

## REVIEW ARTICLE



# Consensus statement for metastatic surveillance of uveal melanoma in Scotland

Vikas Chadha<sup>1</sup>✉, Paul Cauchi<sup>1</sup>, Wilma Kincaid<sup>2</sup>, Ashita Waterston<sup>3</sup>, Stefano Schipani<sup>3</sup>, Sachin Salvi<sup>4</sup>, Oliver Cram<sup>2</sup> and Diana Ritchie<sup>3</sup>

© The Author(s), under exclusive licence to The Royal College of Ophthalmologists 2022

Ophthalmic treatments are successful in managing uveal melanomas achieving good local control. However, a large number still metastasise, primarily to the liver, resulting in mortality. There is no consensus across the world on the mode, frequency, duration or utility of regular liver surveillance for metastasis and there are no published protocols. The Scottish Ocular Oncology Service (SOOS) constituted a Scottish Consensus Statement Group (SCSG) which included ocular oncologists, medical oncologists, radiologists and a uveal melanoma patient as a lay member. This group carried out an extensive review of literature followed by discussions to arrive at a consensus regarding surveillance planning for posterior uveal melanoma patients in Scotland. The Consensus Statement would provide a framework to guide each patient's surveillance plan and provide all patients with clarity and transparency on the issue. The SCSG was unable to find adequate evidence on which to base the strategy. The consensus statement recommends a risk-stratified approach to surveillance for these patients dividing them into low to medium-risk and high-risk groups defining the mode and duration of surveillance for each. It supplements the UK-wide Uveal Melanoma National Guidelines and allows a more uniform consensus-based approach to surveillance in Scotland. It has been adopted nationally by all health care providers in Scotland as a guideline and is available to patients on a publicly accessible website.

Eye (2023) 37:894–899; <https://doi.org/10.1038/s41433-022-02198-w>

## INTRODUCTION

Uveal melanoma is a rare tumour with an incidence of ~2–8 per million per year in Caucasians [1]. More than 90% involve the choroid, the remainder being confined to iris and ciliary body [2]. Both sexes are affected in equal numbers [3]. All suspected uveal melanomas in the UK are referred to one of the four regional ocular oncology centres at London, Liverpool, Sheffield and Glasgow. All patients from Scotland are referred to the Scottish Ocular Oncology Service in Glasgow which diagnoses between 50–60 uveal melanomas per year.

Staging in uveal melanoma is performed using the American Joint Committee on Cancer (AJCC 8th Edition) Tumour-Node-Metastasis (TNM) staging system for eye cancer [4, 5]. Outcomes for patients with uveal melanoma vary widely, but are better for patients with smaller tumours. In a cohort of 8033 patients, the 10-year metastatic rate for a 1-mm-thick uveal melanoma was 5%, for a 2-mm-thick uveal melanoma was 10%, and for a 6-mm-thick uveal melanoma was 30% [6]. When grouping 7621 uveal melanomas into small (0–3 mm thick, 29.8%), medium (3.1–8 mm thick, 49%) or large (>8 mm thick, 20.9%) tumours, the 10-year rates of detecting metastases were 11.5%, 25.5% and 49.2% respectively [6]. The AJCC stage specific survival rates have been studied by Kujala et al. and then validated by the AJCC Ophthalmic Oncology Task Force. The 5-year survival rate ranges from 96–97% for Stage I to 25–26% for Stage IIIC [5, 7].

## CURRENT UVEAL MELANOMA GUIDELINES

A group of experts from England were supported by “Melanoma Focus” to develop the Uveal Melanoma Guidelines [8] which were published in January 2015. These were subsequently approved by The National Institute of Health and Care Excellence (NICE). The aim of these guidelines was to optimise patient care by providing recommendations based on the best available scientific evidence. Adequate evidence was found lacking in a number of areas and, in these situations, the guideline development group (GDG) arrived at an expert consensus where possible. The Group, however, recognised that each patient is an individual and the guidelines clearly stated that they “should therefore neither be prescriptive nor dictate clinical care”.

