J of Nuclear Medicine Technology, first published online April 5, 2021 as doi:10.2967/jnmt.120.260539

Nuclear Medicine and Molecular Imaging in Nodal Staging and Surveillance of Ocular Melanoma: Cases Report and Review of Literature

Kenneth S. Zurcher, MD[1], Odette M. Houghton, MD[2], Joanne F. Shen, MD[2], Mahesh Seetharam, MD[3], Michael C. Roarke, MD, MS[1], Ming Yang, MD[1*]

[1]Department of Radiology, [2]Ophthalmology, [3]Hematology/Oncology

Mayo Clinic Arizona

***CORRESPONDING AUTHOR:**

Ming Yang, MD.

Department of Radiology

Mayo Clinic Arizona.

13400 E Shea BLVD,

Scottsdale, AZ 85259

Tel: 480-342-0988

Email: yang.ming@mayo.edu

All authors disclose no relevant conflicts of interest.

SHORT TITLE: Nuclear medicine staging ocular melanoma

Abstract

Ocular melanoma (OM) is a rare noncutaneous malignancy and consists of 2 different subtypes based on anatomic location in the eye: uveal melanoma (UM) and conjunctival melanoma (CM). As in cutaneous melanoma, nuclear medicine and molecular imaging play valuable roles in the nodal staging and clinical management of OM. Through the illustration of 2 distinctive cases, we aim to demonstrate the complementary roles of standard lymphoscintigraphy, advanced single-photon emission computed tomography/computed tomography, ^{18}F-fludeoxyglucose positron emission tomography/computed tomography, and hybrid positron emission tomography/magnetic resonance imaging in accurate nodal staging and surveillance of OM. We also review the epidemiology, existing staging guidelines and management of UM and CM.

Keywords: conjunctival melanoma; FDG/PET; lymphoscintigraphy; SPECT; uveal melanoma

Introduction

Ocular melanoma (OM) represents the most common form of rare noncutaneous melanoma and the most common primary ocular tumor in adults.(*1*) There are 2 subtypes of OM based on anatomic location in the eye: uveal melanoma (UM), which involves the choroid, retina, iris, and/or ciliary body and accounts for 95% of OM cases; and rarer conjunctival melanoma (CM), which mainly involves the bulbar conjunctiva and comprises only about 5% of OM cases. The clinical manifestations and treatment approaches of OM vary between UM and CM, and accurate staging outside the eyes is crucial in the assessment of treatment response and surveillance of UM and CM. (*2-4*).

Given the differences in lymphatic drainage and potential sites of metastases between UM and CM, distinct considerations must be made in regard to tumor staging strategies. Nuclear medicine and molecular imaging (i.e., technetium 99m [Tc 99m] sulfur colloid lymphoscintigraphy–guided sentinel lymph node biopsy [SLNB] and whole body ^{18}F-fludeoxyglucose–positron emission tomography/computed tomography [FDG-PET/CT]) have proven value in staging melanoma in the discovery of tracer avid locoregional nodal and visceral metastases.(*5-8*) While limited data exist on the optimal imaging modality for staging CM, which has a similar lymphatic spread pattern as cutaneous melanoma, Tc-99m sulfur colloid lymphoscintigraphy and single-photon emission computed tomography (SPECT)/CT-guided SLNB have emerged as valuable tools. Given the technical skill required for subconjunctival radiotracer injection, they have been used only at some specialized eye institutions.(*9-12*) Hybrid PET/magnetic resonance imaging (MRI) systems have become increasingly available and allow for combined whole body molecular imaging and high-resolution, targeted, diagnostic MRI in an

"one-stop"[i] imaging examination model. PET/MRI enables diagnosis of hepatic and brain metastasis and evaluation of tumor burden, as well as assists in clinical management of OM.(*13*)

In this study, we present 2 distinct cases to demonstrate the clinical utility of standard and advanced nuclear medicine imaging modalities in OM, followed by a review of OM epidemiology and existing guidelines on staging and management. Specifically, we aim to underscore the importance of FDG-PET/CT and/or hybrid PET/MRI in the staging or restaging of OM and the use of Tc-99m sulfur colloid (SC) lymphoscintigraphy and SPECT/CT in CM. This study is complied with institutional review board policy.

