What is uveal melanoma, and why should you think fast when you see it?

Though it may start as an isolated tumor of the eye, uveal melanoma (UM) metastasizes in up to 50% of patients, becoming a systemic disease.¹

As metastatic UM (mUM) runs its course, treatment options are limited and patients face a median survival of up to 12 months.² So, when you see mUM, think fast.
The following information is intended to elevate awareness of uveal melanoma as a condition distinct from cutaneous melanoma (CM).\(^3\) UM has a poor prognosis if not detected early, and currently, there is no universally accepted optimal management or treatment for metastatic UM.\(^1\) Want to learn more? Visit ThinkUvealMelanoma.com for more information on UM risk factors and symptoms and to sign up for e-mails featuring clinical perspectives and patient resources.
When you see uveal melanoma,
think fast

“I was fitted for the contacts, and afterward, during the eye exam, the ophthalmologist said, ‘There’s a shadow in the back of your left eye. May I dilate your eye?’ He came back and said, ‘I’ve scheduled an appointment for you to see a specialist . . . I was hoping I wouldn’t need to tell you this, but this may be a matter of life and death. I’m very serious—you need to keep this eye appointment.’”

—Patient with UM
Uveal melanoma is a rare tumor of the eye\textsuperscript{1,9}

UM is the most common primary intraocular malignancy.\textsuperscript{10} While UM can arise from melanocytes anywhere in the uveal tract, it most commonly occurs in the choroid.\textsuperscript{9}

Other, less common primary intraocular malignancies include vitreoretinal lymphoma and retinoblastoma.\textsuperscript{14}

\begin{itemize}
  \item ≈8,000 people per year are diagnosed with UM globally.\textsuperscript{5}
  \item 1,600-2,000 are diagnosed in the US\textsuperscript{12,15}
  \item ≈2,500 are diagnosed in the EU\textsuperscript{27}\textsuperscript{16}
  \item UM accounts for only ≈4% of all melanomas\textsuperscript{1,10}
\end{itemize}

EU\textsuperscript{27}, the 27 countries constituting the European Union.
Detection and diagnosis

The vast majority of cases of UM, more than 90%, show no signs of systemic disease at diagnosis. To learn more about the symptoms, visit ThinkUvealMelanoma.com.

Given that patient survival correlates with tumor size and staging, early and accurate diagnosis is particularly important for patient outcomes. Detection and diagnosis of UM can be challenging depending on the size, location, and appearance of the lesion.

Would you recognize a patient at risk?

Risk factors that predispose patients to developing UM include:

- Caucasian
- light-colored irides
- median age: 62 years, with peak incidence at 55 years
- BAP1 mutation

*Patients carrying the BAP1 mutation typically present at a younger age, between 30 and 59 years of age. BAP1, BRCA1-associated protein 1; BRCA1, breast cancer 1.

Additional risk factors may include:

Preexisting medical conditions such as congenital ocular melanocytosis, melanocytoma, neurofibromatosis, and ocular nevi (benign melanocytic lesions that can rarely develop into melanomas).

Symptoms of UM

Closer investigation may be warranted if your patients are experiencing:

- blurred vision
- visual field defects
- photopsia
- metamorphopsia
- other symptoms

Approximately 30% of patients with UM present without symptoms. Patients can also present with headache, experience ocular pain, or report seeing flashes of light. Thus, annual dilated eye exams may be beneficial. Care must be taken to consider UM as a source of these symptoms, since attributing these symptoms to migraine, sinusitis, dental infection, or emotional distress may result in delayed diagnosis.

Patient treatment and prognosis

Surgery and radiation are the primary treatment options for UM. Enucleation (removal of the eye) does not seem to improve survival compared with brachytherapy (focal delivery of radiation to the tumor). Therefore, treatment for primary disease has focused on vision- and eye-preserving techniques.
Histologically, UM and CM may look similar, but they are actually unique diseases. While UM and CM both arise from melanocytes, they have distinct mechanisms of disease and require different therapeutic approaches.3-6

When you see uveal melanoma, think differently

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Distinct genotypes and phenotypes

The differences in oncogenic drivers and immunogenicity between UM and CM result in distinct mechanisms of disease.5

Oncogenic drivers of UM and CM5

<table>
<thead>
<tr>
<th>UM</th>
<th>CM</th>
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<tbody>
<tr>
<td>GNAQ/GNA11</td>
<td>BRAF</td>
</tr>
<tr>
<td>SF3B1</td>
<td>NRAS</td>
</tr>
<tr>
<td>EIF1AX</td>
<td>MEK1/2</td>
</tr>
<tr>
<td>CYSTLR2</td>
<td>PIK3CA</td>
</tr>
<tr>
<td>PLCB4</td>
<td>PIK3CG</td>
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<tr>
<td></td>
<td>AKT1/AKT3</td>
</tr>
<tr>
<td></td>
<td>RAC1</td>
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<td>KIT</td>
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Intrinsically different

