Uveal Melanoma

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Richard L. S. Jennelle, Jesse L. Berry, and Jonathan W. Kim

Learning Objectives

At the conclusion of this chapter, you should be able to:

- Discuss the different types of uveal melanoma identified by molecular profiling and the importance of each with regard to prognosis.
- Discuss the diagnostic criteria that establish the clinical diagnosis of uveal melanoma.
- Discuss the epidemiology and natural history of uveal melanoma.
- Discuss the various conservative surgical options for the treatment of uveal melanoma.
- Discuss the various types of radiotherapy that have been used to treat uveal melanoma and be able to compare and contrast the different techniques.
- Discuss the evidence that supports the eye-conserving treatment of uveal melanoma.
- Discuss the expected outcomes of conservative treatment for the different stages of uveal melanoma.
- Know the various isotopes used in brachytherapy for the treatment of uveal melanoma.
- Understand the late effects of radiotherapy used to treat uveal melanoma.
- Discuss the evolution of plaque brachytherapy with special attention to the impact of computerized treatment planning.

R. L. S. Jennelle (✉) · J. W. Kim
Children's Hospital Los Angeles, Keck School of Medicine, Los Angeles, CA, USA
e-mail: Jennelle@usc.edu

J. L. Berry
USC Roski Eye Institute, Keck School of Medicine of USC, Los Angeles, CA, USA

Children's Hospital Los Angeles, Keck School of Medicine, Los Angeles, CA, USA

Epidemiology

Primary uveal melanoma (UM) is a spectrum of disease, which encompasses intraocular tumors of the iris, ciliary body, and choroid. Uveal melanoma accounts for only 5% of melanomas in the United States [1], the remaining being predominantly skin in origin. However, mucous membranes and the conjunctiva can also harbor melanoma. It is, however, the second most common location for melanoma [2] and the most common primary intraocular malignancy in adults and the most common of all intraocular malignancies after metastatic lesions to the choroid [3]. The incidence of UM is approximately six cases per million people in the United States for an overall incidence of approximately 1500 cases per year [2]. Patients with uveal melanoma are generally 55–60 years of age, Caucasian, with light blue or green eyes and blonde or red hair [4]. Males and females are affected approximately equally [5]. Choroidal, cutaneous and iris nevi are all predisposing conditions for UM [6–8]. Ultraviolet light exposure (including via welding) [9–11] and family history [12–14] have also been correlated as risk factors. Other risk factors for the development of UM are predisposing medical conditions including dysplastic nevus syndrome [15, 16], neurofibromatosis type 1 [17–20], breast cancer-associated protein (BAP1) mutations [21, 22], and ocular melanocytosis [21–24] (GNAQ/11mutation) which significantly increases the risk of development of UM to 1/400 [25], and these individuals must be very closely monitored. Patients with choroidal nevi with known risk factors for malignant transformation must also be monitored very closely for evidence of growth, which suggests transformation. These risk factors include height >2 mm, presence of subretinal fluid, symptoms including decreased vision, flashes or floaters, presence of orange pigmentation, location adjacent the optic nerve or fovea, absence of a halo or drusen, and low internal reflectivity on B-scan ultrasonography [26–29].

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Diagnosis

Diagnosis of UM is made clinically with 99% accuracy [30]. It is based on indirect ophthalmoscopy and B-scan ultrasonography. Clinical exam generally shows an elevated, pigmented dome-shaped choroidal lesion with orange pigmentation on the surface and subretinal fluid at the base [28, 31]. There may sometimes be hemorrhage overlying the tumor; however generally there is not extensive subretinal or vitreous hemorrhage with uveal melanoma [32–34]. Amelanotic lesions are not rare but are definitely less common [35, 36]. Additionally, extensive subretinal fluid leading to a complete exudative retinal detachment can be present particularly with larger tumors [37–39].