Cases

Case 1

A 74-year-old man presented with visual changes in his left eye. On ophthalmologic examination, the patient was found to have retinal detachment with a large pigmented uveal mass, consistent with diagnosis of ciliochoroidal melanoma. Staging CT and MRI of the liver demonstrated multiple hepatic lesions. Metastatic ciliochoroidal melanoma was confirmed on following ultrasound-guided biopsy of liver lesion, revealing stage T4bN0M1 disease. The patient underwent gamma knife radiotherapy to the left eye lesion and was initiated on systemic therapy with pembrolizumab. To evaluate response to therapy, FDG-PET/MR was performed on a GE Signa 3 Tesla PET/MR system (Milwaukee, WI). The customized PET/MR protocol consists of two parts: part 1): whole body FDG-PET/MR survey scan with 370 MBq FDG intravenous injection, 60-minute uptake time, 6-8 bed positions covering the whole body (each bed position imaging time around 4 minutes). Simultaneous T1 DIXON LAVA (water, fat, in-phase, and out-phase) sequences were acquired for attenuation correction and localization; and part 2): focused contrast enhanced liver MRI scan. The whole body FDG-PET/MRI

demonstrated recurrent or residual tracer avid primary left eye lesion on survey scan with progression of hepatic metastases (Figure 1). The patient did not response to chemotherapy and deceased 15 months after the initial diagnosis of UM.

Case 2

A 64-year-old woman with a history of primary acquired melanosis (PAM) presented with a rapidly enlarging mobile lesion of the right eye. On examination, a mobile pigmented lesion involving the right superior temporal conjunctiva was noted, with surrounding melanosis and without scleral invasion. The patient underwent excisional biopsy and cryotherapy. Pathology revealed invasive bulbar CM with 2.6-mm depth of invasion. Nasal and temporal margins were positive for residual PAM with atypia only. Further staging workup was performed, including whole body FDG-PET/CT (same dosage and uptake time as whole body FDG-PET/MR) and MRI of the brain and neck, both of which were negative for recurrent lesion or metastatic disease. Lymphoscintigraphy for the purposes of SLNB was also performed. Subconjunctival radiotracer injection was performed by an ophthalmologist (J.F.S.) with a valid authorized user status. In detail, 4% lidocaine was topically applied with cotton tip applicator to injection site of the right eye following a dedicated sterile preparation protocol. With patient's eyelids were manually held open by the ophthalmologist and patient was instructed to look in the opposite direction from the injection site, two 0.2 ml normal saline aliquots containing 11.1 MBq Tc-99m filtered SC were successfully injected in the subconjunctival space separately in the area of the excised melanoma. Dynamic and static planar scintigraphy images of head/neck were performed followed by SPECT/CT to localize the sentinel node. On both planar and SPECT images, there was a right parotid sentinel node identified which was resected through superficial parotidectomy and was negative for metastasis on final pathology (Figure 2). The patient was

staged as T1cN0M0. The patient remained negative for tumor recurrence or metastasis on repeated biopsy and multimodality image studies, including whole body FDG-PET/CT and PET/MRI (Figure 3).

Discussion

OM is a rare type of noncutaneous melanoma and the second most common melanoma after cutaneous melanoma.(*1*) Based on its anatomic location, OM is categorized as UM or CM (Figure 4). There are distinctive differences in epidemiology, pathophysiology, and the clinical management between these 2 subtypes. Similar to their cutaneous melanoma counterpart, accurate staging and appropriate clinical surveillance may guide clinical management and ultimately improve prognosis. From SLNB to whole body FDG-PET/CT, nuclear medicine and molecular imaging have a well-established role in staging and surveillance of cutaneous melanoma. Given the complex anatomy of the eye and rarity of OM, we present these 2 cases to demonstrate that the variety of nuclear medicine and molecular imaging modalities provides excellent imaging tools in staging and surveillance of OM.

Uveal Melanoma

Epidemiology and Pathophysiology

UM represents the most common primary intraocular malignancy in adults, with a mean age-adjusted incidence of 5.1 per million population.(*1,14-16*) Based on Surveillance, Epidemiology, and End Results data collected in the US between 1973 and 2008, UM represented approximately 3.1% of all melanoma cases, with 5- and 15-year survival rates of 81.6% and 45%, respectively.(*15,16*) UM develops from melanocytes along the uveal tract and most frequently arises from the choroid (85%), with retinal, iris, and ciliary body involvement comprising the remainder of cases.(*14,17*) Increased rates of UM are seen in white populations.

