Patients presenting with stage IV uveal melanoma: Lessons learned

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Challenges persist in identifying patients with stage IV uveal melanoma. While clinical, histopathologic, and genetic features of the primary tumor have been shown to provide prognostic value for assessing metastatic risk, biopsy-related genetic analyses are expensive and not universally available. Therefore, this review will focus on clinical characteristics. Initial staging and follow-up screening protocols have evolved for patients with uveal melanoma. The Collaborative Ocular Melanoma Study (COMS) required a physical examination, chest X-ray, and hematologic survey (primarily liver function tests). Though these studies were found to have a high specificity, COMS investigators typically found late-stage metastases. More recently, protocols have concentrated on liver imaging (abdominal ultrasound, computed tomography, and magnetic resonance imaging). Though hepatic radiographic imaging has been found more likely to reveal earlier metastatic uveal melanoma, by definition it cannot detect most extrahepatic and multiorgan metastases. An international multicenter registry study recently focused on patients who were diagnosed with stage IV uveal melanoma simultaneously with their primary intraocular melanoma. Therein, utilizing center-specific diagnostic methods, stage IV was found to occur in about 2% of patients. However, subgroup analysis found that a disproportionate number of multi-organ metastases were discovered when whole-body positron emission tomography/computed tomography was used for staging. Herein, we review the literature on patients who present with stage IV uveal melanoma, how they were detected, and their outcomes.

Key words: Metastatic uveal melanoma, PET/CT, stage 4 uveal melanoma, uveal melanoma, uveal melanoma metastasis

Multicenter, international registry-based studies have found that approximately 50% of patients with uveal melanoma (UM) will develop metastasis.¹⁻³ However, even with whole-body positron emission tomography/computed tomography (PET/CT) scanning, less than 4% are found to have metastasis (stage IV disease) at the time of diagnosis of their ocular tumor.⁴ This means that even if treatment could achieve 100% local control, death will still occur because of subclinical micrometastases present at the time of initial diagnosis.¹⁻³⁷ This increases the importance of early detection of metastases that could impact progression-free and overall survival.⁸⁻⁹ Though in the absence of staging the evidence remains weak, patients stage IV UM who have received chemoinmunotherapy, selective internal radiation therapy, or surgical resection have survived longer.⁸⁻¹⁰

The routes of metastasis depend on ocular anatomy.¹¹ In that the eye contains no lymphatics except for the conjunctiva, obligate venous spread leads to early hepatic involvement. An exception can be found in eyes with anterior extrascleral tumor extension, where the melanoma is exposed to the conjunctival lymphatics. Here, we occasionally see regional lymph node involvement.¹³⁻¹⁵ This pathophysiology and preference for hepatic surveillance has translated to 90% of metastatic UM presenting in the liver, while though in a minority of cases other sites include bone, lungs, skin, brain, and lymph nodes.¹⁻³ Clearly, abdominal imaging alone misses some potentially treatable, extrahepatic metastatic disease.¹²

No universal agreement exists regarding the use of ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), or PET/CT to detect metastatic UM. Until recently, no description of specific ocular tumor- or patient-related risk factors that could inform screening for stage IV uveal melanoma was available.¹⁻³

Factors that could be used to predict the risk of metastasis have been described: (A) largest basal tumor diameter, (B) ciliary body involvement, (C) extrascleral extension, (D) epithelioid melanoma cytomorphology, (E) high mitotic rate, (F) extravascular matrix patterns such as closed loops, (G) microvascular density, (H) chromosome 3 monosomy, 8q gain and lack of 6p gain, and (I) a class 2 gene expression profile.⁷ Most of these predictors require histopathologic, genetic, or molecular evaluation of tumor tissue, and require a biopsy that risks extrascleral seeding or extension (a known risk factor for metastasis). Only the first three (A-C) are based on clinical features, all of which are incorporated in the current 8th edition of the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system for UM.³ Three

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large retrospective studies (two multicenter and one single
center) cumulatively analyzing 18,477 patient records have all
confirmed that the AJCC anatomic categories and the stages
derived from them provide a reliable noninvasive measure of the
risk for metastasis from UM.[3,13,16–20]