B-scan ultrasonography classically demonstrates a choroidal tumor with dome (Fig. 17.1) or button-collar shape (Fig. 17.2) if the tumor has broken through Bruch's membrane [28, 40]. Generally B-scan is also used to measure these tumors [41]. While there are no strict measurements that determine whether or not a tumor is melanoma, in general, with the appropriate clinical features, pigmented lesions <5 mm at the base and <1 mm in height are considered choroidal nevi and lesions >10 mm at the base and >2.5 mm in height are concerning for choroidal melanoma [29]. Based on the collaborative ocular melanoma studies (COMS), small choroidal melanomas are >5 to <10 mm at the base and >1 to <2.5 mm in height and medium-sized choroidal melanomas are >10 to <15 mm at the base and >2.5 to <10 mm in height, with large-sized melanomas measuring greater than these dimensions in either the base of the height [42]. There is an indeterminate area between a choroidal nevus and a small choroidal melanoma wherein a lesion, often aptly termed an indeterminate choroidal lesion, may be a choroidal nevus with high-risk features or a small uveal melanoma. In these cases, clinical features and particularly presence or absence of growth over a short interval of monitoring are critical in the ultimate diagnosis [27]. It is also helpful to obtain a diagnostic A-scan evaluation, which for uveal melanoma classically shows a low to medium internal reflectivity lesion with descending reflectivity posteriorly after an initial high spike termed a positive angle kappa [40].

In our case presentation, the patient's tumor would be classified as a medium-sized choroidal melanoma in the COMS study based upon a tumor height measurement of 3.1 mm; however he would not have been offered brachytherapy based upon proximity to the optic disc. By AJCC criteria, the tumor would be a size category 1 (Fig. 17.3), stage T1a tumor. Table 17.1 summarizes the staging criteria for choroidal melanomas (the staging of iris melanomas differs) according to the AJCC cancer staging manual eighth edition [43]. There was no evidence of nodal or distant metastasis by imaging so the stage is T1a N0 M0 Stage IA (Table 17.1) choroidal melanoma of the right eye [43]. A biopsy is not required for diagnosis but is sometimes performed [44]. The approach to biopsy depends on the location of the tumor in the eye: biopsy may be done by fine needle aspiration (FNAB) trans-vitreally for posterior tumors and trans-sclerally for anterior tumors [45]. While biopsy is not routinely done for diagnosis, it is frequently done for prognostication regarding the risk of development of metastatic disease, with which current treatment strategies portend an extremely poor prognosis [46–48].

The differential diagnosis for choroidal melanoma includes choroidal nevus, melanocytoma, combined hamartoma of the retina and retinal pigment epithelium (RPE), congenital hypertrophy of the RPE, choroidal osteoma, choroidal hemangioma, choroidal metastases, choroidal disciform lesion, and choroidal hemorrhage [49].