As part of the guidelines, the GDG addressed the issue of surveillance and performed an extensive search of literature to gather evidence on the issue. The GDG concluded that some of the evidence in the literature appeared to suggest that offering surveillance to all patients may be futile. However, there was a consensus supporting the concept of conducting surveillance with an emphasis on liver screening. It recommended that all patients, irrespective of risk, should have a holistic assessment to discuss the risk, benefits and consequences of entry into a surveillance programme.

The GDG was unable to agree on a definition of high metastatic risk and therefore did not give any opinion regarding a risk-

<sup>1</sup>Scottish Ocular Oncology Service, Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow, UK. <sup>2</sup>Department of Radiology, Gartnavel General Hospital, Glasgow, UK. <sup>3</sup>Beatson West of Scotland Cancer Centre, Glasgow, UK. <sup>4</sup>Sheffield Ocular Oncology Service, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. ✉email: vchdh@aol.com

Received: 27 February 2022 Revised: 29 June 2022 Accepted: 28 July 2022

Published online: 9 August 2022

adapted strategy for surveillance. It was recognised that some centres employ MRI with or without contrast in “high-risk” uveal melanoma while others indicated that they would remain with the initial hepatic assessment using ultrasound and only progress to other modalities when the ultrasound detected an abnormality. Consensus was achieved amongst the GDG for lifelong 6-monthly liver screening in all melanoma patients despite the lack of evidence in the literature supporting this practice. It recommended that patients judged at high-risk of developing metastases should have 6-monthly lifelong surveillance incorporating a clinical review, nurse specialist support and liver-specific imaging by a non-ionising modality.

It is apparent from the above guidelines that there was a consensus amongst the group that there was inadequate evidence to be prescriptive about the recommended modality for surveillance. These guidelines seem to have been interpreted by various clinicians, patients and patient groups in different ways and surveillance continues to be performed variably across the United Kingdom. There was no representation from Scotland in the discussions that led to the above guidelines and, in Scotland, a petition was filed in December 2016 challenging the surveillance protocols followed for these patients in Scotland. The absence of any such detailed published protocols or guidelines led us to this attempt to achieve consensus across Scotland regarding surveillance planning.

The Scottish Consensus Statement Group (SCSG) group statement does not intend to replace the NICE-accredited Uveal Melanoma National Guidelines published in January 2015 and due to be updated in 2020. This statement should be seen as complementary to the above guidelines and is applicable to uveal melanoma patients in Scotland and may be useful for patients outside Scotland.

## METHODS

The SCSG was constituted to include ophthalmologists specialising in ocular oncology (ocular oncologists), radiologists, oncologists and a lay member who is a uveal melanoma patient under the care of the SOOS. The group also included two eminent members from England—an ocular oncologist and a medical oncologist. The terms of reference were accepted by all committee members and outline of issues was circulated amongst the group. An extensive review of literature was carried out by the group members. The group met to discuss all aspects of the statement and, eventually, the final version was drafted and approved by the group. This statement was then approved by National Services Division of Scotland which oversees and funds the Scottish Ocular Oncology Service and circulated amongst all Health Boards in Scotland.

## METASTASIS FROM UVEAL MELANOMA

The relative 5-year survival of uveal melanoma has been reported to remain unchanged in the past three decades [9]. Survival drops off significantly once metastatic disease is present. One-year overall survival of patients with metastases is reported to be 15–43%, with reported median survival ranging from 4 to 15 months [10–13] but may only be 2 months without treatment [6].

The most common site of metastasis is the liver, with liver lesions present in 77–94% of patients with metastatic disease [14–17]. Other common sites of metastasis include lung and bone. Liver involvement is the cause of death in most patients with metastatic uveal melanoma [18].

## Management options for metastatic uveal melanoma

Chemotherapeutic agents for systemic metastases from uveal melanoma have shown disappointing results [19]. Immunotherapeutic

drugs including Ipilimumab, Nivolumab and Pembrolizumab have all shown low response rates [19, 20].

