Surveillance Options for Patients with Uveal Melanoma Following Definitive Management

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OVERVIEW

Even though less than 1% of uveal melanoma patients are found to have radiographic or clinical evidence of distant disease at the time of treatment for their intraocular disease, they carry a lifetime risk of disease recurrence, with approximately 50% of patients ultimately developing fatal metastases. Despite this significant risk, there is no consensus within the ophthalmologic or oncologic community regarding the role of surveillance for detection of metastatic disease in these patients. The lack of consensus is due to the notable absence of clear data regarding the best radiologic or serum surveillance modalities, the optimal frequency of testing, or the ideal length of follow-up. Given the ability to assess prognosis by cytogenetics, gene expression profiling, or other methods, questions remain about whether surveillance strategies should be tailored by level of risk. Importantly, no survival benefit from the early detection of asymptomatic disease in uveal melanoma has been documented, resulting in controversy over the value of routine surveillance and advocacy from some clinicians to forego surveillance altogether. However, there are several factors supporting surveillance: the patient’s enhanced emotional well-being, the potential to identify oligometastatic disease amenable to surgery or other local therapies, decreased morbidity/complications from advanced disease, and identification of patients eligible for clinical trials that assess novel therapies for advanced uveal melanoma. The selection of surveillance modality used varies according to local expertise and resources and may include serum markers (liver function tests and others) and/or imaging (chest x-ray, abdominal ultrasound, computed tomography, positron emission tomography, and magnetic resonance imaging).

Uveal melanoma is the most common primary intraocular malignancy, with an annual incidence of six per million adults in the United States. Despite successful treatment of the primary tumor, patients remain at risk for development of metastatic disease. In one of the largest multicenter randomized trials, the Collaborative Ocular Melanoma Study (COMS), 5- and 10-year cumulative metastasis rates were 25% and 34%, respectively, and the median time from diagnosis of metastasis to death was six months. In this study, less than 1% of patients had evidence of metastatic disease at the time of diagnosis of the primary lesion. Uveal melanoma spreads predominantly via a hematogenous route, with the liver the most common site of both initial metastases detected and involvement of metastases at death. Other sites can be affected. The sites of metastases at death in the COMS included liver in 91%, lung in 26%, bone in 18%, skin in 12%, and lymph nodes in 11% of patients.

There is significant debate about the role of routine disease surveillance following definitive management of uveal melanoma, which may be reflective of the differing patient populations and practice patterns between ophthalmology and oncology. The risks of over-diagnosis and false-positive or false-negative results, as well as a poor cost-to-benefit ratio, must be balanced against the potential benefit that early diagnosis of recurrent disease could prevent premature death. Early detection of asymptomatic metastases may increase the ability to identify disease at a time when potentially curative treatments for oligometastatic disease could be attempted, reduce the risk of developing significant tumor-related morbidity, and identify patients who may be eligible for participation on a clinical trial assessing novel agents for the treatment of uveal melanoma. Indeed, recent advancements in understanding the underlying biology of uveal melanoma and the development of novel targeted agents offer new optimism in what was once a dismal landscape. Finally, even if the effect of surveillance on survival is minimal, surveillance may provide the patient and family with other valuable advantages, including an improved emotional well-being and an opportunity to make future plans.

Although no prospective randomized trials of routine surveillance have been conducted in uveal melanoma, they have been conducted in patients with resected colorectal cancer. Individual randomized trials in patients with colorectal cancer did not demonstrate a survival benefit from surveillance, but three meta-analyses did suggest a modest and significant survival benefit. Currently, the National Comprehensive...
Cancer Network (NCCN) recommends routine surveillance of colon cancer with clinical exam, serum marker, and computed tomography (CT) scans. In contrast, there are only scattered reports of surveillance in patients with uveal melanoma, with some suggesting a survival benefit due to identifying patients eligible for resection or other locoregional treatment techniques for oligometastatic disease.4-6 However, the effects of lead-time bias on these reports are unclear, and a literature review of 31 articles failed to demonstrate convincing evidence of a survival advantage from routine surveillance.7,8 These findings have cast doubt over the utility of surveillance for metastatic uveal melanoma. Although various proposals have been suggested (at least for preoperative testing),9 there is no current universally accepted screening approach. Questions remain regarding whether routine surveillance should be conducted, for whom surveillance should be performed, the frequency of testing, the duration of follow-up, and the optimal surveillance methodologies. Given the lack of consensus regarding routine surveillance in many cancers, it is important for patients to be educated regarding the pros and cons of surveillance, as well as the surveillance options that exist.

The discussion below examines the considerations surrounding routine surveillance for the development of metastatic disease following definitive management of a primary uveal melanoma and outlines the various surveillance methodologies that are available (summarized in Table 1).

**SERUM MARKERS**

**Liver Function Tests**

Given the overwhelming preponderance of hepatic involvement, the liver has become the primary focus of metastatic surveillance strategies.