At all stages of disease, UM and CM are intrinsically different in:

<table>
<thead>
<tr>
<th>The number of affected patients</th>
<th>UM: 8,000 new cases per year globally</th>
<th>CM: 230,000 new cases per year globally</th>
</tr>
</thead>
<tbody>
<tr>
<td>How they develop</td>
<td>No UV radiation—driven mutations; Familial inheritance: ~1%-2% Oncogenic drivers: GNAQ, GNA11</td>
<td>UV radiation—driven mutation: yes Familial inheritance: ~10% Oncogenic drivers: BRAF, NRAS</td>
</tr>
<tr>
<td>How often they metastasize</td>
<td>Up to 50% of patients develop metastases</td>
<td>~16% of patients develop metastases</td>
</tr>
<tr>
<td>How and where they metastasize</td>
<td>Hematogenous spread, most commonly to the liver</td>
<td>Lymphatic and hematogenous spread to lymph nodes, lungs, liver, bones, and brain</td>
</tr>
<tr>
<td>Their prognosis</td>
<td>Poor and has remained stagnant; median survival of ~6-12 months for patients with distant metastases</td>
<td>Improving, with many new treatment options; combination therapies have demonstrated median survival of ≥24 months for patients with advanced disease</td>
</tr>
</tbody>
</table>

*May be a risk factor for iris melanoma.

- No therapy has demonstrated a substantial benefit specifically for patients with metastatic UM.
- Numerous therapies have demonstrated a benefit for patients with metastatic CM.

While treatment options for UM are limited, patients should be referred to a multidisciplinary team for consideration of available systemic options.
**Metastatic disease**

Although local control of tumors is associated with impressive response rates, up to 50% of patients will go on to develop metastatic UM.\(^1,30\)

**Sites of metastasis**\(^5,31\)

UM cells spread hematogenously, most commonly metastasizing to the liver and becoming a systemic disease that can also involve the lungs, skin, and bones.\(^5,31\)

**Rationale for targeted therapies**

Because CM has a high incidence of \(BRAF\) mutations, effective treatment options for CM include anti-\(BRAF\) and anti-MEK therapies.\(^5\)

Because UM lacks \(BRAF\) mutations, there is little support for the use of anti-\(BRAF\) therapies in the treatment of UM.\(^5\)

**Rationale for checkpoint inhibitors**

Immunotherapy has increasingly become the latest pillar of systemic therapy in oncology, and the recent approvals of checkpoint inhibitors for CM have served as breakthrough options for many patients.\(^5\) Unfortunately, these therapies have not demonstrated the same efficacy in the treatment of UM.\(^1,^5,32\)

In addition to having different oncogenic drivers, UM and CM have distinct mutation burdens.\(^5,33\)
Tumor mutation burden varies by tumor type\textsuperscript{33}

In a study of more than 100 tumor types, CM was among those with the highest tumor mutation burden, while UM was among those with the lowest.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutations/Mb</th>
</tr>
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<tbody>
<tr>
<td>Skin squamous cell carcinoma</td>
<td></td>
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<tr>
<td>Skin melanoma</td>
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<tr>
<td>Lung squamous cell carcinoma</td>
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<tr>
<td>Brain glioblastoma</td>
<td></td>
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<tr>
<td>Eye intraocular melanoma</td>
<td></td>
</tr>
<tr>
<td>Bone marrow myelodysplastic syndrome</td>
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</table>

Mb, megabase.

UM tumor immunogenicity

The immune tumor microenvironment factors into the distinction between UM and CM. While CM contains adequate numbers of effector T cells and is inflamed ("hot"), the effector T cells surrounding UM are limited to the tumor periphery (immunologically "cold").\textsuperscript{32-36}

PD-L1 expression differs significantly between metastases of UM and those of CM. Only 5.1\% (4 of 78) of metastatic UM specimens expressed PD-L1 in comparison to 26.1\% (77 of 295) of metastatic CM specimens.\textsuperscript{32}

mCM, metastatic cutaneous melanoma; mUM, metastatic uveal melanoma; PD-L1, programmed death ligand 1.
While guidelines for the management of UM are emerging, evidence-based treatments for progressive disease are still needed.\(^3,^30\)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\(^3^)\) for Uveal Melanoma were first published in 2018 and were most recently updated in May 2020.\(^6,^37\)

Other national guidelines include\(^2,^19,^38-^40^)\:
- Guidance from the National Cancer Institute (NCI)
- Uveal Melanoma UK National Guidelines (NICE-accredited)
- The French Cancer Society
- The Netherlands’ Recommendations for Uveal Melanomas Treatment Guidelines
- A consensus-based guideline from Canada
Poor prognosis for advanced disease

While effective therapies targeting the primary tumor in the eye have been developed, up to half of patients develop metastatic disease, most commonly spreading to the liver. The prognosis for metastatic uveal melanoma remains poor, with a median survival of up to 12 months. 