Staging

Due to a relative lack of lymphatics within the eye, metastatic spread of UM predominantly occurs in a hematogenous manner. While metastases can be found in a number of organ systems, UM demonstrates a notorious propensity for liver metastasis. Although this mechanism is not well understood, an estimated 71% to 95% of patients with metastatic disease demonstrate hepatic lesions; other metastatic sites include bone, lung, skin, and other organ systems.(*14,18,19*)

Staging of OM is guided by the American Joint Committee on Cancer , with imaging playing a vital role in identifying metastatic disease.(*16*) Consensus-based guidelines on staging workup of UM were proposed by Weis et al(*16*) in 2016 and recommend 1 of the following be obtained: CT of the chest and abdomen (liver protocol for abdomen), whole body FDG-PET/CT, or liver MRI with chest CT.

Recent studies have highlighted the sensitivity and positive predictive value (PPV) of both FDG-PET/CT and MRI in assessing metastatic UM. A 2012 study by Freton et al(*20*) highlighted FDG-PET/CT as an effective screening modality for hepatic and extrahepatic metastasis with 100% PPV. Of 333 consecutive patients with UM who underwent screening with FDG-PET/CT, 7 demonstrated biopsy-proven liver metastases, and 2 of those 7 (29%) had multi-organ involvement. In a 2005 study by Kurli et al,(*19*) 20 patients with suspected metastatic UM underwent FDG-PET/CT to identify metastatic disease. Of 8 patients with positive metastasis, 8 (100%) demonstrated liver metastasis and 6 (75%) showed multi-organ involvement-, resulting in a sensitivity of 100%. Klingenstein et al(*21*) in 2010 further established FDG-PET/CT as an effective tool in imaging staging and follow-up of metastatic UM.

In specifically determining the presence of isolated hepatic metastatic disease, a 2010 study by Servois et al(*22*) reported the sensitivity and PPV of liver MRI to be 67% and 95%, respectively, compared to 41% and 100% for FDG-PET/CT. This increased sensitivity of MRI over FDG-PET/CT in detecting liver lesions was further corroborated in a 2012 study by Orcurto et al,(*23*) in which MRI outweighed FDG-PET/CT in detecting small lesions (<1.2 cm). Importantly, in their study, FDG-PET/CT identified at least 1 metastatic liver lesion per patient as well as changes in FDG uptake not related to size change, which suggests a potential role in determining early therapy response.

While a single optimal imaging modality has not yet been determined in the staging of UM, benefits exist for both FDG-PET/CT (identifying extrahepatic disease with good sensitivity and PPV for hepatic lesions) and MRI (improved sensitivity for identifying hepatic lesions). In case 1, FDG-PET/MRI was chosen as the optimal surveillance modality, which demonstrated excellent performance in delineating both the primary lesion and hepatic metastases in the advantageous 1-stop imaging pattern. The hybrid diagnostic liver FDG-PET/MRI demonstrated its unique advantage in combining morphologic and molecular imaging information in diagnosis of liver metastasis in melanoma. If available or feasible, FDG-PET/MRI may represent an alternative that combines the described advantages of both modalities, with reduced radiation dose compared to whole body FDG-PET/CT.

Management

Management of UM is highly specialized and requires multidisciplinary support. With regards to surgical management, enucleation remains the preferred treatment for lesions greater than 10 mm in thickness or 18 mm in diameter.(*16*) Local resection can be considered in select

ciliary body or iris lesions. Lesions best suited for brachytherapy include those less than 10 mm in thickness and 18 mm in maximal diameter, as well as high-risk indeterminate lesions.

The appropriate imaging surveillance strategy for patients with metastatic UM remains to be fully established. However, annual follow-up with FDG-PET/CT or liver MRI and/or liver ultrasonography and chest radiography are recommended. While a prospective study of 188 high-risk UM patients showed that semiannual liver MRI detected metastases in 92% of patients before symptoms, a survival benefit of such a regimen remains to be established.(*24*)

Conjunctival Melanoma

Epidemiology and Pathophysiology

CM represents a considerably rarer entity compared to UM, occurring approximately one-fortieth as often, with an estimated annual incidence of 0.2 to 0.8 cases per million.(*25-29*) CM is predominantly seen in middle-aged to older white populations, without a definite sex predilection. Five- and 8-year mortalities have been most recently estimated at 7% and 13%, respectively.(*30*) While risk factors commonly associated with cutaneous melanoma have not been demonstrated in CM (e.g., family history, ultraviolet light exposure, fair skin and hair), an association between PAM and CM has been well established. Of CM cases, 57% to 76% are thought to be attributable to PAM—with PAM with severe atypia transforming into CM at a high frequency.(*30,31*) CM results from malignant proliferation of melanocytes—specifically from conjunctiva. Anatomically, the conjunctiva represents a clear mucous membrane that lines the posterior surface of the eyelids (palpebral conjunctiva), as well as anterior portions of the globe and in the superior and inferior fornices (bulbar and forniceal conjunctiva, respectively).(*25*) However, there is no particular quadrant prediction, with the following quadrant incidence

ranges reported: superior (16-34%), inferior (22-39%), nasal (17-34%), and temporal (26-63%) (*30,32*).