### KEY POINTS

- Approximately half of uveal melanoma patients develop metastases, which are ultimately fatal.
- It is difficult to demonstrate that routine surveillance or earlier detection of metastatic disease improves patient survival.
- Several factors support surveillance: the patient’s enhanced emotional well-being, the potential to identify oligometastatic disease amenable to surgery or other local therapies, decreased morbidity/complications from advanced disease, and identification of patients eligible for clinical trials that assess novel therapies for advanced uveal melanoma.
- Surveillance strategies vary and include monitoring serum markers such as liver function tests and radiographic imaging studies, including abdominal ultrasonography, CT, PET, and MRI.
- Given the ability to assess prognosis by cytogenetics, gene expression profiling, or other methods, it may be sensible to stratify surveillance methods by risk of metastases.

This collection of serum liver function tests (LFTs) provides an indirect measure of hepatic function. It has the advantage of being relatively inexpensive and widely available. However, LFTs are limited by low sensitivity and a poor positive predictive value (PPV).10 Elevations in LFTs are not specific to uveal melanoma but may be the result of inflammation, infection, other malignancies, or liver disease including alcohol and drugs. Groups have disagreed about the most sensitive component of the LFT panel, with some supporting lactate dehydrogenase and others favoring gamma-glutamyl transpeptidase and alkaline phosphatase.15,12 Nevertheless, Hicks and colleagues determined that no component had a sensitivity greater than 25%, and none had a positive predictive power greater than 50%.12 This compares to troponin assays having a sensitivity of 98% and a PPV of approximately 96% in the diagnosis of myocardial infarction.13 The COMS performed semi-annual LFTs in conjunction with annual chest x-rays, and the determinations of sensitivity and specificity were consistent with earlier reports. The authors concluded that “better tests are needed to identify earlier metastatic disease.”2 A group from Canada agreed with the ineffectiveness of LFTs as a surveillance method, but it also highlighted a potential benefit of its high negative predictive value.10 By that group’s calculation, it is important for patients to know “that they have a 97.5% chance or more of having no metastasis in the case of normal LFT results.”10 Of note, it has been suggested that LFTs in combination with other tests may be of value. Eskelin and colleagues from Finland predicted that semiannual LFTs in combination with an annual abdominal ultrasound will detect greater than 95% of asymptomatic patients.11

### Other Serum Markers

Other serum markers have been assessed as potential surveillance tools, including markers assessed in cutaneous melanoma (S-100B); those elevated in other cancers (osteopontin, vascular endothelial growth factor, insulin-like growth factor 1, growth differentiation factor-15); and those found on histologic sections of metastatic uveal melanoma (melanoma inhibitory activity).14-16 Despite predictions that combined multiple serum parameters may detect hepatic metastases at higher sensitivity than LFTs, these markers have not proven to be a robust predictor of metastatic disease nor have they been adopted into universal clinical practice. It is suggested that even although absolute serum levels are not useful, changes in levels over time may be.14-16 Retrospective studies have demonstrated increasing levels of various markers in patients who have developed metastatic disease, but levels may also increase (to a different degree) in disease-free patients. Although they may increase in patients with recurrent disease, all of these values may remain within normal limits.14,15 No study has prospectively analyzed these as predictive markers for metastatic disease in a large cohort.

### Circulating Tumor Cells and Tumor DNA

As with other malignancies, there has been some interest in the detection of circulating uveal melanoma cells in peripheral
Although false-negative rates have been reported as low as 2%, operator dependence of ultrasonography can result in false-negative rates as high as 20% to 25%. Moreover, ultrasonographic evaluation can be limited by body habitus. For example, 1 cm of body fat results in attenuation of beam intensity by 50%. In the United States, where one-third of American adults are obese, ultrasonography may not be the imaging modality of choice.

Computed Tomography
CT has been used by some for routine radiographic surveillance in uveal melanoma, and it is used as a confirmatory study following an abnormal serum marker or abdominal ultrasound by others. It is less expensive, faster, and has greater availability in comparison to magnetic resonance imaging (MRI), and the whole-body can be imaged with relative ease. Compared with ultrasound, CT is operator-independent as patient images are generated by using a computed algorithm rather than via technician proficiency. There is no published study comparing CT and MRI for surveillance in uveal melanoma, and it is therefore difficult to make a useful comment on the appropriate choice between these approaches; however, there are reported cases in which only isolated foci of metastatic disease to the liver are imaged on CT, with more extensive disease identified by contemporaneous MRI. A representative case is shown in Figure 1. This may argue for greater sensitivity of MRI for extent of metastasis detection, but it does not necessarily translate into earlier detection of metastasis.

CT does have the disadvantage of possessing a very low positive predictive value. In a retrospective review at our center, 50 (55%) patients had abnormalities identified during their baseline surveillance CT of the abdomen, with only three ultimately diagnosed with confirmed metastases. This lack of specificity was present regardless of the institution where the scan was performed or whether a triphasic protocol CT scan was performed. The high false-positive rate may result in further investigational procedures and potentially invasive diagnostic measures to explore what is ultimately benign disease.
The high false-positive and false-negative results derived from PET images. In addition, even though the concomitant CT scan aids in localization of lesions, it also exposes the patient to radiation (see above). Therefore, PET/CT may be of limited value in the surveillance of uveal melanoma, with particular concerns of small metastases being overlooked.

