastatic Uveal Melanoma (Alliance A091201)</td>
</tr>
<tr>
<td>Nathan</td>
<td>2019</td>
<td>SELPAC: a 3 arm randomised phase II study of the MEK inhibitor selumetinib alone or in combination with paclitaxel (PT) in metastatic uveal melanoma (UM)</td>
</tr>
<tr>
<td>Piperno-Neumann</td>
<td>2020</td>
<td>Genomic Profiling of Metastatic Uveal Melanoma and Clinical Results of a Phase I Study of the Protein Kinase C Inhibitor AEB071.</td>
</tr>
</tbody>
</table>
4.5.1.4 Summary of evidence

Studies of multiple agents

Five systematic reviews were identified, three of which assessed multiple classes of systemic therapy (115,270,271) In the Khoja et al meta-analysis, an exploratory analysis showed patients treated with liver directed treatments (LDT) had numerically higher PFS and OS (compared to the rest combined), and treatment with LDT remained a prognostic factor in a multivariate analysis (ie accounting for tumour burden, gender etc). No statistical differences were observed between other classes of intervention (chemotherapy, immunotherapy, targeted therapy, anti-angiogenesis) and individual
treatments were not assessed (due to insufficient numbers). In the Rantala et al meta-analysis, minor statistically significant differences in survival were observed with LDT (surgery or immune-embolisation) but were subject to confounding factors. A third systematic review was predominantly descriptive and did not allow for comparison of agents (271).

A further six case series reported on outcomes for multiple different therapies (307,308,312,317,320,322), but did not allow for robust statistical comparisons between different agents. While the Rantala and Khoja meta-analyses did not provide evidence to guide use and/or choice of systemic therapy, these provide important benchmarking for PFS and OS for future studies, as well as confirming the role of prognostic factors (principally LDH and ALP).

Chemotherapy

Since the previous guidelines were published in 2015 the evidence base for chemotherapy now includes a further two prospective single-arm trials, a retrospective single-centre case series and one unpublished randomised trial in which chemotherapy was the control arm.

Sacco et al (281) randomised 84 uveal melanoma (UM) patients to receive sunitinib or dacarbazine, and reported an objective response rate of 8% in the chemotherapy control arm. No significant differences in survival were observed, with a modest progression-free survival (PFS) of 2.8 months and overall survival (OS) of 7.4 months in those treated with dacarbazine.

The two single-arm trials provide limited data on a modest 35 UM patients. Schinzari et al (298) assessed first-line cisplatin, dacarbazine and vinblastine in 25 patients. Partial responses were observed in 20% of cases whilst 48% had stable disease. Median PFS was 5.5 months and OS was 13 months, with 20% experiencing CTCAE grade 3-4 toxicity. Lee et al (291) reported outcomes on 10 patients who received second line docetaxel and carboplatin. The best response was stable disease with a median PFS 7.6 months and OS of 9.9 months. Peuker et al (321) reported a single-centre case series of 287 UM patients comparing systemic chemotherapy (gemcitabine and treosulfan) with transarterial chemo-embolisation. 82 patients received systemic treatment with a modest objective response rate (ORR) of 6.8% and PFS of 2.8 months.

Targeted treatment

As our understanding of the unique genomic landscape of uveal melanoma has improved, the number of potential targeted agents in trials has increased significantly. For example, the identification of GNAQ and GNA11 mutations in up to 90% of cases has led to multiple trials of agents targeting the MAPK signalling pathway; which is activated by GNAQ/GNA11 mutations. As mentioned in the 2015 iteration of the guidelines, one of these earlier trials by Carvajal (274) in 2014 reported a doubling of PFS with selumetinib versus temozolamide (15.9 weeks vs 7 weeks). However, subsequent studies of MEK inhibitors, both in combination or as monotherapy, have not shown significant activity or improved survival. The phase III randomised SUMIT trial of selumetinib plus dacarbazine versus placebo plus dacarbazine in 129 UM patients did not demonstrate a significant improvement in PFS (2.8 vs 1.8 months respectively). Nathan et al (280) presented an abstract for a phase II study (SELPAC) assessing selumetinib alone or in combination with paclitaxel. There was a small but significant improvement in PFS with combination therapy (4.8 months vs 3.4 months) without additional toxicity. However, a response rate of only 4% in the selumetinib group did not suggest significant anti-tumour activity. Most of these trials were included in a systematic review of six studies and 363 patients assessing several MEK inhibitors including selumetinib, trametinib and binimetinib either alone or in combination with chemotherapy or other targeted agents (272). Of these, SUMIT was the sole randomised controlled trial (RCT) and survival data was not consistently reported. The mean response rate was 2.5% and PFS ranged from 3.1 to 16 weeks.
PKC is a crucial node in signalling downstream of GNAQ/GNA11. In a large phase I trial of the PKC inhibitor AEB07 (n of 153), the response rate was reported as 3% with best response of stable disease in 50%; overall survival has not yet been reported. Studies of other PKC inhibitors, alone or in combination, are underway but yet to report full results. (326)

There have also been numerous trials of multi-receptor tyrosine kinase inhibitors including sorafenib, sunitinib and cabozantinib. A phase II randomised discontinuation study of sorafenib versus placebo in chemotherapy-naïve patients found no improvement in OS (14.8 vs 14.4 months; (284), while a similarly designed trial of the MET and VEGF inhibitor cabozantinib reported no objective responses in metastatic UM patients(276). Randomised phase II studies of cabozantinib (279)and sunitinib (281) compared with dacarbazine chemotherapy were both terminated due to futility after interim analysis showed no significant differences in PFS or OS.

Immunotherapy

One of the main areas of growth in the evidence base for systemic therapy has been immune checkpoint inhibitors, with anti-PD-1 and anti-CTLA-4 agents used as monotherapy and in combination. Heppt et al (269) published a systematic review of single-agent and combination treatment. Unfortunately, it’s publication in 2017 means a number of more recent notable trials were not included. With the exclusion of retrospective studies only 12 eligible trials were identified, none of which were RCTs. Data on combination treatment was limited to one expanded access program involving six patients, with no objective responses observed and a median PFS of 2.9 months. The authors concluded minimal activity of ipilimumab monotherapy from five studies of 186 patients, with a median PFS of less than three months and OS between 5.2 and 9.8 months. Two studies reported on pembrolizumab and nivolumab monotherapy, with ORRs of 30% (n of 10) and 6% (n of 75) respectively.

Notable trials of single-agent treatment include two single-arm phase II studies and two case series. Published in 2019, the Checkmate 172 (293) open-label phase II trial assessed nivolumab monotherapy following disease progression on or after ipilimumab. Efficacy was assessed across a range of disease sub-types, including 103 UM patients in whom median OS was reported as 12.6 months. Other studies of monotherapy are limited by small patient numbers and considerable heterogeneity in terms of previous lines of treatment. Estimated synthesis of these monotherapy trials suggests an average response rate of 5% and OS of approximately 12 months.

Evidence for combination anti-CTLA-4 and anti-PD-1 treatment was derived from two single-arm open-label trials, and three retrospective case series. Though efficacy was limited and reported survival rates varied considerably, average response rates of 15% and OS of up to 16 months suggested increased activity in comparison with monotherapy. For example, in a phase II open label trial of ipilimumab plus nivolumab in 35 metastatic UM patients, Pelster et al (327) reported an objective response rate of 18% and median OS of 19.1 months. On the other hand in the GEM-1402 trial of ipilimumab plus nivolumab in treatment-naïve UM patients (n= 52), Piulats et al (328) reported a response rate of 11.5% and median OS of 12.7 months.