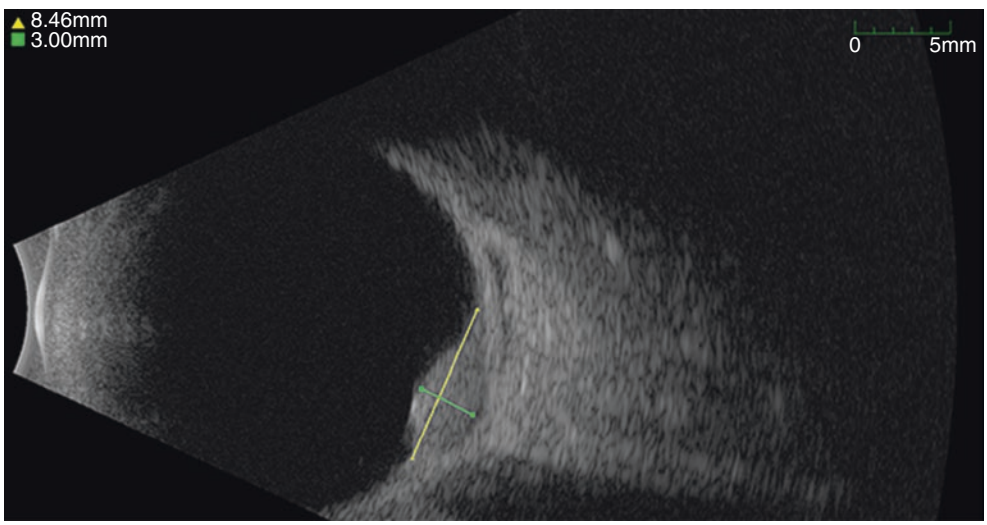

Fig. 17.1 Ultrasound appearance of classic dome-shaped tumor

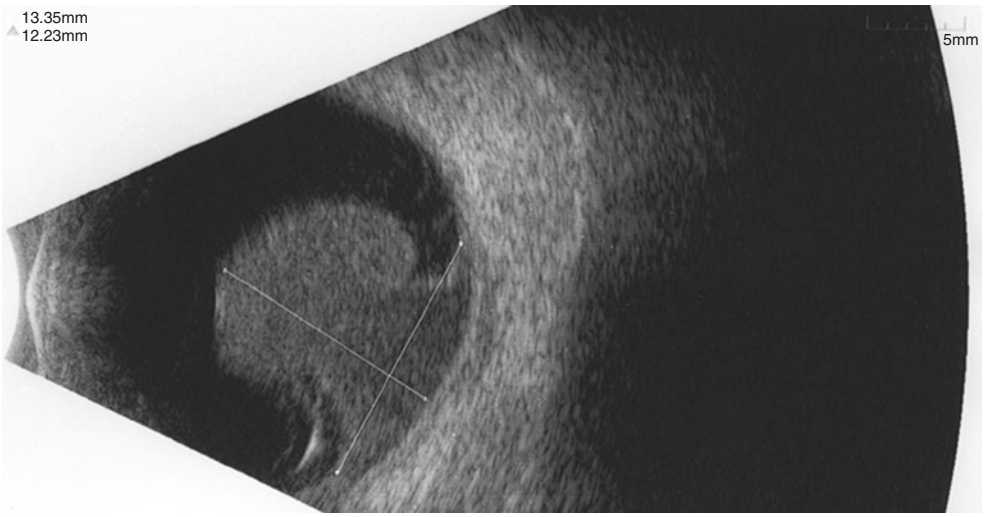

Fig. 17.2 Ultrasound appearance of "mushroom" or "collar button" choroidal melanoma

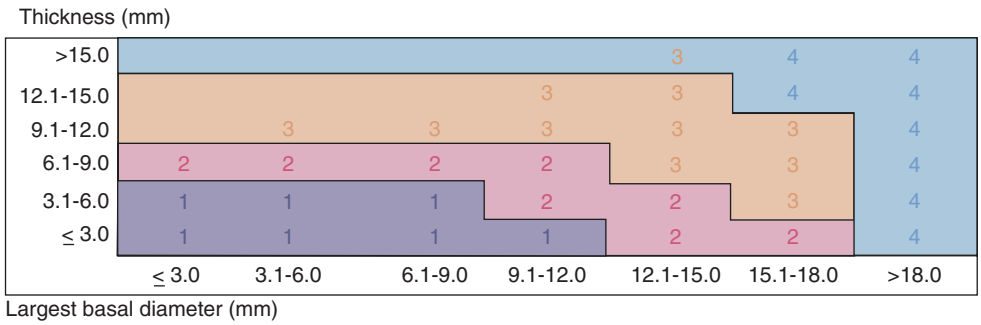

Fig. 17.3 AJCC eighth edition size classification table. [Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing]

