

Nine Black Pearls in the Management of Uveal Melanoma

Tips for clinicians for better management of this often misunderstood disease.

BY CAROL L. SHIELDS, MD

The Black Pearl sailed the dark, salty seas in the film, *Pirates of the Caribbean*. Captained by Jack Sparrow, this haunted ship was threatening in many ways, especially with its black hull and sails. She sailed in the pitch dark and was “nigh uncatchable,” faster than any ship at sea. Her ghostly appearance potentially yielded a deathly curse.

An analogy can easily be made to uveal melanoma, which is known to hide in the dark hollows of the eye, often “nigh uncatchable,” masquerading as less serious conditions, and ultimately leading to a lifelong curse. The curse of melanoma could lead to metastasis—even before the malignancy is recognized in the eye.

In 2009, what new tips, information, or “black pearls” can improve our understanding of uveal melanoma?

BLACK PEARL #1

Arc Welding Is related to Development of Melanoma

There have been numerous investigations into the causes of uveal melanoma. In 2006, Weis and coworkers¹ provided a meta-analysis of 132 published reports on host factors that were important in the development of uveal melanoma. They found that light eye color, fair skin color, and an inability to tan were risks for melanoma. These same investigators, under the direction of Shah,² performed a meta-analysis of 132 published reports on environmental factors as the cause of melanoma. They found only arc welding

to be a risk factor. Geographic birth location near the equator and at high altitude, a known risk factor for skin melanoma, was not a risk for uveal melanoma. Intermittent intensive sunlight exposure such as tropical vacation, a known risk factor for skin melanoma, was not a risk for uveal melanoma. However, chronic sunlight exposure such as long-term outdoor employment was a borderline risk for uveal melanoma.

BLACK PEARL #2

Melanomas in the Macular Region are Smaller Than Those in the Periphery

In an analysis of 8,033 patients with uveal melanoma, the tumor epicenter location was found to be superior (22%), temporal (28%), inferior (22%), nasal (21%), macular (4%), and diffuse (3%).³ Further analysis of this data showed that mean tumor thickness for melanoma in the

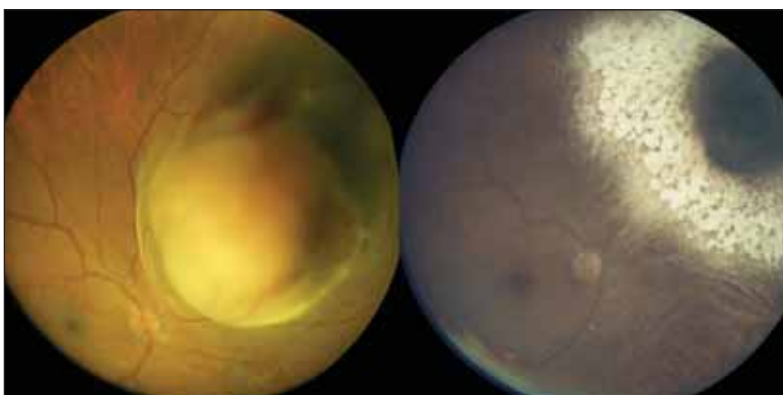


Figure 1. Large choroidal melanoma measuring 8.5 mm thickness before and after plaque radiotherapy.

macula was 2.6 mm, at the equator was 4.3 mm, and at the ora serrata was 7.0 mm. Macular melanomas tended to be thinner than melanoma, at other locations. The risk for metastasis at 5 years paralleled thickness, with 5% metastasis for macular melanoma, 16% for equatorial location, and 18% for ora serrata location.

BLACK PEARL #3

Melanoma-related Prognosis Depends on Tumor Size

Kujala and associates⁴ in Helsinki, Finland reported very long-term prognosis of patients with uveal melanoma.