These studies also highlighted the importance of patient selection. In the GEM-1402 trial Piulats et al (328) reported a trend towards longer OS in patients with extra-hepatic disease (23.5 months) versus those with liver-confined metastasis (9.2 months). A similar picture was seen in a large retrospective case review across multiple German centres of patients with liver metastases from uveal melanoma, with or without extra-hepatic metastases treated with immune checkpoint inhibitors (325). 178 patients were identified and split into two cohorts with either liver metastases alone (55 patients) or both liver and extra-hepatic metastases (123 patients). All patients were treated with either single agent or combination checkpoint inhibitors. The overall survival for those with extra-hepatic disease was 18.2 months vs 6.1 months for those with liver metastases alone.
Response rates to combination immunotherapy were lower in the liver metastases alone cohort at 8.7% vs 16.7% in those with liver and extra-hepatic disease. Although a retrospective review this seems to support the signal seen in the two prospective studies of combination checkpoint inhibitors in which patients with liver only metastatic disease responding less well to treatment.

Several other immunotherapy approaches have been assessed. Chandran et al (286) were the first to report on adoptive transfer of autologous TILs in metastatic UM. Their single-arm phase II study of 21 patients, 43% of whom had received prior immunotherapy, demonstrated objective tumour regression in 35% of cases. However, no survival data has been presented and it was notable that most partial responses were not durable, with subsequent disease progression within nine months in 57% of these cases.

Sacco et al (282) presented data from a phase II trial of tebentafusp, a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector. The engineered receptor binds to the antigen gp100 on UM cells presented by the MHC class I protein HLA-A*02:01, while the anti-CD3 antibody then activates CD3-positive T cells. In 127 previously treated, HLA-A*02:01-positive patients, the ORR was 5%, with a median OS of 16.8 months and a 12-month OS rate of 62%. Toxicities were predictable and manageable, and although 86% of patients experienced cytokine release syndrome, only 4% of cases were grade 3-4.

The subsequent randomised open-label phase III trial (80) allocated patients 378 treatment-naïve patients with a 2:1 randomisation to tebentafusp versus investigators’ choice of dacarbazine, ipilimumab or pembrolizumab showed 82% of patients in the control arm received pembrolizumab. The study showed longer OS with tebentafusp with a median OS 21.7 months vs 16 months for the control arm. OS at one year was 73% with tebentafusp and 59% in the control group. PFS was also significantly higher in the tebentafusp group (31% vs 19% at 6 months). This is the first prospective randomised trial to show a survival advantage against an active agent in metastatic uveal melanoma. Although patients in the control arm received monotherapy rather than combination ipilimumab plus nivolumab immunotherapy, it remains unclear how much additional benefit is seen for combination checkpoint inhibitor treatment in the absence of randomised data. The median OS of 16 months in the control arm is comparable to that seen with ipilimumab and nivolumab in the two prospective phase II studies described above at 19.1 months and 12.7 months respectively.

4.5.1.5 Economic evidence

No economic evidence was identified.

4.5.1.6 Evidence statements

- There is no robust evidence to support an improvement in survival with cytotoxic chemotherapy.
- Studies of selumetinib (or other MEK inhibitors) either as monotherapy or in various combinations suggest low activity in metastatic UM.
- Similarly, sunitinib, cabozantinib, sorafenib and other targeted agents have not demonstrated clinical efficacy in clinical trials.
- Response rates to immune checkpoint inhibitors are low; ~5% for single agent therapy and in the region of 12-18% for combination; however, this is possibly not fully representative of clinical benefit.
- Immune checkpoint inhibitors have been used a default standard of care in contemporary clinical trials; however, their activity has never been compared to placebo or no treatment.
Adoptive T cell therapy has shown activity in a single-phase II trial but randomised or other confirmatory data are not available.

Tebentafusp has demonstrated improved survival in the first line setting in a randomised phase III trial, as well as prolonged survival in a separate single arm study in the second+ line, compared to historical controls.

Tebentafusp only has activity in patients with the HLA-A*02:01 genotype.

### 4.5.1.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>53. Pending licencing and availability consider offering tebentafusp to HLA-A*02:01 positive fit patients with metastatic disease. [2022]</td>
</tr>
<tr>
<td>54. Patients should be considered for clinical trials wherever possible and be informed of available trial options at other centres. [2022]</td>
</tr>
<tr>
<td>55. 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. [2022]</td>
</tr>
<tr>
<td>56. Specialist centres should be involved in treatment decisions and review, but a patient may prefer to receive supportive care and systemic treatment locally if possible. [2022]</td>
</tr>
<tr>
<td>57. Systemic immune checkpoint inhibitors (ICI) can be considered in the absence of relevant clinical trials. Without clear evidence of superiority, treatment decisions between single agent and combination ICI require careful discussion regarding the risk of significant toxicity and modest potential additional benefits. [2022]</td>
</tr>
<tr>
<td>58. For patients with liver only or liver predominant disease, local or locoregional therapy may also be considered (see Section 4.5.2)</td>
</tr>
<tr>
<td>59. Chemotherapy has limited, if any, efficacy in uveal melanoma, and as such should only be used in the absence of other options and with full discussion of risks and impact on quality of life [2022]</td>
</tr>
<tr>
<td>60. Targeted therapy should only be used in the context of a clinical trial. [2022]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Clinical studies, biobanking, and/or participation in patient registries should be considered for all patients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discussion of the evidence to recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There was extensive discussion amongst the group over the lack of comparative data between single agent and combination checkpoint inhibitor treatment. It was felt that patients considering combination treatment should be counselled</td>
</tr>
</tbody>
</table>
as to the possible small increase in overall survival in the context of a significant difference in toxicity profile.

- The group discussed the challenges around interpreting the tebentafusp data randomised against single agent investigators choice therapy (predominantly single agent pembrolizumab) together with single arm studies of combination ipilimumab and nivolumab. The group felt that on level of evidence then randomised phase III data showing a survival advantage over alternative active treatment gave the most robust results.

### 4.5.2 Impact on choice of therapy for metastatic disease

#### 4.5.2.1 Review question: Do the results of the molecular profiling of the primary or metastatic tissue, or patient’s germline impact on choice of therapy for metastatic disease?

Table 14: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>HLA-A*02:01+ patients with diagnosed primary uveal melanoma and clinical evidence of metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation</td>
<td>bispecific molecule tebentafusp</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>investigator’s choice (pembrolizumab, ipilimumab or dacarbazine)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>OS benefit</td>
</tr>
<tr>
<td>Study design</td>
<td>randomized, open-label, phase 3 trial in first line setting in HLA-A*02:01+ patients</td>
</tr>
</tbody>
</table>

#### 4.5.2.2 Clinical Evidence

Currently the only validated biomarker that can aid the choice of systemic treatment for metastatic uveal melanoma (mUM) is the HLA allele HLA-A*02:01, the presence of which prioritises patients for treatment with tebentafusp. No tumour molecular features have been validated as predictive biomarkers to date.

Virtually all primary uveal melanomas harbour mutations in either **GNAQ/GNA11/PLCB4/or CYSTLR2**, genes all of which converge on the Gaq signalling pathway (48,52,53,329). Blockade of the pathways downstream of Gaq including PKC, mTOR, PI3K and MAPK pathways has been evaluated in clinical trials, with very limited benefit (273,283,326,330). The reason for the failure of these trials is complex but likely includes negative feedback loops, alternative survival pathways utilised by cancer cells under blockade, and sub-optimal pharmacology of the trialled inhibitors (331).