Table 17.1 Summarized AJCC eighth edition staging system for uveal melanoma

T stage choroidal	T substage	N stage	M stage
T1 (size category 1)	a (no ciliary body involvement or extraocular extension)	N0 (no regional nodes or discrete tumor deposits in the orbit not contiguous with the eye)	M0 (no distant metastasis by clinical classification)
T2 (size category 2)	b (with ciliary body involvement)	N1a (regional nodal involvement)	M1a (largest diameter of largest metastasis ≤3 cm)
T3 (size category 3)	c (with extraocular extension ≤5 mm)	N1b (discrete tumor deposits in the orbit not contiguous with the eye)	M1b (largest diameter of largest metastasis 3.1–8 cm)
T4 (size category 4)	d (with both ciliary body involvement and extraocular extension ≤5 mm)		M1c (largest diameter of largest metastasis ≥8.1 cm)
T4e	Any size tumor with extraocular extension >5 mm		
Overall stage	TNM		
I	T1aN0M0		
IIA	T1b-dN0M0 T2aN0M0		
IIB	T2bN0M0 T3aN0M0		
IIIA	T2c-dN0M0 T3b-cN0M0 T4aN0M0		
IIIB	T3dN0M0 T4b-cN0M0		
IIIC	T4d-eN0M0		
IV	Any T N1 and/or M1		

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Pathology

Histopathologic analysis of UM shows pigmented spindle or epithelioid-shaped melanocytes with high nuclear to cytoplasmic ratio and high mitotic and proliferation indices. Spindle cell melanomas have a better prognosis than epithelioid cell melanomas. Mixed cell type is also common and has an intermediate prognosis between the two [50, 51].

Prognosis

Prognosis for UM depends on the risk of developing metastatic disease, which most commonly manifests in the liver (93%), the lung (24%), or the bone (16%) [52]. The risk of metastatic disease can be prognosticated based on clinical parameters such as size of the tumor, involvement of the ciliary body, and age of the patient [53, 54]. Based on COMS, the 5-year risk of tumor-specific mortality is <1% for small tumors, 10% for medium-sized tumors, and 35% for large tumors [52, 55–57]. Currently, gene expression profiling guides prognosis for metastatic disease development but does not impact choice of therapy.

Many centers now offer FNAB biopsy with various clinically available tests to evaluate cytogenetic abnormalities in chromosome 1, 3, 6, and 8 (loss of 1p, 3, and 6q and gain of 6p and 8q or 8) or gene expression profiles [58–64]. Frequent mutations have been described in the following five genes GNA11, GNAQ, BAP1, EIF1AX, and SF3B1 which are thought to be driver mutations for the development of UM [22, 65].

Gene expression profiling classifies the risk at Class 1A, 1B, and 2 with a 5-year risk of development of metastatic disease as 2%, 21%, and 72% [66]. It has never been shown that treatment modality modifies the risk of development of metastatic disease; however intraocular recurrences after treatment do occur [67, 68] and may increase this risk [69]. Our patient did not elect to have a biopsy performed, but his overall prognosis is good with an expected overall survival rate of 85% at 15 years (Fig. 17.4) [43].

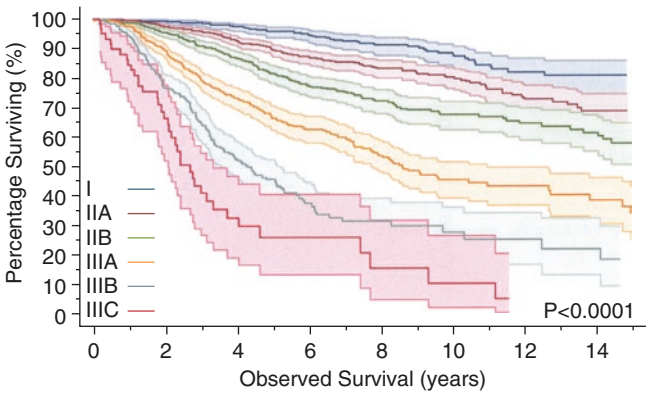

Fig. 17.4 Survival according to AJCC eighth edition by overall stage. [Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing]

Treatment Paradigms

In this section, we will discuss treatment paradigms for uveal melanoma including trans-scleral local resection, transpupillary thermotherapy, and brachytherapy.