Magnetic Resonance Imaging
MRI is a popular method for surveillance of uveal melanoma, particularly in high-risk patients. It is expensive and is limited by body habitus, the presence of metallic implants, and claustrophobia. It also restricts investigation to one region of the body rather than whole-body imaging. Similar to other techniques, MRI also has the drawback of false-positive findings: although it may be superior at identifying concerning lesions, it may not be adequate at distinguishing benign from malignant causes. Like other imaging modalities, this may complicate the screening process with additional diagnostic assessments, taxing resources and placing patients at risk with invasive procedures. However, MRI does have advantages over other imaging devices. It provides high-resolution images, relative accessibility compared with PET/CT at some institutions, and functions without the use of radiation, making it a safe option for repeated testing, particularly for young women.

In other subspecialties of oncology, there is deliberation over which imaging modality is superior for detecting metastatic disease to the liver. In colorectal cancer, meta-analyses have been conducted to determine the optimal instrument. It was previously believed that, on a per-patient basis, PET was the most accurate test, and on a per-lesion basis, no difference could be found between a 1.5 tesla MRI and PET. However, an updated meta-analysis offers more data supporting the choice of MRI in the detection of colorectal metastases to the liver, particularly following administration of liver-specific contrast agents.

No meta-analysis of specific imaging modalities has been performed in uveal melanoma surveillance; however, the strength of MRI testing has been reported. The most convincing evidence in the literature comes from a group in England that prospectively evaluated the ability of MRI to detect asymptomatic liver metastases in high-risk uveal melanoma. MRIIs performed every six months were successful in detecting metastatic disease in 92% of patients before they had symptoms, and almost half the patients had fewer than five lesions measuring less than 2 cm in diameter.

TAILORING OF SURVEILLANCE PLAN BY RISK OF RECURRENCE
There is a question as to whether surveillance of metastatic uveal melanoma should be stratified by risk of disease recurrence. Over the past decade, our ability to categorize uveal melanoma into low- and high-risk has increased thanks to contributions from genetic advancements. Molecular techniques for prognostication have become more sophisticated...
in recent years and include fluorescent in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), single nucleotide polymorphism (SNP) array, and gene expression profiling (GEP). An analysis that considers multiple variables such as clinical (age, presence of subretinal fluid or orange pigment, size of primary tumor, etc.); histologic (epitheloid cells, extrascleral invasion, intratumoral microvascular networks, higher mitotic activity, etc.); and genetic (chromosomal alterations, molecular pathway defects, GEP class or gene defects such as BAP1, etc.) risk factors can be used to determine a patient’s risk for metastatic disease.

It may be sensible, therefore, to tailor surveillance measures to the patient’s estimated risk of recurrence. For example, this may decrease the frequency and shorten the duration of testing for low-risk patients, while doing the opposite for those at high-risk (who may require, e.g., an MRI every 3 to 6 months for 5 to 10 years). Because some patients are prone to late metastases, one could argue that their screening should be prolonged.

Marshall and colleagues instituted a semiannual MRI screening program that targeted high-risk patients, defined as predicted risk of metastatic death at five years greater than 50%, and detected asymptomatic disease in 83/90 (92%) of patients. 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.

CONCLUSION
There is an absence of clear data regarding appropriate radiographic surveillance for patients with uveal melanoma following treatment of the primary lesion. Opinions vary regarding the utility of routine surveillance, the ideal patient in need of aggressive surveillance, the optimal blood tests and imaging modalities for use in surveillance, the appropriate interval between testing, and the ideal duration of follow-up.

The optimal imaging modality or modalities used for routine surveillance can vary depending on local resources and expertise. MRI appears superior to other imaging modalities at detecting small liver metastases, particularly those measuring less than 1 cm in diameter, but is not necessarily superior at detecting metastasis at an earlier rate that impacts survival. CT imaging of the total body with triphasic liver images may be equally as sensitive at detecting early metastasis; however, this must be balanced with the frequency and duration of radiation exposure. Ultrasonography is often used in Europe and, depending on the operator and the characteristics of the patient, can also be sensitive for the detection of small liver lesions. PET/CT appears less sensitive than traditional CT or MRI for detection of small disease in the liver and may have a higher false-positive rate.

Given the limited data available, the decision to pursue a structured surveillance should be made after a detailed discussion regarding the risks, benefits, and limitations of available tests is conducted between the patient and physician performing the surveillance. If surveillance is elected, the interval could be tailored to the estimated risk of recurrence, with consideration for a more intensive surveillance schedule for those at higher risk of recurrence. For these patients, it may be reasonable to perform routine imaging on an every 3- to 6-month interval. For those at lower risk, imaging at an every 6- to 12-month interval may be appropriate. The optimal duration of follow-up remains controversial. Although late recurrences (more than 10 years after the initial diagnosis of disease) are well documented in uveal melanoma, the benefit of routine radiographic follow-up beyond 10 years must be weighed against the risks and costs associated with continued imaging.