The approach to systemic treatment for mUM therapies is largely based on evidence generated in the setting of the more common cutaneous melanoma (CM), including immune checkpoint blockade (CPI). The response rates to CPI are significantly lower in mUM compared with CM: 5% vs. 40–50% for single

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7 information for this section was reviewed, presented and drafted by Drs Samra Turajlic and Camille Gerard
agent anti-PD1, and 12-17% vs. ~60% for the combination of anti-CTLA4 and anti-PD1 (318,327,332–335) Notable is the absence of complete responses in mUM.

Biomarkers of response to CPI across different tumour indications include tumour mutational burden (TMB), presence of DNA mismatch repair defect (dMMR/MSI-H), PD-L1 expression on tumour cells, presence of tumour-infiltrating lymphocytes (TILs), and interferon-gamma (IFN-) signature (336,337). A high TMB is a predictor of response to CPI in multiple solid cancers, including CM (338,339) and recently FDA approved the use of pembrolizumab for any tumours with high TMB (H-TMB ≥ 10 mutations per Mb (340). Uveal melanoma exhibits one of the lowest TMB in solid cancers with an average of 0.5 mutations per Mb (341,342) consistent with the lack of UV exposure. (56) Two case reports have shown that UM patients with germline loss-of-function MBD4 mutations and somatic loss of heterozygosity are associated with high level of CpG>TpG mutations and higher TMB than expected for uveal melanoma. Rodrigues et al found 1/42 mUM patients (<1%) treated with an anti-PD1 and had a complete response in the liver, lung and bone metastases, had a germline MBD4 mutation. (202) Another patient with MBD4 germline mutation and mUM was treated with anti-PD1 and anti-CTLA4, and had stable disease for 10 months and two-year overall survival (OS), more than is expected in this setting. (203) In the context of colorectal cancer, germline MBD4 mutations are associated with dMMR deficiency, which itself is a tumour-agnostic indication for the use of pembrolizumab. (343) In addition, somatic MBD4 pathogenic variants are also found in UM. (33,34) These observations indicate that infrequently patients with mUM can have uncharacteristically high TMB, potentially as a result of MBD4 mutations or other alterations (33,34). Thus, if the patient's tumour or germline are undergoing molecular profiling the mutational status of MBD4 as well as the TMB estimate should be noted.

There is no evidence that any of the frequent mutations in UM influence response to CPI. BAP1 mutations are present in 47% of pUM and associate with a more aggressive disease course (344,345). Loss of BAP1 expression has been linked with an immunosuppressive microenvironment in both primary UM and mUM (90,346) (hence BAP1 mutational status may well be an important biomarker in the future to understand response and resistance to immunotherapy in mUM.

PD-L1 expression does not predict response to pembrolizumab in metastatic breast, non-small cell lung (NSCLC) or bladder cancers (347), while it does in oesophageal cancer (347–349). To date, the association with PDL1 status has not been reported in mUM, although an obvious caveat for assessment of any biomarker in this setting is small sample size and a low number of responders. A tumour IFN- gene expression signature present at the baseline in associates with CPI response in CM (330,350,351). In the samples from various anatomical site of treatment naïve mUM patients, a distinct set of 12 genes have been identified as potential predictive biomarkers of response to CPI: CDH1, HLA DRB4, HLAG, TLR3, IFITM2, SOCS1, SLAMF1, CASP3, ATF1, TBK1, CD164 and IITCH (352); however, this was a retrospective analysis of a small number of patients and will require validation in larger cohorts. There is evidence of expression of additional immune checkpoints, such as LAG3 in UM (239,345) and relatlimab, an anti-LAG3 antibody is currently under investigation in combination with nivolumab in mUM (NCT4552223), although patients are not selected based on LAG3 expression.

Adoptive transfer of TILs is a promising new therapy across several cancers including CM (ref 27-29). Early results from a phase II trial of 20 patients with mUM showed a 35% objective tumour regression rate (95% CI 16-59), with six partial responses and one complete response (286). The TIL product in responding patients (n=5) versus non-responding patients (n=12) had a greater frequency of tumour-reactive T cells, greater absolute numbers of tumour-reactive T cells, and higher levels of IFN-γ release after autologous tumour stimulation. These indices could potentially be used to evaluate the TIL products that are more likely to result in patient benefit.
Gp100, a melanocytic antigen, is highly expressed in UM and has been targeted with a novel bispecific fusion protein, Tebentafusp, which can redirect T cells to target gp100-positive (gp100+) tumour cells (80,353). The treatment is restricted to patients with HLA-A*02:01, which is found in 50% of UM patients (354) Tebentafusp demonstrated an overall survival benefit in mUM over investigators’ choice (80) Preliminary data identified low levels of pre-treatment CD163:CD3 ratio in the tumour biopsy and low serum IL-6 as potential biomarkers of response to tebentafusp as well as OS (355). In addition to gp100, UM express a range of antigens such as PRAME (preferentially expressed antigen in melanoma), Melan-A/ MART-1, tyrosinase, MAGE and NY-ESO (356–358) PRAME is already targeted by a bispecific molecule in an on-going trial [NCT04262466] in solid tumours, including UM. However, patients are not selected based on PRAME expression of their tumours.

Liquid biopsy is an emerging alternative approach to analyse the molecular features of tumours. UM shows a preference for hematogenous dissemination. Therefore, the blood permits to detect and monitor disease progression, recurrence, and response to treatment. Recently, lower levels of circulating tumour DNA (ctDNA) prior to treatment with a PKC-inhibitor is associated with response in a small number of uveal melanoma patients, but likely reflects disease burden rather than a mechanistic biomarker (359). To note, the patient with a germline MBD4 mutation who responded to CPI, was monitored using ctDNA, which correlated well with imaging results (202). Intriguingly, changes in ctDNA were more strongly associated with outcome and significantly outperformed RECIST assessment in pre-treated patients who received tebentafusp in the phase 2 trial (360).

Evidence statements
- For most patients, results of molecular profiling of either primary or metastatic tumour, or germline do not impact on the choice of therapy in the context of metastatic disease.
- Emerging evidence suggests that a small subset of uveal melanoma patients may have a high TMB with an underlying germline MBD4 mutations (<1% patients) and therefore are more likely to respond to immune checkpoint inhibitors in the metastatic setting.
- Uveal melanoma patients with HLA-A*02:01 can receive tebentafusp in the metastatic setting (see section 4.5.1).

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>61.</strong> Screen fit patients for HLA-A*02:01 to identify those who may benefit from tebentafusp [2022]</td>
</tr>
<tr>
<td><strong>62.</strong> Bio-banking and similar efforts in UM should conform to agreed best practices that ultimately could allow for pooling of molecular and clinical data collected in clinical trials and routine care to maximise the likelihood of successfully validating predictive biomarkers. [2022]</td>
</tr>
</tbody>
</table>

Linking evidence to recommendations
The GDG [Guideline Development Group] recommend that tebentafusp be considered for HLA-A*02:01 patients, pending NICE approval. Early access programs are in set up across multiple hospitals; referral of patients for assessment at these centres is strongly recommended. There is an unmet need to identify predictive biomarkers, and therefore the GDG would advocate for translational studies to be integrated in the clinic to further characterise mechanisms of response and resistance.(80)
4.5.3 The loco-regional management of hepatic predominant metastatic disease

4.5.3.1 Introduction

The liver remains the most common site of metastatic disease for patients who develop systemic relapse of uveal melanoma with at least 85% of patients developing hepatic metastatic disease. For approximately 50% of patients the liver will be the sole site of metastatic disease providing a rationale for therapeutic targeting of a single organ.

The 2015 guidelines identified evidence from case series to support liver resection where this could result in complete macroscopic clearance of radiologically identified metastatic disease in the absence of extra-hepatic involvement. There was no evidence to support debulking surgery. Early data on regional liver directed therapies was reviewed with the suggestion of improved outcomes in selected patients compared with historical controls, but with no ability to differentiate that one intervention was superior to another in terms of outcomes.