Liver disease is usually multifocal but some patients may develop oligometastatic metastases enabling surgical removal [21–23] which has been reported to be associated with prolonged survival. Other targeted therapies such as radiofrequency ablation [23] and selective internal radiotherapy [20] have also been used in patients with limited liver metastases. Recently there has been interest in percutaneous hepatic perfusion of melphalan [24, 25]. Despite a multi-centre study concluding that it can be part of an integrated multimodality treatment approach in appropriately selected UM patients [25], randomised data not confounded by crossover are unavailable.

A number of groups have recently reviewed the treatment of metastatic uveal melanoma. Carvajal et al. concluded that neither is there a standard of care for the treatment of metastatic disease nor has any therapy been shown to improve overall survival [20]. Similar conclusions were drawn by Yang et al. [20] and Kinsey and Salam [26].

A systematic review and meta-analysis which looked at 78 studies and pooled data on 2494 patients found no clinically significant difference in overall survival by treatment modality or decade [27]. They concluded that most of the difference in reported overall survival likely is attributable to surveillance, selection, and publication bias rather than treatment-related prolongation.

Triozzi and Singh emphasised that participation in well-designed, scientifically sound clinical trials is essential to develop effective adjuvant therapies [28]. Most recently, Khoja et al. conducted a meta-analysis and concluded that that progression-free survival and overall survival from metastatic uveal melanoma generally remained poor in clinical trials published over the last 13 years [13].

In summary, despite a number of novel therapies being trialled, there is no evidence that any of the currently available management options improve overall survival by any significant degree.

## Rationale for surveillance for metastases from uveal melanoma

In the absence of proven systemic therapies and limited success with liver directed treatments, there are many multi-centred trials looking at treatment for metastatic disease with the hope of finding a cure or a treatment that prolongs survival. This has led to the introduction of surveillance programmes with the aim of identifying metastases early, allowing for liver directed treatments, clinical trial entry or standard systemic treatment whilst the patient has good performance status and end organ function.

It has been previously shown that surveillance allows early detection of metastases prior to the development of symptoms. Although a survival benefit to surveillance has not been proven, most centres perform periodic screening of all or high-risk uveal melanoma patients, and surveillance is now considered to be good clinical practice. The uveal melanoma guidelines achieved a consensus for lifelong 6-monthly liver screening in all melanoma patients despite the lack of evidence in the literature supporting this practice [8]. Factors supporting surveillance include improved potential to identify oligometastatic disease, which may be amenable to local therapies such as ablation or resection, reduced morbidity from advanced disease, more therapeutic options with standard treatments if patients have good performance status and organ function, and identifying patients eligible for clinical trials [29].

## Surveillance protocols

Surveillance protocols varies widely between institutions with no universally accepted protocol based on serological or radiological investigations [30, 31]. Liver function tests have been proven irrelevant in the diagnosis of hepatic metastases from uveal

melanoma [32]. A wide variation exists concerning the choice of the imaging examination and the frequency of the surveillance [29].

In Europe, ultrasound of the liver is typically performed every 6 months for 10 years, with CT or MRI being performed if a suspicious lesion is identified [33]. At some tertiary-care centres in the USA, surveillance is usually carried out in a twofold manner, using contrast enhanced MRI for the liver and CT chest, abdomen and pelvis for whole-body surveillance, with the timing based on the risk of metastasis indicated by the tumour histology and genetic profile [34]. It should be borne in mind that financial incentives, fear of malpractice and patient pressure/request are well recognised factors resulting in excessive investigations and over treatment in the USA [35].