Trans-Scleral Local Resection

Local trans-scleral resection of uveal melanoma is not commonly practiced in the United States and was pioneered in England for management of large tumors not amenable to brachytherapy with ruthenium plaques [70]. The rates of local recurrence, systemic metastasis, and ocular complications are all higher after local resection compared to brachytherapy, but this disparity is likely associated with the larger tumors being treated with the former technique. Following local resection for large uveal melanomas, 40% of eyes were noted to have residual or recurrent tumor, with 53% of these eyes undergoing enucleation [71, 72]. The technique involves the creation of a lamellar scleral flap, which provides exposure to remove the choroidal tumor with a thin layer of attached sclera while leaving the retina undisturbed. Partial ocular decompression from a limited pars plana vitrectomy is thought to facilitate local excision by reducing retinal prolapse during the procedure and improving access to the posterior uvea. Anterior tumors are more amenable for local resection as are those tumors with overlying subretinal fluid and the absence of retinal invasion. A portion of the ciliary body can also be resected along with the choroidal component although removing more than 3 clock hours of the pars plicata can cause hypotony. Patients with large areas of extraocular extension, diffuse uveal melanomas, or optic disc involvement are poor candidates for local resection. There is no absolute size limit for local resection, but a higher rate of tumor recurrence rate has been noted with tumors greater than 15 mm in diameter [71]. For patients with uveal melanomas deemed to be too large for ruthenium plaques, local resection may be a viable alternative to enucleation for appropriate candidates.

One source of concern with surgical resection is that the majority of uveal melanomas demonstrate local invasion of the sclera, as well as the retina, which may not be completely removed with local resection. In addition, hypotensive anesthesia was thought to be necessary to decrease the chances for bleeding during the procedure and subsequent seeding of

the orbit with tumor cells. The first concern has been alleviated with the common practice of using brachytherapy following local resection, treating to a tumor height of 3–5 mm post resection for any residual cells in the sclera or retina [71, 73]. The need for hypotensive anesthesia remains somewhat controversial, but it is recommended that bleeding from the procedure be carefully controlled to avoid orbital seeding. Patients should be counseled regarding the significant risk of intraocular complications such as retinal detachment, vitreous hemorrhage, and local tumor recurrence following local resection.

As mentioned, profound hypotensive anesthesia with systolic blood pressure being reduced as low as 50 mm Hg can greatly reduce the risk of intraoperative hemorrhage. The hypotensive anesthesia is typically initiated from the time the deep scleral incision is started to the moment when the scleral flap has been closed, lasting approximately 1 h. Cerebral functioning is monitored with an electroencephalogram (EEG), and an arterial line closely tracks the blood pressure. After marking the margins of the tumor, a rectangular, lamellar scleral flap is outlined 3–5 mm from the tumor borders, hinged posteriorly beyond the posterior margin of the tumor. The depth of the lamellar scleral flap is typically about 2/3 of the thickness of the sclera. Partial ocular decompression via a limited pars plana vitrectomy facilitates the rest of the procedure as it keeps the retina away from the tumor and surgical field. The deep scleral incision is made just inside the margins of the previously created scleral flap. The deep scleral incision is then extended around the tumor using corneoscleral scissors, separating the thin sclera over the base of the tumor from the surrounding sclera. The choroidal layer is then incised, and the subretinal space is entered, typically starting anteriorly and proceeding laterally and then posteriorly. Once the choroidal layer has been completely incised, the thin layer of sclera over the base of the tumor can then be used to remove the entire tumor from the eye. The retina typically peels away from the choroid, but gentle blunt dissection may be required. Once the tumor has been removed, new instruments are then used for the closure. The intraocular pressure is elevated using either a gas bubble or an intravitreal saline injection to prevent subretinal hematoma formation. The scleral flap is then closed with interrupted 8-0 nylon sutures, closing the corners first followed by the rest of the flap. Intravitreal fluid is then injected to elevate the intraocular pressure into a normal range. At this point in the procedure with the scleral flap closed and the intraocular pressure normalized, brachytherapy can be performed to prevent tumor recurrence in the retina and scleral flap. A more detailed description of the local resection procedure is beyond the scope of this chapter, but several excellent references are available in the literature [71, 73].