**AJCC T Category (Size)**

The AJCC Ophthalmic Oncology Task Force (OOTF) registry of
3866 patients with UM had an intraocular tumor with a
median height of 4.7 mm (range, 1–23) and a largest basal
diameter (LBD) of 11.8 mm (range, 2–30).[21] The subgroup of
patients who presented with metastasis (stage IV) at
initial diagnosis revealed a larger median tumor height of
7.7 mm (range, 2.0–24.5) and LBD 15.0 mm (range, 2.9–25.0).[1]

A single nation-based study that reported data for 274 UM
who developed metastasis on follow-up reported a comparable
median tumor height and LBD of 7.0 mm and 13.0 mm (range,
1–20 and 3–25), respectively.[19] A large referral-based single-center
study of 8033 patients with UM found an increasing risk of
metastasis with increase in tumor height.[17,18] At 10 years, the
risk was approximately 6% (for 0–1.0 mm thickness),
12% (1.1–3.0 mm), 16% (3.1–4.0 mm), 27–28% (4.1–6.0 mm),
29% (6.1–7.0 mm), 41% (7.1–8.0 mm), 50–51% (8.1–18 mm). When
analyzing 7731 patients with posterior UM, the same center
inferred that the risk of metastasis and death in comparison with
AJCC category T1 (small) was 2 times for T2 (medium-sized),
4 times for T3 (large), and 8 times for T4 (very large tumors).[13]

The study of patients who presented with stage IV at
initial diagnosis likewise proved that the risk of synchronous
metastasis increased with increasing T-size category T1 to
T4 (odds ratio [OR] 1.0, 2.3, 3.5, and 10.9, respectively).[17] We
therefore conclude that a higher AJCC tumor category can
(in part) be used to direct the intensity of metastatic surveys.

**AJCC T Subcategory (Local Invasion)**

The AJCC-OOTF registry studies revealed a 24.6% frequency of
ciliary body involvement (CBI; subcategory b and d) in patients
with synchronous metastasis.[12,13] They also revealed a 1.7% and
17.4% incidence of extraciliary extension (ESE; subcategories
c–e) in patients without and with synchronous metastasis,
respectively. In the population-based study, ESE occurred in
10% of UM patients who developed metastasis on follow-up.[19]
The large single-center study found that ESE was associated with
increasing T category among its 7731 posterior UM.[13] The
frequency of ESE was 1%, 4%, and 12% based on AJCC size
categories T1–T2, T3, and T4, respectively. The AJCC-OOTF
concluded that the risk of synchronous metastasis increases
significantly with increasing subcategories a (no CBI or ESE),
b (CBI), c (ESE), and d (CBI and ESE) (OR 1.0, 1.3, 3.4, and 7.2,
respectively).[19] Therefore, we can infer that the prevalence of CBI
or ESE can also be used to direct metastatic surveys.

**AJCC N and M Categories (Regional and Systemic Metas-
tases)**

UM is capable of metastasizing to multiple sites [Table 1], with
a high predilection for the liver, 81% (range, 71%–91%).[14,17,22]
It is reasonable to consider that at the time when the COMS
was using physical examination, chest X-ray (CXR), and liver
function tests (LFTs), late disease and thus multorgan metastases
were more commonly found. Today metastatic surveys rely on
abdominal imaging, and the liver is the most commonly evaluated
organ. Different diagnostic modalities have also been emphasized
including: Ancillary CXR and LFTs by Collaborative Ocular
Melanoma Study (COMS) in 1985, abdominal imaging (USG,
CT, MRI), and whole-body PET/CT.[14,17,21,22]

**Initial Staging for Metastasis**

Though the literature suggests that 90% of UM metastasis
present in the liver, there is a selection bias due to focused
abdominal-hepatic imaging. Table 1 reveals that over 25% of
patients were reported to have multi-organ involvement.
Therefore, it is reasonable to assume that the practice of
initial abdominal imaging will miss some of the patients with
extrahepatic disease and that those may undergo unnecessary
ocular surgery and experience diminished length of survival.
Therefore, all UM patients would benefit from initial staging with
total body radiographic imaging (e.g., PET/CT).

