Perspective

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.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1478_21

Quick Response Code:

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.[1,5-7] 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 chemoimmunotherapy, 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.[1,3,11] 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.[1,7]

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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Received: 02-Jun-2021
Accepted: 21-Aug-2021 Published: 23-Dec-2021

Cite this article as: Garg G, Kivelä TT, Finger PT. Patients presenting with stage IV uveal melanoma: Lessons learned. Indian J Ophthalmol 2022;70:271-4.

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.[1-3,5,13]

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).[2] 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.[5] A large referral-based single-center study of 8033 patients with UM found an increasing risk of metastasis with increase in tumor height.[14] 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– 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).[15]

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 7.6, respectively).[1] Therefore, we 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.[1,2] They also revealed a 1.7% and 17.4% incidence of extrascleral 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.[5] The large single-center study found that ESE was associated with increasing T category among its 7731 posterior UM.[15] 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).[1] Therefore, we can infer that the presence of CBI or ESE can also be used to direct metastatic surveys.

AJCC N and M Categories (Regional and Systemic Metastases)

UM is capable of metastasizing to multiple sites [Table 1], with a high predilection for the liver, 81% (range, 71%–91%).[1,16-20] 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 multi-organ 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.[1,4,17,21,22]

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 extrahepatic and hepatic metastases, as well as 3.3% of patients who had second nonocular malignancies.[4] 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 extrahepatic 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 pelvis scans.[4,25] These doses are associated with a lifetime cancer risk of up to 0.6%.[25] 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.[26] 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 extrahepatic 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

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[1]	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

risk of metastasis (hazard ratio, 6.3).[27] The COMS and three single-center studies reported a widely varying frequency of 10.3%, 15.7%, 6.1%, and 3.2%.[28-31] 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.[28,31] 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.[29,30] 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.[27]

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.[32]

Consider that peritumoral hemorrhage (around the tumors' base) can block transillumination light and thus artifactually enlarge an intraoperative tumor shadow, leading to potential decentration of the plaque.[33] 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.[34]

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.[2] 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 IIIC, respectively.[13]

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.

Financial support and sponsorship

Dr. Garg received an ophthalmic oncology fellowship grant to study with Dr. Finger (from The Eye Cancer Foundation). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest

There are no conflicts of interest.

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