Similarly, the duration of the surveillance in various centres is also non-uniform. The Uveal Melanoma guidelines suggested lifelong surveillance [8] but, in practice, very few institutions perform regular scanning for life. For example, the WCC in Memphis has a protocol of performing surveillance 6-monthly for 2 years and then annually up to 5 years [36]. They have no set protocol for the 5 to 10-year period but generally surveillance stops 10 years after diagnosis. Marshall and colleagues instituted a semi-annual MRI screening programme that targeted high-risk patients, defined as predicted risk of metastatic death at 5 years greater than 50%, and detected asymptomatic disease in 83/90 (92%) of patients [37]. Stratifying surveillance strategies by risk may make better use of resources and be both time and cost effective. However, the benefit of prolonged and more frequent surveillance must be weighed against the risks associated with extended imaging including heightened patient anxiety and concerns surrounding contrast accumulation [38, 39].

There are a number of cancers that have surveillance protocols for metastases (e.g. lung, prostate, etc). Generally, the surveillance protocols are conducted for 5–10 years. The aim is to detect locoregional recurrence or metastatic disease at an early stage with the assumption that an early salvage treatment can lead to better survival. However, intensified follow-up programmes are controversial. For example, a large meta-analysis showed that there is no overall survival benefit for intensifying the follow-up of patients after curative surgery for colorectal cancer [40]. The majority of screening strategies for recurrent colorectal cancer do not extend beyond 5 years [41]. Recently, a randomised study showed that SABR (Stereotactic Ablative Radiotherapy) in oligometastatic patients (from various primary cancers including breast, colorectal, lung and prostate) improves overall survival compared to standard of care palliative treatments [42]. However, in metastatic uveal melanoma there is no evidence that an early detection improves survival.

Few metastases are detected after 10 years of the diagnosis of uveal melanoma and it is rare for metastatic lesions to be picked up after 15 years post-diagnosis [43, 44]. The incidence of systemic recurrence from melanomas after 10 years ranges from 0.98 to 6.7%. One study from a tertiary referral centre found that 13.2% of metastatic uveal melanoma patients had their metastases diagnosed after 10 years [43]. In general, clinical monitoring with radiologic imaging for tumour recurrence beyond 10 years post therapy of the primary tumour is not cost-effective because of the rarity of delayed recurrence [43]. Further, prolonged surveillance after 10 years may increase patient anxiety.

### Mode of surveillance

There is a wide variation in the non-ionising modality used to image the liver for surveillance in these patients. In the UK, it is recognised that some centres employ MRI with or without contrast in “high-risk” uveal melanoma while others perform the initial hepatic assessment using ultrasound and only progress to other modalities when ultrasound detected abnormalities are seen [8].

Beliverie et al. reviewed the imaging characteristics of incidental common benign liver lesions and contrasted them with uveal melanoma metastases. Their paper lays out the advantages and disadvantages of the differing liver imaging modalities in a tabular form [45]. In summary, liver ultrasound is low-cost, widely available, non-invasive and has no side-effects but may not be able to scan the whole liver due to body habitus and is operator dependent. The MRI with contrast is the most specific modality for picking up small liver metastases and is at least as sensitive as CT [34]. However, it is expensive, time-consuming and not suitable in all patients (e.g., with metallic implants, pace-maker, claustrophobia, etc) and has a high false positive rate. This contributes further to heightened patient anxiety [38]. There is also evidence that repeated MRI scanning with contrast results in accumulation of the contrast medium in the brain [39].

Chaudhary et al. conducted a retrospective cohort study of their patients looking at 1390 hepatic ultrasound scans [46]. They used a stepwise surveillance protocol based on serial hepatic ultrasounds followed by confirmatory scans such as computed tomography and MRI. They found that the sensitivity, specificity, and positive predictive value of hepatic USG for findings that were indeterminate or suspicious for metastasis were 96%, 88% and 45% respectively. The specificity of the confirmatory scan was greater than that of hepatic USG (93% vs. 88%, respectively). They concluded that this approach offers a high likelihood of detecting asymptomatic metastases in patients with primary uveal melanoma.

It is generally accepted that MRI is more sensitive than ultrasound in detecting smaller liver metastases [34]; however, there is no evidence to suggest that routine surveillance with MRI scanning (as opposed to ultrasound scanning) confers a survival advantage to uveal melanoma. There have been no comparative studies or controlled trials between these modalities in this respect.