In their small cohort of 289 patients, they found melanoma-related mortality at 25 years in 15% of patients with small melanoma, 55% with medium melanoma, and 68% with large melanoma. Small melanoma was defined as basal diameter less than 10 mm, medium as 10 mm to 15 mm, and large as greater than 16 mm. Shields and associates³ evaluated a large cohort of 8,033 patients and found melanoma-related metastasis at 20 years in 16% of patients with small melanoma, 30% with medium melanoma, and 61% with large melanoma. Small melanoma was defined by thickness rather than base, so small tumors were less than 3 mm thickness, medium were 3 mm to 8 mm thickness, and large were greater than 8 mm thickness. Using similar parameters, Diener-West⁵ and colleagues found death at 5 years in 16% of patients with small melanoma, 32% with medium melanoma, and 53% with large melanoma.

BLACK PEARL #4

Plaque Radiotherapy Control for Medium Uveal Melanoma

There are numerous treatments for melanoma, including laser photocoagulation, thermotherapy, plaque radiotherapy, charged particle radiotherapy, resection, enucleation, and exenteration. The chosen treatment depends on many factors including tumor size, tumor location, status of the opposite eye, patient age, patient health, and patient desires and fears. Treatment parameters for plaque radiotherapy include 8,000 cGy to the tumor apex and approximately 30,000 cGy to the tumor base, delivered over a 5-day period. Radioactive iodine 125 (I-125) plaques can be custom fit to each eye, tumor size, and tumor location.

Much of our current knowledge about plaque radiotherapy for uveal melanoma is from numerous contributions over the past 3 decades as well as the more recent Collaborative Ocular Melanoma Study (COMS). The COMS



Figure 2. Circumpapillary choroidal melanoma before and after custom fit notched plaque radiotherapy.

investigators conducted two multicenter trials regarding therapy for uveal melanoma. In the medium tumor trial (2.5 mm to 10-mm thickness and basal diameter less than 16 mm), eyes were randomized to I-125 brachytherapy vs enucleation. In this trial, melanoma-related mortality at 5, 10, and 12 years was 10%, 18%, and 21% respectively, for patients in the I-125 brachytherapy arm, and 11%, 17%, and 17% for those in the enucleation arm.^{6,7} In the large tumor trial (greater than 10-mm thickness or less than 2-mm thickness and greater than 16-mm basal diameter), eyes were randomized to enucleation vs external beam radiotherapy preceding enucleation. In that trial, melanoma-related mortality at 5 and 10 years was 28% and 40% for patients in the enucleation arm and 26% and 45% in the external beam radiotherapy preceding enucleation arm.^{8,9}

The COMS did not assess plaque radiotherapy for small tumors under 2.5 mm thickness, large tumors over 10-mm thickness, or tumors touching the optic disc (juxtapapillary). The Oncology Service at Wills Eye Institute has conducted independent studies on these subsets of patients, and these are listed below.

BLACK PEARL #5

Plaque Radiotherapy Control for Small Uveal Melanoma

Small melanoma is usually defined as tumor less than 3-mm thickness. Many such tumors show overlapping features with choroidal nevus. Risk factors for small melanoma can help differentiate the melanoma from the nevus. These factors include:

- T tumor Thickness over 2 mm
- F subretinal Fluid
- S Symptoms
- O Orange pigment and
- M tumor Margin within 3 mm of the disc.

These features are remembered by the mnemonic To Find Small Ocular Melanoma (TFSOM).¹⁰ Three or

more features suggest 50% chance or greater for tumor growth. Tumors as thin as 1.0 mm can manifest metastatic disease.

At the International Society of Ocular Oncology in Siena Italy (2007), Shields and associates¹¹ presented their evaluation of 334 patients with small choroidal melanoma treated with plaque radiotherapy; they found tumor recurrence in 1% at 2 years, 4% at 5 years, and 5% at 10 years. The main factor for recurrence was increasing tumor thickness. Melanoma metastasis was found in less than 1% at 2 years, 7% at 5 years, and 14% at 10 years. Increasing tumor diameter and thickness were independent risks for metastasis.