Transpupillary Thermotherapy (TTT)

Using a diode laser to heat a tumor and produce cell necrosis through a transpupillary technique has been termed TTT (transpupillary thermotherapy) [74]. To perform TTT for a choroidal melanoma, an 810 nm diode laser is used either through a slit-lamp attachment or through an indirect delivery system. The technique involves treating the tumor with the diode laser at a power level which causes a visible color change (i.e., whitening) within the 45–60 s duration, which has been correlated to produce a temperature within the tumor between 45 and 60 °C. A choroidal melanoma treated with TTT has demonstrated tumor necrosis on histopathology up to a depth of 3.9 mm [75, 76].

Initial clinical series demonstrated a high rate of success in causing tumor regression for tumors less than 4 mm in thickness, and TTT was touted to be an effective primary modality for treating small posterior uveal melanomas [77, 78]. Vascular obstruction and retinal traction were observed complications [79], although overall visual results were much better than with brachytherapy [78, 80]. The margins of treatment for TTT are sharper than for brachytherapy or proton beam radiotherapy, and this factor likely explains the visual advantage for TTT. However, with longer follow-up, tumor recurrences were noted, and subsequent studies showed a 76–78% rate of long-term success for tumor control [81, 82]. Some tumor recurrences were massive and led to loss of the globe, and late recurrences many years after TTT were also noted [82]. The tumors after TTT typically demonstrate almost complete atrophy of the retina and choroid, with sharply circumscribed scars showing bare sclera. However, viable melanoma cells have been shown to invade into the sclera and emissary canals as well as the surrounding retina, and these residual cells are likely responsible for these tumor recurrences. Therefore, TTT is not thought to be curative as the sole modality for many choroidal melanomas even when treating small tumors.

Currently, TTT is utilized for choroidal melanomas in specific clinical situations. For example, TTT is an option for controlling the growth of small suspicious choroidal nevus, particularly in older patients who want to avoid brachytherapy in tumors near the optic disc. TTT is also used in combination with radiotherapy (called “sandwich” therapy), with TTT treating the apex of the tumor and brachytherapy being performed at the base [83–85]. TTT can also be used at the posterior margin of a macular tumor so that a smaller treatment zone can be used near the macula by brachytherapy to preserve vision. Finally, TTT has been used successfully to treat small edge tumor recurrences after brachytherapy [82]. Whenever TTT is used to treat a melanocytic tumor, patients require careful, long-term follow-up to monitor the patient for complications and possible local tumor recurrence.

Tumor recurrences after TTT can be treated with either brachytherapy or enucleation, depending on the level of visual acuity, size of recurrence, and metastatic status of the patient.

The technique of using TTT for melanocytic choroidal tumors has been described for both the slit-lamp application (3 mm spot size) and indirect delivery system (1.4 mm spot size). Since the spot size for the indirect system is smaller, power levels required to reach the desired temperature are also typically lower. In general, power levels should be adjusted until the desired color change (i.e., mild whitening) between 45–60 s is achieved; if the color change occurs before 45 s, then the power level is decreased. The entire surface of the tumor is treated with overlapping treatment burns, covering the margins of the tumor for 1.5 mm. Pigmented tumors are the best candidates for TTT, but even for the darkest tumors typically more than one session is required to achieve complete regression. It has been reported that the absorption of TTT may be enhanced by the intravenous infusion of ICG in amelanotic tumors [86], although we do not have experience with this technique. Treatment should be repeated for two to three sessions until the lesion has flattened significantly and very little viable tumor remains. It should be kept in mind that continued regression of the tumor can be observed for several months after the last laser session and often an atrophic scar will form at the treated site.