### Risk stratification

The risk of metastasis in uveal melanoma is determined by multiple factors, including clinicopathological features such as tumour size and location [6] and molecular genetic abnormalities, most notably the loss of chromosome 3 [47, 48]. Therefore, some tumours are at higher risk for metastasising than others [49, 50]. For patients with high-risk tumours, oncologists often recommend either more frequent and/or more intensive surveillance such as inclusion of hepatic CT/MRI in addition to hepatic ultrasonography [46, 51].

Targeted surveillance, 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 [8]. 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 is made by either using the AJCC TNM staging (8th Edition) or from cytogenetic testing on biopsy material or from enucleated eyes. Although routinely offered, very few patients in the SOOS seem to be keen on a biopsy for prognostication (unpublished data). In this setting, defining a high-risk melanoma can only depend on non-pathological and non-cytogenetic factors except in cases where an enucleation or biopsy has been performed. The Uveal Melanoma Guidelines group suggested that a high-risk melanoma may entail inclusion of various factors including large tumour size, ciliary body involvement and an AJCC stage which prognosticates a more than 30% chance of death in 5 years [8]. On the basis of the AJCC 8th edition, this translates to Stage IIIA and above.

**Table 1.** Consensus on definition of high-risk uveal melanomas in Scotland.

1. Choroidal and Ciliary Body melanomas which are Stage IIIA or worse as per the AJCC (8th Edition) staging
2. Cytogenetic testing confirms Monosomy 3
3. Cytogenetic testing confirms abnormalities in Chromosome 8 (8p loss, 8q gain)
4. Cytogenetic testing confirms BAP-1 mutations
5. In the absence of cytogenetics testing, pathological features indicating high-risk include extra-scleral extension, epithelioid cells and closed vascular loops—decision to be made at the multi-disciplinary meeting (MDT)
6. Any other features of the tumour or other factors that may indicate a high risk of metastases—decision to be made at the MDT

All melanomas that are not classified as “High-Risk” will fall into the “Low or Medium-Risk Group” for surveillance purposes.

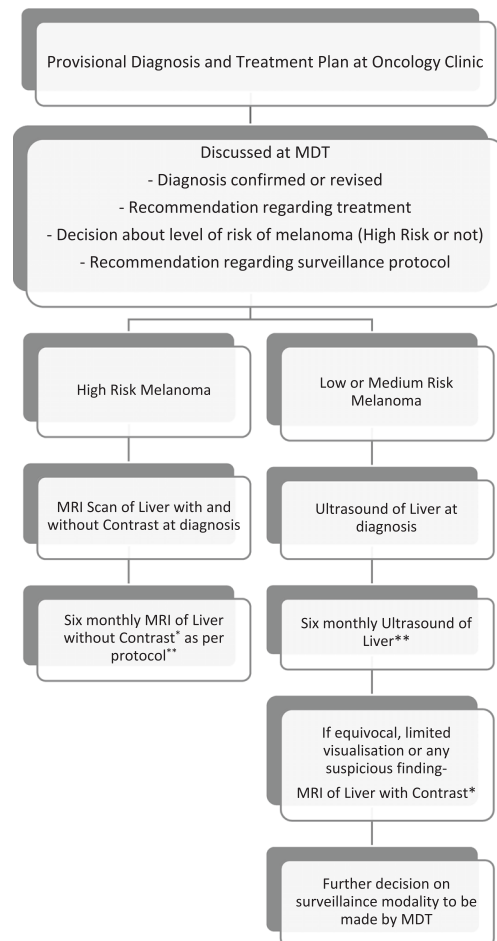
## RECOMMENDATIONS FOR METASTATIC SURVEILLANCE OF UVEAL MELANOMA IN SCOTLAND

The above extensive review of literature and ensuing discussions have resulted in the SCSG formulating recommendations that would help guide the metastatic surveillance of uveal melanoma patients. These are:

- (1) All uveal melanomas diagnosed at the Scottish Ocular Oncology Service are staged as per AJCC (8th Edition) and are offered a prognostic biopsy. A detailed pathological examination and cytogenetic testing is performed for patients undergoing enucleation.
- (2) The melanoma is categorised into either “high-risk” or “low or medium-risk” on the basis of staging, pathology and cytogenetics as well as any other factors. This recommendation is based on a discussion by a multi-disciplinary team (MDT) meeting constituting ocular oncologists, pathologists, radiologists and clinical oncologists.
- (3) A melanoma may, therefore, be deemed “high risk” based on the following (Table 1):
  - AJCC (8th Edition) Stage IIIA or worse [8].
  - Presence of high-risk pathological features including epithelioid cells, extra-scleral extension and the presence of closed connective tissue loops [8].
  - Presence of Monosomy 3 [34, 49].
  - Presence of abnormalities in Chromosome 8 (8p loss, 8q gain) [34, 48].
  - Presence of BAP-1 mutations [49, 52].
- (4) The recommendation is discussed with the patient and a surveillance plan is put into place. Figure 1 shows the recommended protocols for high-risk and low to medium-risk melanomas.
- (5) The recommended duration of surveillance is 10 years from the diagnosis of the uveal melanoma.
- (6) The surveillance plan is reviewed by the MDT if the clinical picture changes, new information becomes available or the patient requests review of the plan.

In summary, the SCSG believes that an effective strategy is to target the high-risk uveal melanoma patients in Scotland with the more sensitive imaging modalities for surveillance of liver metastases. These recommendations bring about greater clarity and transparency to this difficult issue and serve as a template for a discussion and combined decision-making with the patient. The SCSG did not consider the issue of surveillance for metastases to other sites such as lung and bone.

This consensus statement supplements the UK-wide Uveal Melanoma National Guidelines and allows a more uniform consensus-based approach to surveillance in Scotland. It has been adopted nationally by all health care providers in Scotland as a guideline and is available to patients on a publicly accessible



**Fig. 1** Pathway for surveillance of liver metastases in uveal melanoma in Scotland (recommended by the Consensus Statement). \*If MRI is contraindicated, triple phase CT scan of liver may be used. \*\*Total duration of surveillance is 10 years from the time of diagnosis.

website. A similar consensus across the UK or even Europe would be in the interest of patients of uveal melanoma.

## REFERENCES

1. Virgili G, Gatta G, Ciccalallo L, Capocaccia R, Biggeri A, Lutz JM, et al. Survival in patients with uveal melanoma in Europe. *Arch Ophthalmol*. 2008;126:1413–8.
2. Damato B. Treatment of primary intraocular melanoma. *Expert Rev Anticancer Ther*. 2006;6:493–506.
3. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. *Cancer*. 2005;103:1000–7.