≈50% of patients with mUM survive for one year after diagnosis.

Surveillance defined by metastatic risk

Studies have indicated that the risk for metastasis varies and is influenced by clinical and histological characteristics of the patient and the tumor, including:

- tumor diameter
- degree of pigmentation
- high mitotic rate
- somatic mutations in the tumor
- tumor thickness
- ciliary body involvement
- advanced age
- male gender

Guidelines recommend surveillance by a multidisciplinary team to identify mUM, but acknowledge that patients should understand both the benefits and the risks of surveillance. Unfortunately, surveillance and early detection have generally not been linked to improved outcomes, likely due to the lack of universally accepted effective therapies for mUM. Several factors do support surveillance, and its use is likely to become more important as more effective treatments for metastatic disease become available.
Therapeutic options for mUM offer only modest efficacy, and clinical trials are currently the recommended course of treatment, when clinically appropriate.\textsuperscript{1,7,8,37}

**Overall survival for mUM treated with conventional chemotherapy or immunotherapy\textsuperscript{8}**

![Graph showing overall survival](image)

- **CHT** (conventional chemotherapy): fotemustine, treosulfan + gemcitabine, cisplatin + treosulfan + gemcitabine, dacarbazine, DHA-paclitaxel, or temozolomide + bevacizumab
- **CPI** (checkpoint inhibitor): anti-CTLA4 antibody, anti–PD-1/anti–PD-L1 antibody

NCCN Guidelines® for Uveal Melanoma recommend stratification by risk for distant metastasis to determine frequency of systemic imaging during follow-up.37

### Risk stratification to determine the frequency of follow-up systemic imaging should be based on the highest risk factor present37

<table>
<thead>
<tr>
<th>Low risk37</th>
<th>Medium risk37</th>
<th>High risk37</th>
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| • Class 1A46  
• Disomy 3  
• Gain of chromosome 6p  
• EIF1AX mutation  
• T1 (AJCC)  
• Spindle cells | • Class 1B46  
• SF3B1 mutation  
• T2 and T3 (AJCC)  
• Mixed histology (spindle and epithelioid cells)  
 | • Class 246  
• Monosomy 3  
• Gain of chromosome 8q  
• BAP1 mutation  
• PRAME expression  
• T4 (AJCC)  
• Epithelioid cells  
• Extraocular extension  
• Ciliary body involvement  

**Surveillance imaging recommendation**:  
Consider surveillance imaging every 6-12 months for 10 years, then as clinically indicated

**Surveillance imaging recommendation**:  
Consider surveillance imaging every 3-6 months for 5 years, then every 6-12 months for years 6-10, then as clinically indicated

AJCC, American Joint Committee on Cancer.

4 The most frequent sites of metastasis are liver, lungs, skin/soft tissue, and bones. For patients who elect to have surveillance imaging, options include contrast-enhanced magnetic resonance or ultrasound of the liver, with modality preference determined by expertise at the treating institution. Additional imaging modalities may include chest/abdominal/pelvic computed tomography with contrast. However, screening should limit radiation exposure whenever possible. Scans should be performed with IV contrast unless contraindicated. Recognizing that there are limited options for systemic recurrence and that regular imaging may cause patient anxiety, patients should discuss with their treating physician the benefits of surveillance imaging, and some patients may elect to forgo surveillance imaging. Participation in a clinical trial is strongly encouraged.37
Taking a multidisciplinary approach

While no approved therapy has demonstrated a substantial benefit specifically for patients with mUM, guidelines recommend a multidisciplinary approach to the management of metastatic disease. Multidisciplinary teams may include expertise from the following areas:

- Medical oncology
- Ophthalmology
- Radiology and radiotherapy
- Pathology
- Surgical oncology
- Nursing specialist
- Hepatology

A collaborative approach may help optimize outcomes for patients with mUM.
When you see uveal melanoma, you can’t afford to wait

Visit ThinkUvealMelanoma.com for more information on UM risk factors and symptoms and to sign up for e-mails featuring clinical perspectives and patient resources.