Given the ongoing interest in loco-regional therapy for this disease, an updated review of the literature has been performed.

4.5.3.2 Review question: What are the best available options for the loco-regional management of hepatic predominant metastatic disease

Table 15: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients diagnosed with uveal melanoma with either resectable or non-resectable liver metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)*</td>
<td>Laser thermal therapy, Ablation, Surgery + ablation, Surgery, PHP, IHP, HAI, Radioembolisation, TACE</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Other liver directed therapy or historical controls.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>OS, PFS, response rate and safety outcomes</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomised controlled trials, single arm clinical trials, case series with at least 10 cases.</td>
</tr>
</tbody>
</table>

Inclusion criteria were:

- Comparator – no standard benchmark
- Liver dominant metastatic disease
- Case series >= 10 cases
- Clinical trial
- Papers in English
- Includes OS in outcome

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8 The information for this section was reviewed, presented and drafted by Drs Sachin Modi and Matthew Wheater
4.5.3.3 Clinical evidence

Twenty-one studies were included in the review; (111,112,368–377,322,361–367) these are summarised in Table 16 below with full details of the included and excluded studies in Appendix A7 in the separate document entitled Appendix 2022.

Surgical and ablative therapy

Relatively little new data has been published in the arena of surgical and ablative therapy since the last guideline. A single centre case series of 15 patients treated over a 10 year period from 2008-2018 showed a median survival of 37 months with no treatment related mortality, although 26.6% of patients developed a post-operative complication (112). Although this is an impressive OS and significantly better than historical controls there were limited data presented on case selection.

A further two studies also investigated outcomes from surgical metastectomy together with ablation. Gomez et al (111) described the outcomes for 18 patients from a single centre who were identified for either surgery or ablation from a cohort of 155 patients identified with liver metastases from an MRI screening programme. Patients were excluded if miliary disease was identified at laparoscopy or extra-hepatic disease on CT. 17 patients underwent resection and one ablation with a median overall survival for the whole group of 27 months, compared with 8 months for those who did not undergo surgery. With the caveats of selection bias for those undergoing a surgical or ablative approach this study supports the approach of complete clearance of radiologically evident metastatic disease when feasible.

Servois et al (373) performed a retrospective review of the characteristics of a series of long-term survivors using an iterative approach including both surgery and ablation. 97 patients were identified from a single institution database who had undergone R0 resection for ocular melanoma liver metastases over a 14-year period. 14 of these went on to develop further liver only recurrence amenable to ablative therapy, either as a percutaneous or surgical approach including 4 patients who underwent a combined second metastectomy with ablation. Median survival for this group of 14 patients was 8 years from the first diagnosis of metastatic disease, showing that for highly selected patients, prolonged survival can be achieved.

Two studies were reviewed investigating ablation as a component of the management of liver only metastatic disease. Eichler et al (364) described the use of MRI guided laser thermal ablation (LTT) in a series of 18 patients for who a total of 44 metastases were treated. Patients were selected either having failed surgery, where surgery was not technically possible, or where bilobar disease was present. Patient selection included up to 5 metastases with a maximum tumour diameter of 5cm. There were no major complications although all patients experienced mild to moderated pain at the treatment site. Follow up was with MRI with no treated tumours showing subsequent relapse. The median overall survival from the date of diagnosis of the treated tumour was 2.8 years. The authors conclude that LITT is a safe and effective treatment for uveal melanoma metastases but with the limitations of a small series with no presented data on prior or subsequent therapy.

White et al (376) reported on an 11 year, single institution experience of thermal ablation for patients with ocular and non-ocular melanoma. Of 33 patients included, 11 had an ocular primary with a median survival of 3.9 years with no major complications and no deaths within 30 days of the procedure. From the overall population of 33 patients, 15% developed recurrence within the ablation site giving a median progression free survival of 4.4 months. Again, interpretation of this data is limited by a small single institution series of highly selected patients.
Chemosaturation/ Percutaneous Hepatic Perfusion (PHP)

There have been a number of new studies relating to melphalan PHP. Although the majority are limited by being single institution mainly retrospective studies which demonstrate varied patient selection, preliminary data from a prospective randomized phase III study have also been published in abstract form.

Artzner et al (361) performed a retrospective single center review of 16 patients undergoing PHP. All patients were UM with liver metastatic disease <50%. This study demonstrated the highest median OS to date at 27.4 months and a mPFS of 11.1 months. SAEs were observed in the majority of patients with most SAEs limited to grades one and two. Thirteen SAEs of grades three and four were observed in seven individual patients. No grade five SAE was observed.

Schonfield et al (372) performed a similar study in 60 patients. Half of the patients were patients with hepatic metastases of uveal melanoma. Patients with UM had the longest mOS, mPFS, and mhPFS with 12, 6, and 6 months, respectively. Adverse events included most frequently significant, but transient, hematologic toxicities (80% of grade 3/4 thrombopenia), less frequently hepatic injury up to liver failure (3.3%) and cardiovascular events including two cases of ischemic insults (5%).

There have been 3 other studies (309,378,379) which all demonstrate similar mOS and mPFS (15.3, 9.6 and 19.1 and 8.1, 12.4 and 7.6 months respectively) with a similar safety profile.

Preliminary data from the international FOCUS study (380) and https://www.globenewswire.com/news-release/2021/03/31/2202310/0/en/Delcath-Systems-Inc-Announces-Positive-Preliminary-Results-from-Phase-3-FOCUS-Trial-of-HEPZATO-in-Patients-with-Metastatic-Ocular-Melanoma.html comparing PHP vs Best Alternative Care (BAC) has been presented. This trial was initially a randomized trial, although later changed to a single arm study with all patients receiving PHP. There was however no cross over from BAC to PHP. The early released data showed, based on the preliminary analysis of 87% of enrolled patients, an overall response rate (ORR) of 29.2% in the Intent to Treat (ITT) population which exceeded the predefined success criteria (21.0%) for the primary ORR endpoint. Patients in the PHP arm had a statistically significant improvement over BAC with ORR of 32.9% versus 13.8% (p<0.05) and median Progression Free Survival (mPFS) of 9.0 months versus 3.1 months for the BAC arm (p<0.001). The data also showed a Disease Control Rate (DCR) of 70.9% versus 37.9% in the BAC arm (p<0.002). Duration of response and OS are not yet evaluable.

The safety profile in this trial was consistent with the safety profile of PHP treatment described in European single-centre and multi-centre publications with no new safety concerns observed. In the PHP population of 94 patients, 38 patients (40.4%) experienced a treatment-emergent serious adverse event. The most commonly reported treatment-emergent serious adverse events were thrombocytopenia (14.9% of patients), neutropenia (10.6%), and leukopenia (4.2%). 5% experienced treatment emergent serious cardiac adverse events. In all cases the events resolved with no ongoing complications. There were no treatment-related deaths in the trial.

Intra Hepatic Perfusion (IHP)

There are no new studies on IHP, and this technique has been largely replaced with the percutaneous approach enabling multiple treatments and a better safety profile.

Radio-embolization (SIRT)

There has been some new data since the previous guideline, but no randomized studies exist. Evidence is again limited by the single center nature of the studies performed.
Gonsalves et al (366) conducted a prospective phase II trial of radioembolisation (RE) for treatment of UM hepatic metastases. Treatment naïve participants (group A) and participants who progressed after immunoembolisation (group B) with hepatic tumour burden less than 50% underwent RE. Outcomes in the two groups were group A: 23 patients, mPFS 8.1 months. OS 18.5 months. Group B: 23 patients, mPFS 5.2 months. OS 19.2 months. Grade 3 treatment-related toxicities included transient lymphopenia (group A, n = 1; group B, n = 1), pain (group A, n = 2) and nausea or vomiting (group A, n = 1). Conclusion Radioembolization is a promising treatment for patients with uveal melanoma hepatic metastases.