4. Kivela T, et al. Uveal melanoma. In: Amin MA, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. editors. *AJCC cancer staging manual*. 8th ed. Springer; 2017. p. 805–17.
5. Kujala E, Damato B, Coupland SE, Desjardins L, Bechrakis NE, Grange JD, et al. Staging of ciliary body and choroidal melanomas based on anatomic extent. *J Clin Oncol*. 2013;31:2825–31.
6. Shields C, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol*. 2009;127:989–98.
7. AJCC Ophthalmic Oncology Task Force. International validation of the American Joint Committee on Cancer's 7th Edition classification of uveal melanoma. *JAMA Ophthalmol*. 2015;133:376–83.
8. Nathan P, et al. Uveal melanoma UK national guidelines. *Eur J Cancer*. 2015;51:2404–12. <https://melanomafocus.com/wp-content/uploads/2015/01/Uveal-Melanoma-National-Guidelines-Full-v5.3.pdf>.
9. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118:1881–5.
10. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol*. 2006;124:1684–93.
11. Augsburger JJ, Corrêa ZM, Shaikh AH. Effectiveness of treatments for metastatic uveal melanoma. *Am J Ophthalmol*. 2009;148:119–27.
12. Postow MA, Kuk D, Bogatch K, Carvajal RD. Assessment of overall survival from time of metastasis in mucosal, uveal, and cutaneous melanoma. *J Clin Oncol*. 2014;32:9074.
13. Khoja L, Atenafu EG, Suci S, Leyvraz S, Sato T, Marshall E, et al. Meta-analysis in metastatic uveal melanoma to determine progression-free and overall survival benchmarks: an International Rare Cancers Initiative (IRCI) ocular melanoma study. *Ann Oncol*. 2019;30:1370–80.
14. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol*. 2005;123:1639–43.
15. Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH, Chapman PB. Variates of survival in metastatic uveal melanoma. *J Clin Oncol*. 2005;23:8076–80.
16. Gragoudas ES, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM, et al. Survival of patients with metastases from uveal melanoma. *Ophthalmology*. 1991;98:383–9.
17. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol*. 2001;119:670–6.
18. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the collaborative ocular melanoma study COMS report no. 15. *Arch Ophthalmol*. 2001;119:670–6.
19. Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol*. 2017;101:38–44.
20. Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? *Ther Adv Med Oncol*. 2018;10:1–17.
21. Tulokas S, Maenpaa H, Peltola E, Kivela T, Vihonen P, Verta A, et al. Selective internal radiation therapy (SIRT) as treatment for hepatic metastases of uveal melanoma: a Finnish nation-wide retrospective experience. *Acta Oncol*. 2018;57:1373–80.
22. Gomez D, Wetherill C, Cheong J, Jones L, Marshall E, Damato B, et al. The Liverpool uveal melanoma liver metastases pathway: outcome following liver resection. *J Surg Oncol*. 2014;109:542–7.
23. Mariani P, Almubarak MM, Kollen M, Wagner M, Plancher C, Audollent R, et al. Radiofrequency ablation and surgical resection of liver metastases from uveal melanoma. *Eur J Surg Oncol*. 2016;42:706–12.
24. Hughes MS, Zager J, Faries M, Alexander HR, Royal RE, Wood B, et al. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. *Ann Surg Oncol*. 2016;23:1309–19.
25. Karydis I, Gangi A, Wheeler MJ, Choi J, Wilson I, Thomas K, et al. Percutaneous hepatic perfusion with melphalan in uveal melanoma: a safe and effective treatment modality in an orphan disease. *J Surg Oncol*. 2018;117:1170–8.
26. Kinsey EN, Salama AKS. Metastatic uveal melanoma—a review of current therapies and future directions. *Oncol Hematol Rev*. 2017;13:100–6.
27. Rantala ES, Hernbergnd M, Kivelä T. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res*. 2019;29:561–8.
28. Triozzi PL, Singh AD. Adjuvant therapy of uveal melanoma: current status. *Ocul Oncol Pathol*. 2015;1:54–5.
29. Francis JH, Patel SP, Gombos DS, Carvajal RD. Surveillance options for patients with uveal melanoma following definitive management. *Am Soc Clin Oncol Educ Book*. 2013:382–7.
30. Kaiserman I, Amer R, Pe'er J. Liver function tests in metastatic uveal melanoma. *Am J Ophthalmol*. 2004;137:236–43.
31. Koutsandrea C, Moschoss MM, Dimissianos M, Goergopoulos G, Ladas I, Apostolopoulos M. Metastasis rates and sites after treatment for choroidal melanoma by proton beam irradiation or by enucleation. *Clin Ophthalmol*. 2008;2:989–95.