Brachytherapy

Historically, the standard of care in the treatment of uveal melanoma has been enucleation. However, beginning in the early part of the twentieth century, several institutions began to evaluate brachytherapy in the management of this disease [87]. The development of plaque brachytherapy required several key elements before the modality took on its current form. Among the first plaques manufactured were those based upon the use of ^{60}Co [87, 88]. This isotope, with a high specific activity, was naturally of interest. It could be made into an applicator that could easily be positioned in proximity to the tumor, but the highly energetic photons would require shielding that was prohibitively large when trying to spare orbital adnexal tissue. Many other isotopes were investigated as well, but it was ^{125}I that eventually became the favored isotope for the COMS study [89] and since then has been the most common isotope for treatment in the United States. It can be incorporated into seeds with sufficiently high activity to be useful, but the relatively low energy of the emitted photons makes shielding the orbital adnexa a much easier task. The inverse square law dominates at short distances and is the key characteristic that allows for the shaping of dose to the tumor and the sparing of other nearby critical structures in all forms of photon brachytherapy [89]. Over the years, many other isotopes with similar characteristics have been developed, but ^{125}I (which decays by electron capture and emits a gamma photon of 35.5 keV) remains the dominant isotope largely because of the impact of the COMS study. In a similar manner, some advocate for the use of ^{103}Pd which also decays by electron capture but with a softer gamma photon at 21 keV. The degree to which the softer gamma photon benefits the treatment or harms it is a topic of discussion within the ocular oncology community.

It is worth mentioning the use of isotopes, most commonly ruthenium, that are beta emitters. These isotopes have an even more rapid fall off of dose from the source related to the relatively short penetration range of beta particles and are typically employed for treatment of thinner tumors [90]. The main limitation of beta-emitting isotopes is excessive dose to the underlying sclera when prescribing to thicker tumors.

Although there was growing evidence, based upon multiple single institution reports, that brachytherapy could be a possible treatment for uveal melanoma, many ophthalmologists were reluctant to risk the possibility of metastatic disease in order to conserve the eye [91]. The COMS study for medium-sized melanomas was undertaken to analyze in a prospective and randomized fashion the effectiveness of plaque brachytherapy in the eye-conserving treatment of uveal melanoma. The COMS study demonstrated that, in medium-sized uveal melanomas, plaque brachytherapy could be used in place of enucleation without any impact on the rate of metastasis or overall survival [55]. A second component of the study, directed at large uveal melanomas, evaluated a short course of preoperative radiation prior to enucleation to see if this prevented metastasis from manipulation at the time of surgery. Short-course preoperative radiation did not impact the development of distant metastasis and so is no longer used [57].

Brachytherapy remains the most common eye-conserving treatment for uveal melanomas and can be used for both posterior and anterior tumors. With some adjustment in technique, brachytherapy can be used successfully for both posterior tumors near the optic nerve and anterior melanomas involving the iris and ciliary body [92–94]. The surgical technique is similar no matter which isotope is used for brachytherapy, including ^{125}I, ^{106}Ru, and ^{103}Pd. However, the specific method used to localize the tumor varies significantly at different centers. Success rates appear to be high with all of the techniques described in this section. Ocular brachytherapy can be performed either under general anesthesia or under a retrobulbar block with conscious sedation. The authors' preference is general anesthesia since the local block can increase swelling and decrease surgical exposure. In addition, any patient discomfort during the procedure may require additional anesthesia and/or compromise the surgical outcome.