Another recent retrospective study by Levey et al (367) was performed at a single centre in patients with UM liver metastases. 12 patients treated with SIRT alone and 12 with SIRT plus immunotherapy. Median OS was 26.3 months. Median OS SIRT + immunotherapy was 26.0 versus 9.5 months for others (p = 0.014). Median hepatic PFS was prolonged in patients treated with Y-90 on concurrent immunotherapy at 10.3 months versus 2.7 months for RE only (p = 0.002).

A further study by Eldredge-Hindy et al (381) from 2016 looked at outcomes from SIRT in 71 patients with UM liver metastases. The majority of patients (82%) received SIRT as salvage therapy. Median hepatic PFS and OS following SIRT were 5.9 months and 12.3 months respectively.

Other SIRT studies in melanoma not specific to UM were not included.

Chemo-embolization (TACE)

There have been limited new studies in chemoembolization of UM liver metastases since 2015 and as with previously described liver directed modalities, evidence is limited by lack of randomization and the single centre retrospective nature of studies. In addition, with chemo-embolisation in particular, a wide variation in techniques and chemotherapy agents was noted.

Carling et al (363) published a study in 2015 using Irinotecan loaded beads where 14 patients were treated. There was a reasonable OS of 9.4 months, but the procedural complications were high with 12 major complications occurring in this small cohort.

Another study from 2015 by Valpione et al (374) was a retrospective analysis on 141 patients who underwent treatment for UM liver metastases, of which 58 were treated with beads loaded with CPT-11. The treatment with TACE conferred a survival advantage (median OS 16.5 vs. 12.2 months, respectively).

Chemoembolization with another agent, 1,3 Bis-(2-Chloroethyl)-1-Nitrosourea, was described by Gonsalves et al (366) in 2015. 50 patients were included in this retrospective review in which treatment naïve patients with metastatic disease replacing 50% or more of the liver were considered. OS was 7.1 months with mPFS at 5 months.

A double blind randomised study by Valsecchi (375) looked at 52 patients with disease burden <50%. Patients were randomized to undergo immunoembolization (IE) or bland embolization (BE). Lobar treatment was performed with GM-CSF or normal saline solution mixed with ethiodized oil followed by embolization with gelatin sponge emulsified with iodinated contrast medium. Embolisation was repeated every 4 weeks. Overall, 25 patients underwent immunoembolisation v 27 having bland embolisation. OS was OS 21.5 v 17.2 (p = 0.047).

The latest study from 2017 by Shibavama (382) looked at 29 UM patients undergoing TACE with cisplatin and gelatin sponge. The overall response rate was 21%. The median survival time was 23 months, and the 1-, 2-, and 5-year survival rates were 72.4, 39.4, and 0%. The common adverse events (AEs) were liver enzyme elevation (100%), nausea (72.4%), abdominal pain (65.5%), vomiting.
post-embolization syndrome (34.5% of patients, 9.6% of TACE procedures), and pyrexia (24.1%). Grade ≥3 AEs consisted of aspartate aminotransferase elevation (34.5%), alanine aminotransferase elevation (51.7%), and serum creatinine elevation (3.4%).

**Hepatic Arterial Infusion (HAI)**

There was one study identified looking at arterial infusion of fotemustine. In this study by Leyraz (368) patients were randomly assigned to receive either intravenous or hepatic arterial infusions of 100mg/m$^2$ on days 1, 8, 12 (and 22 in the HAI arm only) and then every 3 weeks as maintenance. 171 patients had an OS assessment, which was 14.6 months in the HAI arm and 13.8 months in the IV arm. There was no OS benefit of HAI vs IV but there was a PFS benefit (4.3 vs 3.5 months) p=0.002 and PFS rate of 24% vs 8%. There were reduced grade 3 or above toxicities in the HAI arm. The authors concluded that this treatment should be considered as experimental.

**Summary**

A systematic review by Rowcroft (371) looking at liver directed therapies for OM metastases included 55 studies with 2446 patients treated overall. Treatment modalities included surgery, IHP/PHP, HAI, TACE, SIRT and IE. Both surgery and liver directed therapies were shown to have benefit in selected patients. The study concluded that the substantial variability in patient selection and study design makes data comparison and formulation of recommendations challenging.

- Although there has been some new published data since the previous guidelines, it remains of low quality with lack of randomised studies and low numbers. Data suggests benefit for surgery/ablation and liver directed therapy compared to historical controls in selected patients.
- No comparative data to suggest benefit of particular modality over others, although OS outcomes of PHP and SIRT are highest amongst the liver directed therapies.
- There is a need for randomized trials of which at least one is ongoing (SIRT v TACE NCT02936388). Another emerging area for future research is combination of liver directed and systemic therapies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
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<tr>
<td>Broman</td>
<td>2019</td>
<td>Intra-arterial perfusion-based therapies for regionally metastatic cutaneous and uveal melanoma.</td>
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<td>Carling</td>
<td>2015</td>
<td>Transarterial Chemoembolization of Liver Metastases from Uveal Melanoma Using Irinotecan-Loaded Beads: Treatment Response and Complications</td>
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<td>Eichler</td>
<td>2014</td>
<td>MR-guided laser induced thermotherapy (LITT) in patients with liver metastases of uveal melanoma</td>
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<td>Eldredge-Hindy</td>
<td>2016</td>
<td>Yttrium-90 microsphere brachytherapy for liver metastases from uveal melanoma: clinical outcomes and the predictive value of fluorodeoxyglucose positron emission tomography.</td>
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<td>Gomez</td>
<td>2014</td>
<td>The Liverpool Uveal Melanoma Liver Metastases Pathway: Outcome following liver resection,</td>
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<td>Gonsalves</td>
<td>2019</td>
<td>A Prospective Phase II Trial of Radioembolization for Treatment of Uveal Melanoma Hepatic Metastasis.</td>
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<td>Gonsalves</td>
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<td>Uveal Melanoma Metastatic to the Liver: Chemoembolization With 1,3-Bis-(2-Chloroethyl)-1-Nitrosourea.</td>
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<td>Hand</td>
<td>2020</td>
<td>Metastatic uveal melanoma: A valid indication for liver resection.</td>
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<td>Karydis</td>
<td>2016</td>
<td>Clinical activity and safety of Pembrolizumab Ipilimumab pre-treated patients with uveal melanoma.</td>
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<td>Levey</td>
<td>2020</td>
<td>Predictors of Overall and Progression-Free Survival in Patients with Ocular Melanoma Metastatic to the Liver Undergoing Y90 Radioembolization.</td>
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<td>Leyvraz</td>
<td>2014</td>
<td>Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial</td>
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<td>Meijer</td>
<td>2021</td>
<td>Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Ocular Melanoma Metastases Confined to the Liver: A Prospective Phase II Study</td>
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<td>Olofsson</td>
<td>2014</td>
<td>Isolated hepatic perfusion for ocular melanoma metastasis: registry data suggests a survival benefit</td>
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<td>Reddy</td>
<td>2014</td>
<td>Isolated hepatic perfusion for patients with liver metastases.</td>
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<tr>
<td>Rowcroft</td>
<td>2020</td>
<td>Systematic review of liver directed therapy for uveal melanoma hepatic metastases.</td>
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<tr>
<td>Schönfeld</td>
<td>2020</td>
<td>Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma.</td>
</tr>
<tr>
<td>Seedor</td>
<td>2020</td>
<td>An Outcome Assessment of a Single Institution’s Longitudinal Experience with Uveal Melanoma Patients with Liver Metastasis.</td>
</tr>
<tr>
<td>Servois</td>
<td>2019</td>
<td>Iterative treatment with surgery and radiofrequency ablation of uveal melanoma liver metastasis: Retrospective analysis of a series of very long-term survivors</td>
</tr>
<tr>
<td>Shibayama</td>
<td>2017</td>
<td>Efficacy and toxicity of transarterial chemoembolization therapy using cisplatin and gelatin sponge in patients with liver metastases from uveal melanoma in an Asian population</td>
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<tr>
<td>Valpione</td>
<td>2015</td>
<td>A retrospective analysis of 141 patients with liver metastases from uveal melanoma: a two-cohort study comparing transarterial chemoembolization with CPT-11 charged microbeads and historical treatments</td>
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<tr>
<td>Valsecchi</td>
<td>2015</td>
<td>Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases</td>
</tr>
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<td>Vogl</td>
<td>2017</td>
<td>Percutaneous isolated hepatic perfusion as a treatment for isolated hepatic metastases of uveal melanoma: patient outcome and safety in a multicentre study.</td>
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<tr>
<td>White</td>
<td>2016</td>
<td>Recurrence and survival outcomes after percutaneous thermal ablation of oligometastatic melanoma,</td>
</tr>
<tr>
<td>Zager</td>
<td>2021</td>
<td>Percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases: Preliminary results of FOCUS (PHP-OCM-301/301A) phase III trial</td>
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<td>Zager</td>
<td>2012</td>
<td>Chemosaturation therapy with percutaneous hepatic perfusions of melphalan versus standard of care in patients with hepatic metastases from melanoma: a randomized multicenter phase 3 study.</td>
</tr>
</tbody>
</table>
4.5.3.4 Economic evidence