Initial staging with whole-body PET/CT has been found to be
more likely to detect both extrathoracic and hepatic metastases, as
well as 3.3% of patients who had second nonocular malignancies.[9]
PET/CT had high sensitivity and positive predictive value in cases of
hepatic metastasis. In other cancers, PET/CT was more accurate
and sensitive than high-definition CT (HDCT) in identifying a
malignant solitary pulmonary nodule (SPN). The sensitivity,
specificity, and accuracy were 81% (64/79), 93% (37/40), and
85% (101/119), respectively, whereas those for PET/CT were
96% (76/79), 88% (35/40), and 93% (111/119), respectively (P = 0.008,
0.73, and 0.011, respectively).[23] Regarding lymph nodes, a
meta-analysis of 67 studies on cervical carcinoma concluded that
PET or PET/CT had the highest specificity among noninvasive
imaging modalities to identify lymph node metastases.[24] To the
best of our knowledge, no study has compared or focused on the
sensitivity, specificity, or accuracy of different modalities of
a screening for both hepatic and extrathoracic metastases as well
as multiorgan site involvement in UM.

**Multiple PET/CT Radiation Exposure Concerns**

With recent more frequent use of PET/CT for diagnosing
tumors and metastases, concerns have legitimately been raised
regarding its radiation dose, especially in young patients. The
effective dose of one 18-F-FDG PET/CT was found to be 18-25
mSv, which could increase to 30 mSv for multiphasic abdominal
and pelvic scans.[14,25] These doses are associated with a lifetime
cancer risk of up to 0.6%.[26] The next question will be to evaluate the
benefit-risk ratio involved in not missing a metastasis vs.
radiation exposure. In the future, a prospective comparative
study on the efficacy and risk related to radiation exposure of
different diagnostic modalities for screening of metastasis may
be able to resolve this issue.

**Post Treatment Metastatic Surveillance**

Liver only, segmental and total body screening

Annual and semiannual screening for metastasis utilizing LFTs
and abdominal USG will detect 59% and 95% of asymptomatic
patients with hepatic metastasis from UM, respectively.[20]
For screening of pulmonary metastases utilizing CXR has a
very low 2% yield.[26] In contrast, segmental radiographic CT
screening (chest, abdomen, and pelvis) has been found more
likely to detect extrathoracic metastases. Evidence also suggests
that contrast-enhanced abdominal MRI is more sensitive for
detecting hepatic metastases as compared to USG or CT. Clearly,
only total body PET/CT allows both anatomic and physiologic
imaging of the entire patient (including the metastatic
subcutaneous [14.8%] and bone [15.9%] sites as noted in Table 1).

**Effect of Local Recurrence on the Risk of Metastasis**

The AJCC-OOTF reported a local recurrence frequency of
4.7% mainly after radiotherapy of UM with an increased
risk of metastasis (hazard ratio, 6.3). The COMS and three single-center studies reported a widely varying frequency of 10.3%, 15.7%, 6.1%, and 3.2%. Of these, the COMS reported an adjusted relative risk for metastasis of 1.5 by multivariable analysis (P = 0.08) whereas a single-center study reported a 4.1 relative risk. The two other studies compared survival proportions without vs. with local tumor recurrence; 87% vs. 58% at 5 years and 84% vs. 43% at 10 years. The pathophysiology that underlies the association between local tumor recurrence and higher risk of metastasis has been attributed to marginal miss, tumor physiology, and various biomarkers, but their prognostic efficacy in identifying patients at high-risk for local treatment failure is yet to be elucidated.

### Effect of Biopsy on Local Control and Metastasis

While histopathologic, genetic, and molecular evaluations have proved effective for identifying patients at high-risk for metastasis, no effective adjuvant treatment is available. Therefore, any discussion of risks and potential benefits of biopsy should include those related to its effect on local control and metastasis. Choroidal melanoma biopsy commonly causes both peritumoral and vitreous hemorrhage.

Consider that peritumoral hemorrhage (around the tumors’ base) can block transillumination light and thus artifically enlarge an intraoperative tumor shadow, leading to potential decentration of the plaque. In addition, vitreous hemorrhage can impede visualization of the tumor, leading to difficulty during scleral-indentation type episcleral plaque localization. Lastly, in melanoma cells that have been isolated from biopsy sclerotomy sites, it is reasonable to assume that biopsy carries a small risk of extraocular or orbital seeding of the tumor.

