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# Management of Posterior Uveal Melanoma: Past, Present, and Future

## *The 2014 Charles L. Schepens Lecture*

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***Purpose:*** To review the management of ciliary body and choroidal melanoma (posterior uveal melanoma [PUM]) over the last century with an emphasis on changing concepts.

***Design:*** Retrospective review.

***Participants:*** Review of personal experience over 40 years and pertinent literature on management of PUM.

***Methods:*** Diagnosis and therapy for PUM.

***Main Outcome Measures:*** Patient survival.

***Results:*** In the early 1900s, most patients presented with a large symptomatic melanoma that necessitated enucleation, and the systemic prognosis was poor. In the 1970s, controversy erupted regarding the role of enucleation for PUM. Some authorities advocated prompt enucleation, and others proposed that enucleation promoted metastasis, known as the "Zimmerman hypothesis." Others recommended observation, withholding treatment until tumor growth was documented. During the 1970s, there was a trend toward eye-saving procedures, including laser photocoagulation, surgical removal of tumor, and techniques of radiotherapy. Despite local treatment success, systemic prognosis remained guarded with approximately 40% mortality overall. However, there was convincing evidence that smaller tumors offered a significantly better prognosis. Currently, there is a movement toward earlier identification and treatment of small melanomas using clinical factors predictive of malignant potential, in keeping with similar philosophy regarding other cancers. Further understanding of melanoma cytogenetics and molecular pathways have helped to recognize patients at risk for metastasis. At-risk patients are offered systemic therapeutic trials to prevent metastasis. We anticipate that the future management of PUM will focus on detection of clinical and imaging clues for earliest diagnosis, prompt local tumor treatment, and systemic targeted therapies for microscopic metastasis or prevention of metastasis. Personalized evaluation of patient-specific melanoma molecular pathway signature could allow for therapeutic intervention at a site specific to the pathway abnormality that leads to the development of melanoma.

***Conclusions:*** Management of PUM has made major strides over the past century from the days of enucleation for massive, fatal tumor to early detection of smallest tumors with a more favorable prognosis. Current and future targeted specific tumor pathway interruption using systemic agents could improve survival. *Ophthalmology 2015;122:414-428 © 2015 by the American Academy of Ophthalmology.*

It is a great honor to be invited to deliver the 2014 Charles L. Schepens lecture this year. Dr. Schepens was one of the most accomplished ophthalmologists of all times and a true pioneer in diseases of the retina and vitreous. He popularized the use of the head-mounted binocular indirect ophthalmoscope that is used by virtually all ophthalmologists today. We have chosen to discuss the management of malignant melanoma of the ciliary body and choroid (posterior uveal melanoma [PUM]), a subject that was of great interest to Dr. Schepens and has been a major focus of our practice of ocular oncology during the last 40 years at Wills Eye Hospital in Philadelphia. We will cover the past, present, and future management of PUM on the basis of personal experience[1] and review of the pertinent literature on the subject.[2–138] There has been great interest on this topic with numerous publications in the literature, and we will reference those that we consider to be most relevant to the topic of management.[2–138] Internal review board approval was obtained.

## The Past

In the early part of the 20th century, there was little published information on the treatment of PUM. At that time, patients often presented to their physician with tumor filling the globe, frequently causing inflammation, secondary glaucoma, pain, or proptosis due to orbital extension of the tumor. Such cases displayed high mortality secondary to metastasis to liver and other sites.[1]

In a review of his experience with 22 cases of uveal melanoma and 239 cases from other clinicians, Fuchs,[2] in



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1882, stated that "sarcoma (melanoma) of the choroid is one of the most malignant of diseases." He advocated early enucleation. In 1905, Parsons[3] concurred with the poor prognosis of uveal melanoma, based on the known clinical course of this malignancy. In the *System of Ophthalmology* in 1966, Duke-Elder and Perkins[4] commented that 13% to 30% of uveal melanoma displayed extraocular extension, and they described cases of far-advanced melanoma with orbital extension being "three times the size of the eye" at the time of clinical diagnosis.[4] Posterior uveal melanoma carried an extremely poor prognosis during those times.

## Melanoma Diagnosis and Misdiagnosis

Before the 1960s, enucleation was performed for most posterior fundus lesions that were suspected to be PUM. At that time, the direct ophthalmoscope was the only available method for fundus examination and enucleation was often done by the general ophthalmologist, because subspecialty services had not yet been conceived. Many enucleated globes were sent to the Armed Forces Institute of Pathology (AFIP) for diagnostic confirmation.