Staging

As the conjunctiva is supplied by both blood vessels and lymphatics, metastatic spread can occur hematogenously or via lymphatic drainage to regional lymph nodes. Initial lymphatic spread is estimated to occur in up to 41% to 62% of patients, with distant metastases in the absence of local nodal involvement occurring in 26% to 50%.(*3,30,33*) Reported risk factors for regional nodal spread include nonlimbal location, tumor thickness greater than 2 mm, large basal diameter, positive resection margins, and orbital extension.(*34*) The lymphatic spread of CM seems to be associated with the location of primary tumor with nasal conjunctiva appear to drain to the submandibular lymph nodes (9%), while tumors of the rest of the conjunctiva primarily drain to the preauricular nodes (73%) and deep cervical lymph nodes (18%).(*3*) Currently, no strict imaging guidelines exist for systemic staging workup or restaging of CM.(*4,31*) Existing recommendations include CT or MRI of the brain, chest, and abdomen/liver or FDG-PET/CT. In contrast to UM, a paucity of data exists assessing the utility of FDG-PET/CT in CM. The largest case series was reported by Kurli et al(*35*) who investigated the performance of FDG-PET/CT in 14 CM patients with 7 for per-operative staging and 7 for restaging after treatments (surgical removal with adjuvant cryotherapy and/or chemotherapy). Among the group of patients, they found 1 patient (T4 stage) of their small cohort has multi-site distant metastases, with involvement of the liver, lung, peritoneal cavity and lumbar spine, etc. The remaining 13 patients (T3 stage) were negative for either loco-regional or distant metastasis. Their study indicated a limited role of F18-FDG PET/CT in initial T and N staging, but valuable in restaging of CM. Damian et al reported a case presenting with hypermetabolic primary left eye

CM lesion and ipsilateral pre-auricular node on restaging FDG PET/CT, without evidence of distant metastasis.(*36*)

Owing to the similar pattern of lymphatic spread between CM and cutaneous melanoma, lymphoscintigraphy with SLNB has arisen as a safe and viable staging tool in the last 1 to 2 decades and has been supported in several small case series.(*11,34,36*) Preoperative SLNB allows for potential detection of otherwise clinically undetectable systemic spread and is performed during or after removal of the primary lesion.(*31*) The success of SLNB requires the sophisticated subconjunctival injection of filtered Tc-99m SC near the existing tumor or site of resection at the nuclear medicine laboratory.(*37*) Dynamic planar images are obtained with a gamma camera in order to identify a sentinel lymph node. The skin is marked in this region, with use of SPECT/CT for further localization. Intraoperatively, a handheld gamma probe and methylene blue injection are also used to localize the sentinel node, followed by surgical dissection, excision, and histologic processing.

Ultimately, further trials are required to fully identify the role and survival benefit of lymphoscintigraphy with SLNB in this population. Given the rarity of CM, existing data remains limited, with a cohort of 18 patients from Cohen et al(*34*) remaining the largest studied population.

Management

Again, owing to the rarity of CM, management of this malignancy is based on case reports and series. Current standard of care includes wide local excision with double freeze-thaw cryotherapy to resection margins.(*4,31*) Enucleation may be required in advanced cases in which wide local excision is not feasible. Topical chemotherapy and brachytherapy have been explored as adjuvant therapy. Unfortunately, 5-year recurrence rates are high, currently estimated at 36%

to 45% following surgical resection.(*31*) As with UM, no optimal or well-researched imaging surveillance for restaging of CM currently exists, with FDG-PET/CT often being employed.

Conclusion: Nuclear medicine and molecular imaging have an established role in the staging and surveillance of OM. Owing to differences in metastatic pathways between UM and CM, imaging strategies for both entities also differ. In patients with UM, whole body FDG-PET/CT may represent mainstays of initial staging and surveillance. The role of emerging hybrid FDG-PET/MRI is promising, especially in the diagnosis and assessment of metastasis in the liver and brain; but it is limited due to availability and needs to be defined with more clinical application. Data on the staging and surveillance of CM remains sparse and is based on limited case series. Since CM may spread to locoregional lymph nodes via the lymphatic drainage channel, it is the rationale to perform SLNB and SPECT/CT in the staging of CM to predict recurrence and survival. Collaboration with ophthalmology at a clinical nuclear medicine practice is crucial to successfully perform the sophisticated subconjunctival radiotracer injection.