### Timing of Metastasis Over Years of Follow-Up

The AJCC-OOTF reported 5- and 10-year metastasis-free point estimates, 90% (95% CI 88–91) and 84% (95% CI 81–86) for no CBI or ESE, 72% (95% CI 66–77) and 67% (95% CI 60–73) for CBI only, 54% (95% CI 29–74; only 5-year available) for ESE only, and 33% (95% CI 13–54) and 33% (95% CI 13–54) for both CBI and ESE, respectively. The European Ocular Oncology Group reported significantly decreasing Kaplan Meier survival estimates for increasing AJCC size categories, subcategories, and stages; T-category: 94%, 89%, 75%, and 53% at 5 years; 89%, 77%, 58%, and 39% at 10 years; and 85%, 69%, 47%, and 29% at 15 years for T1 to T4, respectively; subcategories: 87%, 69%, 59%, and 47% at 5 years; and 78%, 51%, 40%, and 19% at 10 years for subcategories a to d; stages: 96%, 89%, 81%, 66%, 45%, and 26% at 5 years; 88%, 80%, 67%, 45%, 27%, and 10% at 10 years; and 81%, 69%, 58%, 34%, 18%, and 0% at 15 years for stages I, IIA, IIB, IIIA, IIIB, and IIIIC, respectively.

### Conclusion

Uveal melanomas with larger basal diameter and thickness, ciliary body involvement and extrascleral extension and, thus, one with a higher AJCC T-category and sub-category and, consequently, higher initial stage was more likely to be diagnosed with or to progress to stage IV. It is important to know that even 0.7% of small AJCC T1 uveal melanomas present with stage IV concurrent metastases. Though it may be reasonable to use abdominal imaging for follow-up surveillance, the capability of UM to metastasize to multiple sites suggests that whole-body imaging offers the most complete method both for initial staging and later restaging.

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### Conflicts of interest

There are no conflicts of interest.

### Table 1: Comparison of Stage IV Uveal Melanoma Among Various Studies

| Study            | Rajpal et al[16] | COMS[17] | Kath et al [18] | Rietschel et al[19] | Jochems et al[20] | AJCC-OOTF[21] | Mean |
|------------------|------------------|---------|----------------|--------------------|------------------|---------------|------|
| Metastasis       | F/U              | F/U     | F/U            | F/U                | F/U              | Presentation | -    |
| Sample Size      | 35               | 739     | 24             | 119                | 175              | 69            | 193.5|
| Liver            | 71.4%            | 89.0%   | 87.0%          | 60.5%              | 88.0%            | 91.3%         | 81.2%|
| Lungs            | 40.0%            | 29.0%   | 46.0%          | 24.4%              | 25.1%            | 15.9%         | 30.1%|
| Lymph Nodes      | 14.3%            | 11.0%   | 4.2%           | 1.7%               | 16.0%            | 13.0%         | 10.0%|
| Bones            | 17.1%            | 17.0%   | 29.0%          | 8.4%               | 15.4%            | 8.7%          | 15.9%|
| Brain            | 5.7%             | 6.1%    | 8.0%           | 4.2%               | 1.7%             | 5.8%          | 5.2% |
| Subcutaneous tissue | 34.3%      | 12.0%   | 17.0%          | 10.9%              | 10.3%            | 4.3%          | 14.8%|
| Others           | 34.3%            | 11.0%   | 37.5%          | N/A                | 23.4%            | 4.2%          | 22.0%|
| Multiple Sites   | N/A              | 43.0%   | 54.2%          | 10.9%              | 5.7%             | 23.2%         | 27.4%|
| Tests            | N/A              | LFTs, CXR, and autopsy | LFTs, CXR, USG, CT, MRI, and autopsy | Radiographic imaging, blood test | Lactose dehydrogenase (LDH), radiographic imaging | USG, CT, MRI, and whole-body-PET or PET/CT | -    |
| Median Survival Time, months (time from metastasis to death) | 2.2 | <6 | 13.2 | 12.5 | 1-year survival-47.8% | 12 | N/A |

F/U=at follow-up, LFTs=Liver Function Tests, CXR=Chest X-ray, USG=Ultrasonography, CT=Computed Tomography, MRI=Magnetic Resonance Imaging, PET=Positron Emission Tomography, N/A=Not Available
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