No economic evidence was found.

4.5.3.5 Evidence statements

- In selected patients, liver resection with the aim of macroscopic clearance may be associated with longer survival than patients who do not undergo surgery.
- There is no evidence of survival benefit to support hepatic de-bulking surgery.
- Regional liver directed treatments (PHP/IHP, SIRT, TACE, IE) can reduce measurable tumour burden. In the absence of randomised data there may be improved outcomes in selected patients compared with historical controls.

4.5.3.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>63. For patients with technically resectable disease, assessment for hepatic resection should be offered where complete macroscopic clearance (RO) can be achieved. [2022]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64. Patient selection to ensure complete macroscopic clearance is important to exclude surgery without benefit, including consideration of early interval imaging in order to exclude rapidly emerging disease. Patent selection should consider these criteria:</td>
</tr>
<tr>
<td></td>
<td>• The extent of liver involved with tumour</td>
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<td></td>
<td>• No more than one site of extra-hepatic disease which is either stable or with an alternative treatment strategy for that site</td>
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<td></td>
<td>• ECOG PS &gt;= 1</td>
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<td></td>
<td>• Functionally significant underlying liver disease [2022]</td>
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<tr>
<td></td>
<td>65. Laparoscopic assessment should be performed in patients with radiologically resectable liver metastases, as many of these patients will have a miliary pattern of disease. [2022]</td>
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<tr>
<td></td>
<td>66. Liver directed and/or systemic treatments should be considered in selected patients with liver dominant disease where resection is not suitable. [2022]</td>
</tr>
</tbody>
</table>

<p>| Linking evidence to recommendations | The GDG found it difficult to compare the studies as treatment was delivered at different times in terms of diagnosis and progression of liver metastases as well as lines of prior therapy. The discussion was focussed on determining whether 1. there was any difference between therapies 2. there was a particular patient group that may benefit. |</p>
<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Unfortunately, the evidence as published does not allow a clear distinction</td>
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<td>between therapies but with the caveat of data quality, PHP and SIRT were</td>
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<td>found to have the longest OS outcomes of the liver directed therapies. In</td>
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<td>terms of patient selection, the group concluded that surgery should only be</td>
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<td>considered if macroscopic clearance was possible with no extra hepatic</td>
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<td>disease and that for liver directed treatments should be considered for less</td>
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<tr>
<td>than 50% liver involvement with metastatic disease, with minimal extra hepatic</td>
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<tr>
<td>disease.</td>
</tr>
</tbody>
</table>
4.6 References [2022]


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246. Suesskind D, Ulmer A, Schiebel U, Fierbeck G, Spitzer B, Spitzer MS, et al. Circulating melanoma cells in peripheral blood of patients with uveal melanoma before and after


5 Original 2015 reviews

5.1 Service configuration (2015)

7. A coordinated approach for the care and follow-up of all patients with uveal melanoma should be established by the Multi-Disciplinary Team (MDT). 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. For advanced disease, the specialist oncology MDT should consist of a medical or clinical oncologist, a diagnostic radiologist, histopathologist and a clinical nurse specialist. Membership by, or referral pathways to an interventional radiologist and hepatobiliary surgical unit with experience in treating metastatic uveal melanoma are also a requirement. MDTs should have direct links to ocular surgical oncology centres. [2015/2021 – The wording has been clarified better to reflect the original intent.]

8. 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. [2015]

9. 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 contemporaneously if possible, and at least annually. [2015]

5.2 General Guidance (2015)

10. 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. [2015]

11. 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. [2015]

12. Each surgical ocular oncology centre should audit their results and share them nationally. [2015]

13. Following identification of a suspected uveal melanoma the referring clinician should urgently refer to the ocular oncology centre. According to national targets the patient needs to be seen and treated within 62 days. [2015]

14. 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. [2015/2021 – The wording has been clarified better to reflect the original intent.]

15. Tumour specimens should be reported by an ophthalmic pathologist within a specialist centre, or by one registered and taking part in annual ophthalmic pathology External Quality Assurance schemes. [2015/2021 – The wording has been clarified better to reflect the original intent.]
16. 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. [2015]

17. Patients should be informed about and recruited into clinical trials wherever possible. [2015]

18. Patients should be offered the opportunity to participate in uveal melanoma specific research. With patient consent, and in compliance with national requirements, samples should be taken surplus to diagnostic requirements and stored in an ethically-approved quality biobank for research purposes. [2015/2021 – The wording has been clarified better to reflect the original intent.]

5.3 Management of the primary tumour [2015]

5.3.1 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.

5.3.2 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>
<tr>
<td>• What is the benefit of staging before primary treatment?</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: Survival/ Distal recurrence Preserving eye Preserving vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary: Quality of life Visual Acuity Local recurrence Side-effects /complications</td>
</tr>
</tbody>
</table>

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.

5.3.3 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.

5.3.4 Evidence Summary

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

5.3.4.1.1 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 Fluodeoxyglucose 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 naevi 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)(Augburger, 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.

5.3.4.1.2 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.

5.3.4.1.3 Intraocular Biopsy for Diagnosis

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

If the diagnosis is still uncertain following the above investigations, then biopsy has a role in distinguishing small melanomas from naevi 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, Schefler 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).
5.3.4.2.1 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).

5.3.4.2.2 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 phosphate (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.

Kaisereman 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 (Kaisereman, 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.

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

No evidence was found to address this question.

5.3.4.3 Question 3. What is the optimal primary treatment?

5.3.4.3.1 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 binocularly. 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).

5.3.4.3.2 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, Kaiseran 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, Kaiseran 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, Kaiseran et al. 2009, 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 I-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 I-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 I-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, De Villiers et al. 2011, Murray, Markoe et al. 2013).