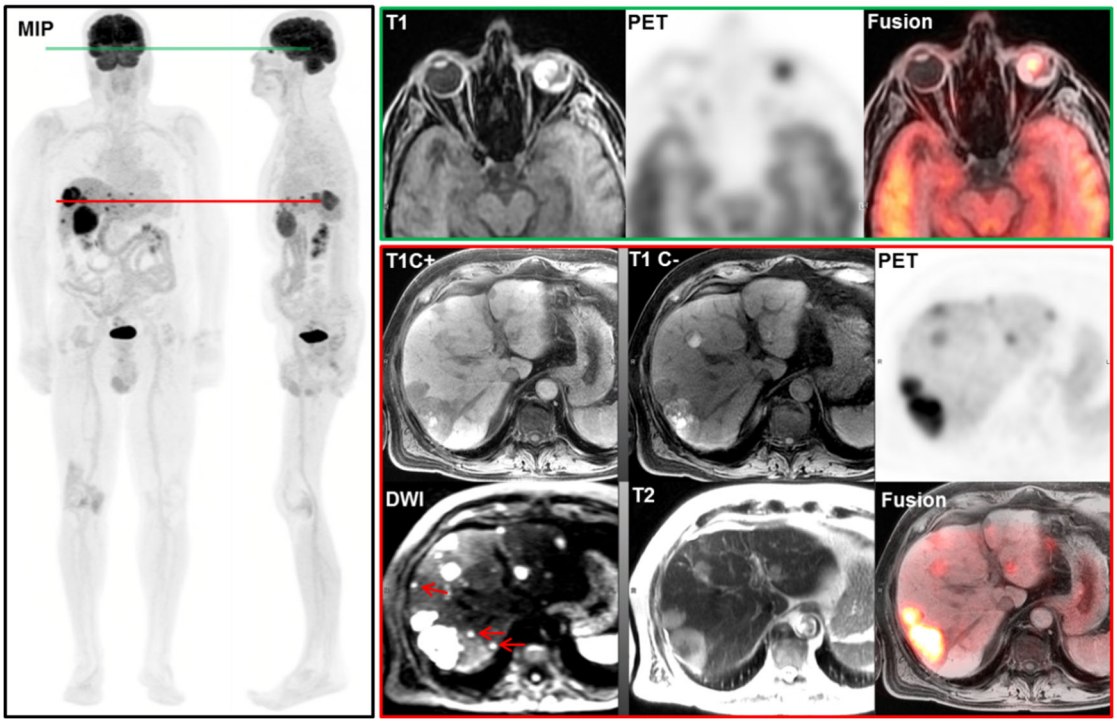

Figure 1. Whole body hybrid FDG-PET/MR in surveillance of uveal melanoma (case #1). Whole body MIP images exhibit tracer avid left eye lesion and numerous tracer avid lesions in the liver. Axial PET/MRI of the left eye demonstrates high T1-signal lesion in the left globe with increased tracer uptake, with SUV max 8.3 (green line, green box). On the representative layer of the liver (red line, red box), multiple liver lesions with variable low and high T1 signals show increased uptake, with SUV max 4.0-11.7. In addition, DWI shows more small metastases with restricted diffusion (red arrows) than post-contrast enhanced images (T1C+) and PET. DWI, diffusion-weighted imaging; MIP, maximal intensity projection.