BLACK PEARL #6

Plaque Radiotherapy Control for Large Uveal Melanoma

Large uveal melanoma is most often managed with enucleation. However, in certain circumstances, such as poor vision in the opposite eye or strong desire to maintain an eye, especially if there is good visual acuity, plaque radiotherapy is provided. In an analysis of 354 patients with large uveal melanoma (greater than 8 mm thickness), tumor recurrence at 5 and 10 years was 9% and 14% (Figure 1).¹² Tumor-related metastasis at 5 and 10 years was 30% and 55%. Large tumor size is a strong predictor of metastatic disease despite complete primary tumor control.

BLACK PEARL #7

Plaque Radiotherapy Control for Juxtapapillary Uveal Melanoma

At the International Society of Ocular Oncology in Siena, Italy (2007), Sagoo and associates¹³ evaluated 650 patients with juxtapapillary choroidal melanoma. These included melanoma that touched, encircled (Figure 2), or overhung the optic disc. This location is the most difficult to treat with plaque radiotherapy and requires precision in radiation design as well as exceptional surgical skills for accuracy in placement. Kaplan-Meier estimates at 5 years were 14% for tumor recurrence, 11% for metastasis, and 4% for death.

BLACK PEARL #8

Genetic Testing Using Fine Needle Aspiration Biopsy

Cytogenetic abnormalities in uveal melanoma have been found on several chromosomes including 1, 3, 6, 8, 11, and 13. Chromosome 3 monosomy is believed to be the most important genetic abnormality predictive of systemic metastasis. Monosomy 3 is found in about 50% of eyes enucleated for melanoma and 30% of eyes treated conservatively with plaque radiotherapy.^{14,15} In

TABLE 1. IMPORTANT PUBLICATIONS ON UVEAL MELANOMA

- Diener-West M, Hakwins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma II. A meta-analysis of 5 year mortality rates following enucleation 1966 through 1988. *Arch Ophthalmol*. 1992; 110:245–250.
- Shields CL, Shields JA, Kiratli H, Cater JR, De Potter P. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology*. 1995;102: 1351–1361.
- Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jöckel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet*. 1996;347:1222–1225.
- Diener-West M, Earle JD, Fine SL, et al; Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. *Arch Ophthalmol*. 2001;119:969–968.
- Kujala E, Makitie T, Kivela T. Very long term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*. 2003;44:4651–4659.

1996, Prescher and coworkers reported on 54 eyes with uveal melanoma that were assessed for copy number of chromosome 3 by karyotype analysis, comparative genomic hybridization, or both and found 30 patients with monosomy 3, 50% of whom developed metastatic disease by 3 years.¹⁴ In the 24 patients with disomy 3, there were no metastases. They identified that monosomy of chromosome 3 was a significant predictor of overall patient survival.

We have further studied genetic testing of uveal melanoma using fine needle aspiration biopsy. In an analysis of 140 cases sampled by needle aspirate, we found larger and more peripheral tumors more likely to manifest monosomy chromosome 3.¹⁵ Using the pars plana approach to biopsy, a yield suitable for genetic testing was achieved in 97% of cases. Even small choroidal melanoma manifested monosomy 3 in 26% of cases, and this was correlated with clinical evidence of tumor growth.

BLACK PEARL #9

Important Publications on Uveal Melanoma

Over the years there have been numerous important publications on uveal melanoma. Highlighted in Table 1 are five, listed in chronological order, that I believe have truly set a landmark and caused us to ponder more deeply this condition. These reports have been discussed above.

In summary, the hunt for the secrets of melanoma¹⁶ is on, and day by day our knowledge improves. Like the Black Pearl in *Pirates of the Caribbean*, uveal melanoma can hide and slither throughout the seas of the human body, but, with some diligence and understanding, we can hope to identify and control its harm. ■

Carol L. Shields, MD, is the Co-Director of the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University. Dr. Shields is a member of the Retina Today Editorial Board. She may be reached at carol.shields@shieldsoncology.com; phone: +1 215 928 3105; fax: +1 215 928 1140. The authors have no financial interest in the devices or medications mentioned in this document.



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3. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol. 2009;in press.
4. Kujala E, Makitie T, Kivela T. Very long term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci. 2003;44:4651–4659.
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