**Local control:**

I-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).

5.3.4.3 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.

5.3.4.3.4 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).

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.

5.3.4.3.5 Transpupillary thermotherapy (TTT)

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). Adjunct 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.

5.3.4.3.6 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).

5.3.4.3.7 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.

5.3.4.3.8 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 albeit 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.

5.3.5 Evidence Statements

5.3.5.1 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. \textit{Level 3}

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

5.3.5.2 Radiological staging before primary treatment

- Tumour size at diagnosis is associated with incidence of metastasis and therefore can be used to aid stratification. \textit{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. \textit{Level 4}
- LFTs are highly specific but not sensitive in detecting metastatic disease. \textit{Level 2+}
- When evaluating biochemical markers of liver function combined GGT and ALP were the most helpful in predicting patients with metastatic disease. \textit{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. \textit{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. \textit{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 (\textit{Level 2}), no reports were found that evaluated the use of MRI to stage uveal melanoma patients at diagnosis of the primary tumour.

5.3.5.3 Primary Treatment

- Choice of primary treatment has not been demonstrated to have a significant impact upon patient survival in uveal melanoma. \textit{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. \textit{Level 2+}
- Five-year local control rates of over 95% have been reported for Ruthenium plaque brachytherapy. \textit{Level 2-}
- Risk factors for local recurrence/poor tumour control include large basal diameter, anterior location, young patient age and foveal location. \textit{Level 3}
- Visual complications of ruthenium plaque brachytherapy are less severe than those recorded from the collateral damage of iodine plaque brachytherapy or PBR. \textit{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. \textit{Level 3}
- Tumour response to brachytherapy may not be a reliable prognostic indicator. \textit{Level 3}
- There is a risk of later extraocular extension following primary TTT, particularly in larger tumours. \textit{Level 3}
- TTT used in conjunction with plaque brachytherapy, known as “sandwich” therapy, provides better 5-year local tumour control (96% versus 83% \textit{p=<0.034}, a better globe preservation (98% versus 87% \textit{p=<0.024}) and recurrence free survival rate (89% versus 67% \textit{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. \textit{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. \textit{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. \textit{Level 3}

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

5.3.6 Recommendations and link to evidence
Pre-operative investigations (2015)

19. Make a diagnosis of uveal melanoma using ophthalmoscopy, fundus photography and conventional ocular ultrasound. [2015]

20. Ciliary body melanoma should be imaged with Ultrasound Biomicroscopy (UBM) or anterior segment Optical Coherence Tomography (OCT). [2015]

21. 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. [2015]

22. Fine needle aspiration biopsy can be performed either with a direct transcleral approach or using a transvitreal approach. [2015]

Radiological staging before primary treatment

23. 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. [2015]

24. 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. [2015]

Treatment of the primary tumour [2015]

25. Patients should be informed that there is no proven survival advantage between any of the offered modalities. [2015]

26. Treat patients using table below [2015]
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Used for</th>
<th>Outcomes</th>
<th>Complications</th>
<th>Comments</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RADIOTHERAPY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Tumour recurrence</td>
<td>A</td>
</tr>
<tr>
<td>Ruthenium 106</td>
<td></td>
<td></td>
<td></td>
<td>Dose and position of plaque can be adjusted to limit the loss of vision</td>
<td></td>
</tr>
<tr>
<td>Iodine 125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton Beam radiotherapy</td>
<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>Loss of the eye from neovascular glaucoma Tumour recurrence</td>
<td>C</td>
</tr>
<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</td>
<td>Radiation related complications Tumour recurrence Not available in all ocular oncology units</td>
<td>C</td>
</tr>
<tr>
<td><strong>PHOTOTHERAPY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transpupillary thermotherapy</td>
<td>Local recurrence and of adjuvant therapy of uveal melanoma</td>
<td>Improves local tumour control</td>
<td>Loss of vision</td>
<td>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.</td>
<td>C</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>Small melanoma</td>
<td>Uncertain</td>
<td>Tumour recurrence</td>
<td>Avoids radiotherapy complications New treatment option not widely used for uveal melanoma. This is an experimental treatment.</td>
<td>D</td>
</tr>
<tr>
<td><strong>SURGERY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exoresection +/- plaque</td>
<td>Medium to large melanoma with a narrow basal diameter</td>
<td>Variable</td>
<td>Retinal detachment Loss of vision Loss of the eye</td>
<td>Tumour recurrence Rarely performed in the UK. Only performed in limited centres. Always performed with brachytherapy to</td>
<td>C</td>
</tr>
</tbody>
</table>
Follow-up after primary treatment

27. 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. [2015]

Link to evidence

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.
5.4 Surveillance of patients at risk of recurrence [2015]\(^9\)

**NOTE: THIS SECTION IS BEING UPDATED AS A SEPARATE PIECE OF WORK IN LATE 2022 CHECK MELANOMA FOCUS WEBSITE**

5.4.1 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.

\(^9\) This section will be updated as a separate piece of work in the near future – please check the Melanoma Focus website.
5.4.2 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), Laparoscopy, CT Scan</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 and genetic features.</td>
<td>LFT, USS, MRI (liver, contrast enhanced), Laparoscopy, CT Scan</td>
<td>Comparing different risk levels to each other</td>
<td>Sensitivity and specificity of metastasis detection, Survival</td>
</tr>
<tr>
<td>What is the optimal imaging modality for surveillance? What is the interval?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>USS, MRI (liver, contrast enhanced), CT Scan</td>
<td>Compared to each other</td>
<td>Sensitivity and specificity of metastasis detection, 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>USS, MRI (liver, contrast enhanced), CT Scan 5 years versus 10 years versus life-long</td>
<td>Compared to each other</td>
<td>Sensitivity and specificity of metastasis detection, Survival</td>
</tr>
</tbody>
</table>

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.
5.4.3 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.

5.4.4 Evidence summary

5.4.4.1 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 having 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.

5.4.4.2 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.

5.4.4.3 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).

5.4.4.4 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, Pyrhonen 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.

5.4.4.5  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.

5.4.5  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.

### 5.4.6 Recommendations and link to the evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>40. Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [2015]</td>
</tr>
<tr>
<td>41. Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features. [2015]</td>
</tr>
<tr>
<td>42. 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. [2015]</td>
</tr>
<tr>
<td>43. Patients judged at high-risk 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. [2015]</td>
</tr>
<tr>
<td>44. Liver function tests alone are an inadequate tool for surveillance for uveal melanoma metastases. [2015]</td>
</tr>
</tbody>
</table>

**Link to the evidence**

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.

5.5 Metastatic disease (Staging and prognosis) [2015]

5.5.1 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 (Orcurto, Denys et al. 2012). MRI was also more sensitive for detecting small liver metastases in a second small study.

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.

5.5.2 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 100cm3 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.
5.5.2.1 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).

5.5.2.2 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).

5.6 Evidence Statements

5.6.1 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
5.6.2 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**

### Recommendations

**Staging [2015]**

47. The burden of liver disease should be assessed by contrast enhanced diffusion weighted MRI scan [2015]

48. Contrast-enhanced CT of chest, abdomen and pelvis and/or PET/CT scan should be used to stage extrahepatic disease. [2015]

49. Brain imaging should not be carried out in the absence of symptoms. [2015]

50. Patients who have symptomatic bony pain should have a bone scan to assess the presence of bony disease. [2015]

**Prognostic method [2015]**

51. 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
- Sex
- Age
- Performance status,
- DFS following definitive primary therapy. [2015]

52. A biopsy should be performed to confirm the diagnosis of metastatic uveal melanoma unless contraindicated. [2015 – edits to wording for clarification 2021]

Linking evidence to recommendations

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.