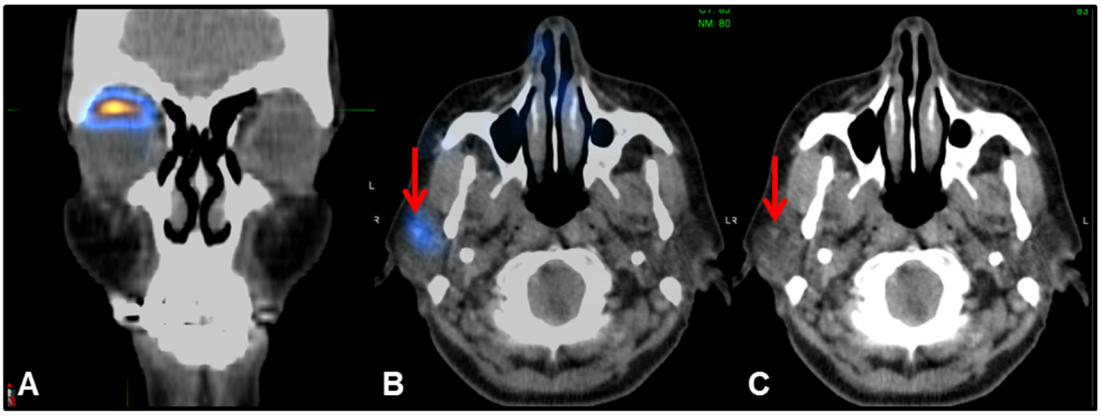

Figure 2. Tc-99m filtered sulfur colloid SPECT/CT (case #2). A: fused coronal image demonstrates successful radiotracer injection to the right eye subconjunctival region by ophthalmologist. B: fused axial image; and C, axial low-dose CT image. A tiny right parotid gland fossa sentinel lymph node was identified (red arrows in B & C). It was negative for metastasis on biopsy.

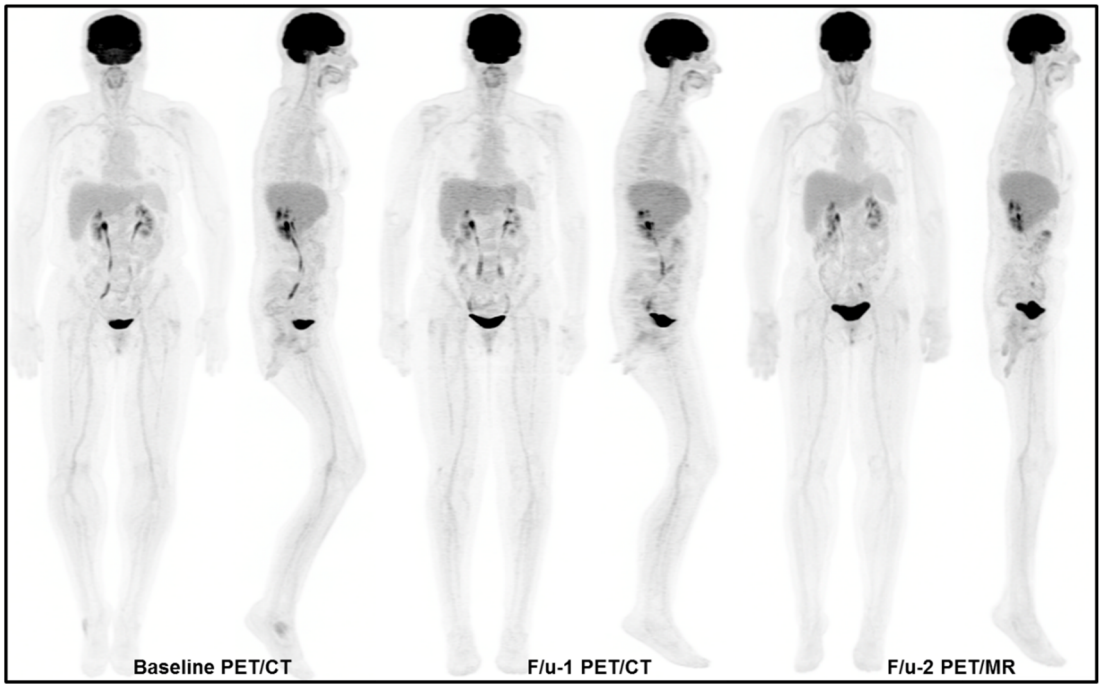

Figure 3. Whole body FDG-PET/CT and PET/MR in surveillance of conjunctival melanoma (case #2). The consecutive MIP images at anterior and right lateral views do not demonstrate hypermetabolic metastasis or recurrence at baseline, follow-up 1 (12 month), or follow-up 2 (16 month) studies. MIP, maximal intensity project.