In 1964, Ferry[6] reported 529 enucleated globes submitted to the AFIP for an ophthalmoscopically visualized fundus lesion believed to be melanoma. He found that 100 (19%) were misdiagnosed and proved histopathologically to have conditions other than melanoma ("pseudomelanomas").[6] In a second study from the AFIP, published 8 years later and intending to update the earlier series, Shields and Zimmerman[7] found that ophthalmologists continued to have a similar rate of misdiagnosis of lesions suspected to be melanoma. The authors speculated that improvements in diagnostic testing at referral centers could reduce mistaken diagnosis.[7] Their speculation was confirmed in a study of 188 patients who underwent enucleation at Wills Eye Hospital during the same time period, with approximately 95% diagnostic accuracy.[8] The Collaborative Ocular Melanoma Study (COMS) subsequently confirmed our prior observations regarding diagnostic precision.[11] The list of pseudomelanomas included rhegmatogenous retinal detachment, disciform macular degeneration, and other benign and malignant tumors, but today almost no eyes are enucleated for these pseudomelanomas.[9,10]

In the mid-1970s, melanoma diagnosis continued to improve, mainly because of the arrival of subspecialty-trained retinal specialists who were more experienced with binocular indirect ophthalmoscopy. In addition, ancillary diagnostic procedures, such as fluorescein angiography, ultrasonography, and the radioactive phosphorus (P32) uptake test, were used to confirm the diagnosis, particularly in more difficult cases. The P32 uptake test became a popular, sophisticated method at several centers for confirming the diagnosis of melanoma before enucleation[12–15] (Fig 1). The interest in the P32 uptake test waned as retinal specialists and ocular oncologists were becoming more adept in differentiating melanoma from pseudomelanomas using

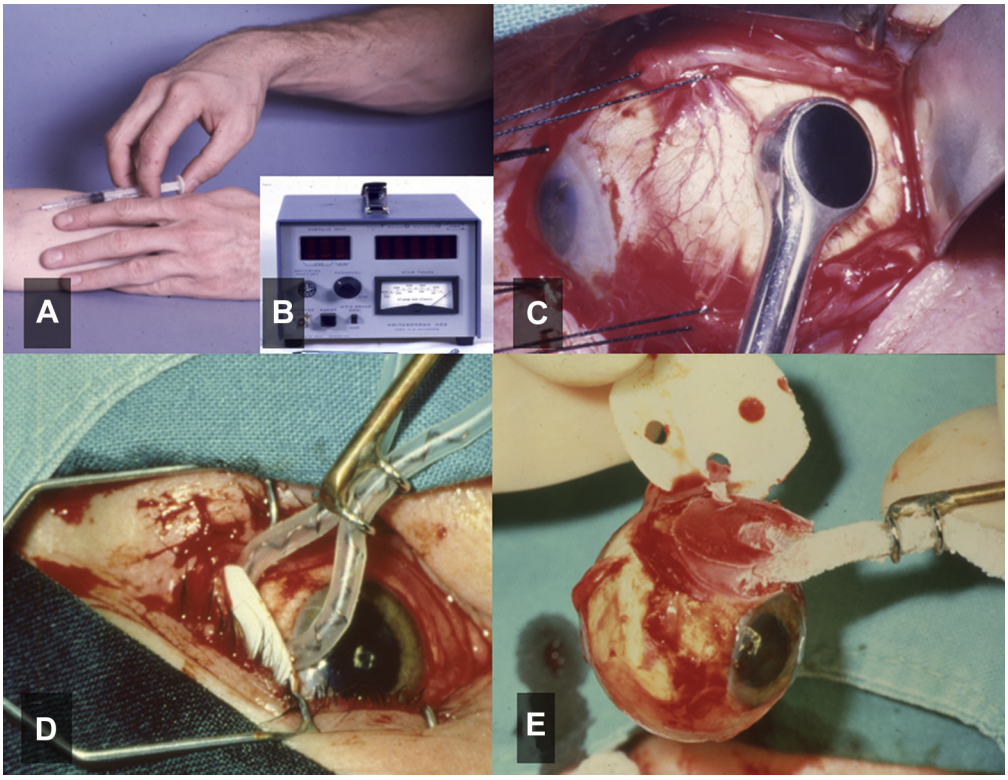


**Figure 1.** Past techniques of uveal melanoma management. The P32 diagnostic test allowed diagnosis of melanoma using **(A)** injection of radioisotope, **(B)** Geiger counter, and **(C)** radioactive sensor on the eye over the melanoma to detect the uptake of phosphorus. The "no touch" enucleation technique using the **(D)** coil placed on the eye over the melanoma and **(E)** frozen coil and eye removed to minimize tumor spread.