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.
5.7 References [2015]

References to the above sections:


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.


# 6 Using and implementing the guideline

## 6.1 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.
6.2 Audit criteria

- Documentation that the contact details including telephone and email address of a named key worker were given to the patient and updated as necessary.
- Documentation that psychological support offered.
- Information provided on the benefits and risks of the treatment options.
- Benefits and risks of prognostic biopsy discussed.
- Minimum RCPath dataset recorded.
- Documentation of a surveillance plan
- For patients with mUM, if ICI offered a full discussion of the options documented
- Patients with mUM screened for HLA-A*02:01
- Laproscopic assessment performed prior to hepatic surgery for patients with radiologically resectable liver metastases

6.3 Review and updates

The guideline was published in May 2022 and a full copy of the guideline and appendices is available on https://melanomafocus.org/for-professionals/rare-melanoma-guidelines/uveal-melanoma-guidelines/. 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 Development Methodology https://melanomafocus.org/wp-content/uploads/2020/10/Melanoma-Focus-Methods-Manual-V4.4.pdf which also contains further details of the update methods.

7 Research recommendations

<table>
<thead>
<tr>
<th>Research recommendation</th>
<th>1. Validation of existing staging systems for metastatic disease</th>
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<tbody>
<tr>
<td></td>
<td>2. Comparative studies of prognostic algorithms</td>
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<tr>
<td></td>
<td>3. Comparative studies of molecular tools supporting precision medicine.</td>
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<td></td>
<td>4. Investigation of circulating blood-borne biomarkers in a research or clinical trial setting.</td>
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</tbody>
</table>
5. High quality clinical trials of adjuvant treatment with associated biobanking for translational research.

6. Audit of all patients with pathological evidence of extra-ocular extension treated (or not) with orbital radiation therapy is recommended.

7. Clinical studies, biobanking, and/or participation in patient registries for all patients.

8. Genetic studies are required to examine the differences between indolent nodular and aggressive diffuse iris melanomas.
## 8 Glossary and Abbreviations

### Glossary

<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 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>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>Term</td>
<td>Definition/Description</td>
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<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 ophtalmoscope. 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 “open” approach where inner organs or tissue are exposed (typically with the use of a scalpel).</td>
</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 cryotheapry.</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 hepatitis</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 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 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>
</tbody>
</table>
**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.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<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>CNV</td>
<td>Copy Number Variants</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>Abbr</td>
<td>Definition</td>
</tr>
<tr>
<td>------</td>
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</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>FISH</td>
<td>Fluorescence In Situ Hybridization</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>HA</td>
<td>H</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>IHP</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>IntrA</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>LUMPO</td>
<td>Liverpool Uveal Melanoma Prognosticator Online</td>
</tr>
<tr>
<td>MFS</td>
<td>Metastatic Free Survival</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mUM</td>
<td>Metastatic Uveal Melanoma</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>ORR</td>
<td>Overall Response Rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PICO</td>
<td>Population Intervention/investigation Comparator Outcomes</td>
</tr>
<tr>
<td>PBR</td>
<td>Proton Beam Radiotherapy</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PHP</td>
<td>Percutaneous Hepatic Perfusion</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>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumor Node Metastasis staging system</td>
</tr>
<tr>
<td>UBM</td>
<td>Ultrasound Biomicroscopy</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>WLE</td>
<td>Wide Local Excision</td>
</tr>
<tr>
<td>Genetic Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ATF1</td>
<td>Activating Transcription Factor 1</td>
</tr>
<tr>
<td>BAP1</td>
<td>BRCA1-associated protein-1</td>
</tr>
<tr>
<td>CASP3</td>
<td>Caspase-3 Protein</td>
</tr>
<tr>
<td>CD164</td>
<td>Sialomucin core protein 24 also known as endolyn or CD164 (cluster of differentiation 164)</td>
</tr>
<tr>
<td>CDH1</td>
<td>Cadherin 1</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Cytotoxic T-Lymphocyte Associated Protein 4</td>
</tr>
<tr>
<td>CYSTLR2</td>
<td>Cysteinyl Leukotriene Receptor 2</td>
</tr>
<tr>
<td>dMMR/MSI-H</td>
<td>Deficient mismatch repair</td>
</tr>
<tr>
<td>EIF1AX</td>
<td>Eukaryotic Translation Initiation Factor 1A X-Linked</td>
</tr>
<tr>
<td>GDF-15</td>
<td>Growth/differentiation factor-15</td>
</tr>
<tr>
<td>GNA11</td>
<td>G Protein Subunit Alpha 11</td>
</tr>
<tr>
<td>GNAQ</td>
<td>G Protein Subunit Alpha Q</td>
</tr>
<tr>
<td>HLA-A*02:01</td>
<td>Human Leukocyte Antigen- A*02:01</td>
</tr>
<tr>
<td>HLA-DRB4</td>
<td>HLA-DRB4 (Major Histocompatibility Complex, Class II, DR Beta 4)</td>
</tr>
<tr>
<td>HLA-G</td>
<td>HLA-G (Major Histocompatibility Complex, Class I, G)</td>
</tr>
<tr>
<td>IFITM2</td>
<td>Interferon Induced Transmembrane Protein 2</td>
</tr>
<tr>
<td>ITCH</td>
<td>Itchy E3 Ubiquitin Protein Ligase</td>
</tr>
<tr>
<td>LAG3</td>
<td>Lymphocyte Activating 3</td>
</tr>
<tr>
<td>MAGE</td>
<td>Melanoma Antigen Gene</td>
</tr>
<tr>
<td>MAPK</td>
<td>Mitogen-Activated Protein kinase</td>
</tr>
<tr>
<td>MBD4</td>
<td>Methyl-CpG Binding Domain 4, DNA Glycosylase</td>
</tr>
<tr>
<td>MBD4</td>
<td>Methyl-CpG-binding domain 4</td>
</tr>
<tr>
<td>Melan-A/ MART-1</td>
<td>MART-1/melan-A is a protein antigen that is found on the surface of melanocytes</td>
</tr>
<tr>
<td>MIA-1</td>
<td>Melanoma inhibitory activity-1</td>
</tr>
<tr>
<td>MLH1</td>
<td>MutL homolog 1</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>NY-ESO</td>
<td>New York esophageal squamous cell carcinoma 1</td>
</tr>
<tr>
<td>PALB2</td>
<td>Partner And Localizer Of BRCA2</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Programmed death-ligand 1</td>
</tr>
<tr>
<td>PI3K</td>
<td>Phosphoinositide 3-kinases</td>
</tr>
<tr>
<td>PKC</td>
<td>Protein kinase C</td>
</tr>
<tr>
<td>PLCB4</td>
<td>Phospholipase C Beta 4</td>
</tr>
<tr>
<td>PRAME</td>
<td>PReferentially expressed Antigen in MElanoma</td>
</tr>
<tr>
<td>S-100B</td>
<td>S100 calcium-binding protein B</td>
</tr>
<tr>
<td>SF3B1</td>
<td>Splicing factor 3b subunit 1</td>
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<tr>
<td>SLAMF1</td>
<td>Signaling Lymphocytic Activation Molecule Family Member 1</td>
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<tr>
<td>SOCS1</td>
<td>Suppressor Of Cytokine Signaling 1</td>
</tr>
<tr>
<td>TBK1</td>
<td>TANK Binding Kinase 1</td>
</tr>
<tr>
<td>TLR3</td>
<td>Toll-like receptor 3</td>
</tr>
<tr>
<td>TPS</td>
<td>Trehalose-6-phosphate synthase (TPS)</td>
</tr>
</tbody>
</table>