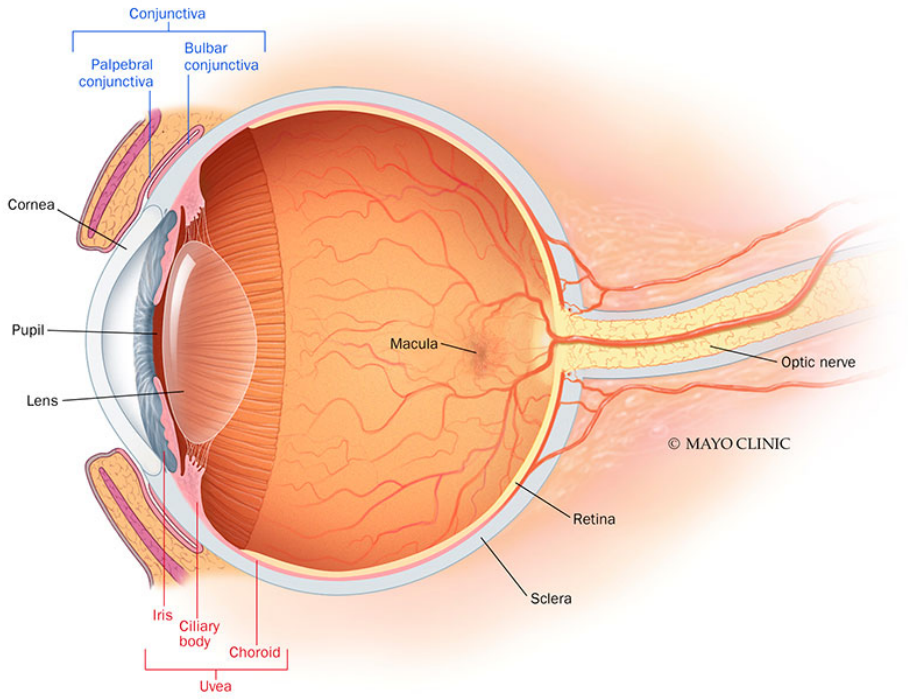

Figure 4. Illustration of eye anatomy. Uveal melanoma occurs at the iris, ciliary body, and choroid (in red). Conjunctival melanoma occurs at palpebral and bulbar conjunctiva (in blue). Figure used with permission.

Reference

1. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. *Cancer.* 2005;103:1000-1007.

2. Aronow ME, Topham AK, Singh AD. Uveal Melanoma: 5-Year Update on Incidence, Treatment, and Survival (SEER 1973-2013). *Ocular Oncology and Pathology.* 2018;4:145-151.

3. Esmaeli B, Wang X, Youssef A, Gershenwald JE. Patterns of regional and distant metastasis in patients with conjunctival melanoma: Experience at a cancer center over four decades. *Ophthalmology.* 2001;108:2101-2105.

4. Vora GK, Demirci H, Marr B, Mruthyunjaya P. Advances in the management of conjunctival melanoma. *Surv Ophthalmol.* 2017;62:26-42.

5. Fuster D, Chiang S, Johnson G, Schuchter LM, Zhuang H, Alavi A. Is 18F-FDG PET more accurate than standard diagnostic procedures in the detection of suspected recurrent melanoma? *J Nucl Med.* 2004;45:1323-1327.

6. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392-399.

7. Steinert Hc HBRABABRBTMBBGvSGK. Malignant melanoma: staging with whole-body positron emission tomography and 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology.* 1995;195:705-709.

8. Wong SL, Faries MB, Kennedy EB, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *Ann Surg Oncol.* 2018;25:356-377.

9. Balasubramanya R, Selvarajan SK, Cox M, et al. Imaging of ocular melanoma metastasis. *The British journal of radiology.* 2016;89:20160092-20160092.

10. Esmaeli B. Sentinel lymph node mapping for patients with cutaneous and conjunctival malignant melanoma. *Ophthalmic plastic and reconstructive surgery.* 2000;16:170-172.

11. Esmaeli B, Eicher S, Popp J, Delpassand E, Prieto VG, Gershenwald JE. Sentinel lymph node biopsy for conjunctival melanoma. *Ophthalmic Plastic and Reconstructive Surgery.* 2001;17:436-442.

12. Reddy S, Kurli M, Tena LB, Finger PT. PET/CT imaging: detection of choroidal melanoma. *The British journal of ophthalmology.* 2005;89:1265-1269.

13. Buchbender C, Heusner TA, Lauenstein TC, Bockisch A, Antoch G. Oncologic PET/MRI, part 2: bone tumors, soft-tissue tumors, melanoma, and lymphoma. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 2012;53:1244-1252.

14. Kalemaki MS, Karantanas AH, Exarchos D, et al. PET/CT and PET/MRI in ophthalmic oncology (Review). *International Journal of Oncology.* 2020;56:407-419.

15. Singh AD, Turell ME, Topham AK. Uveal melanoma: Trends in incidence, treatment, and survival. *Ophthalmology.* 2011;118:1881-1885.