32. Mouriaux F, Diorio C, Bergeron D, Berchi C, Rousseau A. Liver function testing is not helpful for early diagnosis of metastatic uveal melanoma. *Ophthalmology*. 2012;119:1590–5.
33. Servois V, Mariani P, Malhaire S, Petras S, Piperno-Neumann S, Plancher C, et al. Pre-operative staging of liver metastases from uveal melanoma by magnetic resonance imaging (MRI) and fluorodeoxyglucose- positron emission tomography (FDG-PET). *Eur J Surg Oncol*. 2010;36:189–94.
34. Balasubramanya R, Selvarajan SK, Cox M, Joshi G, Deshmukh S, Mitchell DG, et al. Imaging of ocular melanoma metastasis. *Br J Radio*. 2016;89:20160092.
35. Lyu H, Xu T, Brotman D, Mayer-Blackwell B, Cooper M, Daniel M, et al. Over-treatment in the United States. *PLoS ONE*. 2017;12:e0181970.
36. Delgado-Ramos GM, Thomas F, VanderWalde A, King B, Wilson M, Pallera AM. Risk factors, clinical outcomes, and natural history of uveal melanoma: a single-institution analysis. *Med Oncol*. 2019;36:17.
37. Marshall E, Romaniuk C, Ghaneh P, Wong H, McKay M, Chopra M, et al. MRI in the detection of hepatic metastases from high-risk uveal melanoma: a prospective study in 188 patients. *Br J Ophthalmol*. 2013;97:159–63.
38. Simpson P. Does active surveillance lead to anxiety and stress? *Br J Nurs*. 2014;23:S4–12.
39. Smith TE, Steven A, Bagert BA. Gadolinium deposition in neurology clinical practice. *Ochsner J*. 2019;19:17–25.
40. Jeffrey M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev*. 2016;11:CD002200.
41. Scheer A. Auer RAC surveillance after curative resection of colorectal cancer. *Clin Colon Rectal Surg*. 2009;22:242–50.
42. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Hasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393:2051–8.
43. Kolandjian NA, Wei C, Patel SP, Richard JL, Dett T, Papadopoulos NE, et al. Delayed systemic recurrence of uveal melanoma. *Am J Clin Oncol*. 2013;36:443–9.
44. Crowley NJ, Seigler HF. Late recurrence of malignant melanoma. Analysis of 168 cases. *Ann Surg*. 1990;212:173–7.
45. Bellerive C, Ouellet E, Kamaya A, Singh AD. Liver imaging techniques: recognition of uveal melanoma metastases. *Ocul Oncol Pathol*. 2018;4:254–60.
46. Choudhary MM, Gupta A, Bena J, Emch T, Singh AD. Hepatic ultrasonography for surveillance in patients with uveal melanoma. *JAMA Ophthalmol*. 2016;134:174–80.
47. Prescher G, Bornefeld N, Hirche H, Horsthemke B, Jockel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet*. 1996;347:1222–5.
48. Damato B, Eleuteri A, Taktak AF, Coupland SE. Estimating prognosis for survival after treatment of choroidal melanoma. *Prog Retin Eye Res*. 2011;30:285–95.
49. Harbour JW. A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile. *Methods Mol Biol*. 2014;1102:427–40.
50. Nichols EE, Richmond A, Daniels AB. Tumor characteristics, genetics, management, and the risk of metastasis in uveal melanoma. *Semin Ophthalmol*. 2016;31:304–9.
51. Aaberg TM, Cook RW, Oelschlagler K, Maetzoid D, Rao PK, Mason JO 3rd, et al. Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. *Clin Ophthalmol*. 2014;8:2449–60.
52. Ewens KG, Lalonde E, Richards-Yutz J, Shields CL, Ganguly A. Comparison of germline versus somatic BAP1 mutations for risk of metastasis in uveal melanoma. *BMC Cancer*. 2018;18:1172.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr Paul Nathan (Consultant Oncologist) and Mr Ronald Blair (layperson member) who were the two non-author members of the Consensus Statement Working Group. Their contribution to the discussions and development of this consensus statement was invaluable.

## AUTHOR CONTRIBUTIONS

VC and PC conceived and formed the Consensus Group which was chaired by VC. All authors acquired, analysed and interpreted data. VC prepared the manuscript which was revised and approved by all authors.

**COMPETING INTERESTS**

The authors declare no competing interests.

**ADDITIONAL INFORMATION**

**Correspondence** and requests for materials should be addressed to Vikas Chadha.

**Reprints and permission information** is available at <http://www.nature.com/reprints>

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.