16. Weis E, Salopek TG, McKinnon JG, et al. Management of uveal melanoma: A consensus-based provincial clinical practice guideline. *Current Oncology.* 2016;23:e57-e64.

17. Yang G, Sau C, Lai W, Cichon J, Li W. Advances in the Managment of Conjunctival Melanoma. 2015;344:1173-1178.

18. Bakalian S, Marshall JC, Logan P, et al. Molecular pathways mediating liver metastasis in patients with uveal melanoma. *Clinical Cancer Research.* 2008;14:951-956.

19. Kurli M, Reddy S, Tena LB, Pavlick AC, Finger PT. Whole body positron emission tomography/computed tomography staging of metastatic choroidal melanoma. *American Journal of Ophthalmology.* 2005;140:193.e191-193.e199.

20. Freton A, Chin KJ, Raut R, Tena LB, Kivelä T, Finger PT. Initial PET/CT staging for choroidal melanoma: AJCC correlation and second nonocular primaries in 333 patients. *European Journal of Ophthalmology.* 2012;22:236-243.

21. Klingenstein A, Haug AR, Nentwich MM, Tiling R, Schaller UC. Whole-body F-18-fluoro-2-deoxyglucose positron emission tomography/computed tomography imaging in the follow-up of metastatic uveal melanoma. *Melanoma Research.* 2010;20:511-516.

22. Servois V, Mariani P, Malhaire C, Petras S, Piperno-neumann S, Plancher C. Preoperative staging of liver metastases from uveal melanoma by magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission. *European Journal of Surgical Oncology.* 2010;36:189-194.

23. Orcurto V, Denys A, Voelter V, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography and magnetic resonance imaging in patients with liver metastases from uveal melanoma: Results from a pilot study. *Melanoma Research.* 2012;22:63-69.

24. Marshall E, Romaniuk C, Ghaneh P, et al. MRI in the detection of hepatic metastases from high-risk uveal melanoma: A prospective study in 188 patients. *British Journal of Ophthalmology.* 2013;97:159-163.

25. Brownstein S. Malignant melanoma of the conjunctiva. *Cancer Control.* 2004;11:310-316.

26. Shildkrot Y, Wilson MW. Conjunctival melanoma: Pitfalls and dilemmas in management. *Current Opinion in Ophthalmology.* 2010;21:380-386.

27. Triay E, Bergman L, Nilsson B, All-Ericsson C, Seregard S. Time trends in the incidence of conjunctival melanoma in Sweden. *British Journal of Ophthalmology.* 2009;93:1524-1528.

28. Tuomaala S, Eskelin S, Tarkkanen A, Kivelä T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. *Investigative Ophthalmology and Visual Science.* 2002;43:3399-3408.

29. Yu GP, Hu DN, McCormick S, Finger PT. Conjunctival melanoma: Is it increasing in the United States? *American Journal of Ophthalmology.* 2003;135:800-806.

30. Shields CL, Shields JA, Gunduz K, et al. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. *Arch Ophthalmol.* 2000;118:1497-1507.

31. Wong JR, Nanjp AA, Galor A, Karp CL. Management of conjunctival malignant melanoma: a review and update. *Expert Rev Ophthalmol*. 2014;9:185-204.

32. Shields CL, Markowitz JS, Belinsky I, et al. Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases. *Ophthalmology.* 2011;118:389-395 e381-382.

33. Tuomaala S, Kivelä T. Metastatic pattern and survival in disseminated conjunctival melanoma: Implications for sentinel lymph node biopsy. *Ophthalmology.* 2004;111:816-821.

34. Cohen VML, Tsimpida M, Hungerford JL, Jan H, Cerio R, Moir G. Prospective study of sentinel lymph node biopsy for conjunctival melanoma. *British Journal of Ophthalmology.* 2013;97:1525-1529.

35. Kurli M, Chin K, Finger PT. Whole-body 18 FDG PET/CT imaging for lymph node and metastatic staging of conjunctival melanoma. *British Journal of Ophthalmology.* 2008;92:479-482.

36. Damian A, Gaudiano J, Engler H, Alonso O. (18)F-FDG PET-CT for Staging of Conjunctival Melanoma. *World J Nucl Med.* 2013;12:45-47.

37. Wainstein AJ, Drummond-Lage AP, Kansaon MJ, et al. Sentinel lymph node biopsy for conjunctival malignant melanoma: Surgical techniques. *Clinical Ophthalmology.* 2014;9:1-6.