Before starting surgery, the surgeon performs indirect ophthalmoscopy through a dilated pupil to confirm the position of the tumor as well as any intraocular findings such as hemorrhage or subretinal fluid. After sterile prepping and draping of the marked eye, a 180 degree conjunctival peritomy is performed at the limbal location which corresponds to the center of the tumor. The Tenon's layer (i.e., capsule) is then dissected off the sclera to ensure that the scleral surface over the tumor is completely exposed. One of the rectus muscles is commonly disinserted to ensure accurate plaque placement, although this may not be necessary if the tumor is small and located in one of the oblique quadrants. The rectus muscle is isolated and imbricated in standard fashion with a double-armed 5-0 Vicryl suture and disinserted, allowing it to reflect back with the attached sutures away from the sclera. A traction suture using a 5-0 Mersilene suture is passed at the muscle insertion site or at the limbus to allow for mobilization of the globe during the procedure. The oblique muscles are thinner and typically do not have to be disinserted. We also do not recommend disturbing the vortex veins in the oblique quadrants. A small malleable retractor is used to gently retract the rectus muscle and orbital fat to visualize the entire scleral surface to ensure that no soft tissues will interfere with the positioning of the plaque on the sclera. Exposing the scleral surface is a critical part of the procedure to ensure complete plaque coverage of the tumor but also to document any areas of scleral extension. Any extra-scleral nodule less than 2 mm in thickness can be covered with the plaque and treated without a significant alteration of the treatment plan or technique.

Once the scleral surface has been exposed, attention is turned to localizing the tumor margins. At our center, three-dimensional tumor modeling is utilized to determine the plaque coordinates preoperatively (Plaque Simulator, Eye Physics LLC). The meridian and distance from the limbus are marked using a toric marker and caliper, respectively. Alternatively, the tumor margins can be determined intraoperatively using either transillumination or indirect ophthalmoscopy or a combination of the two techniques. Transillumination is most useful for pigmented, anterior tumors, and indirect ophthalmoscopy is invaluable for posterior tumors. For tumors located in the macula or near the optic nerve, it can be difficult to visualize the posterior margin, and in these cases, it may need to be estimated from the preoperative ultrasound. Transillumination is performed with a rubber adapter on a light source, with the light being directed through the pupil and the shadow of the tumor being outlined on the sclera. It should be kept in mind that highly elevated tumors can create variable shadows on the sclera depending on the angle of illumination, and amelanotic tumors may be difficult to visualize with this technique. Indirect ophthalmoscopy can be performed with scleral depression and a marking pen, or a diathermy tip. One of the most effective devices for this technique is the diathermy-transillumination unit (MIRA 1 electrode handle) with a scleral transilluminator electrode. With the fiber-optic light marking the perimeter of the tumor (viewed with indirect ophthalmoscopy), a low intensity diathermy mark can be made on the sclera at the anterior, medial, lateral, and posterior margins. Once the surgeon has confirmed the scleral markings of the tumor margins, the dummy plaque is placed.

The dummy plaque is positioned on the sclera and partial thickness scleral passes made with two 5-0 Mersilene sutures at the position of the two eyelets. It is critical to first complete the partial thickness passes through the sclera, before passing the needle through the eyelet of the plaque. Engaging the needle through the eyelet and then sclera will lead to scleral perforation due to the angle of the needle with this technique. The passed scleral sutures are then secured to the eyelets of the dummy plaque with a temporary loop knot. The indirect ophthalmoscope is then placed on the surgeon by an assistant (maintaining sterility), and the margins of the plaque are depressed to ensure that there is complete coverage of the tumor. The depression is usually performed with a metal scleral depressor, with the assistant moving the globe with the traction suture to allow the depressor to follow the outlines of the dummy plaque. The fiber-optic light source on the MIRA unit can also be used for this indication. Ultrasound confirmation of the plaque position is becoming popular to ensure complete coverage of the tumor margins and appears to increase the accuracy of brachytherapy [95–98]. Visualizing the relationship of the plaque and scleral surface on the B-scan can also be used to assess whether posterior tilting of the plaque is occurring. However, any thin areas of tumor extension should be noted on fundoscopy and taken into account when using ultrasound confirmation. In addition, the probe of the ultrasound tip must be covered during its intraoperative use to maintain sterility.

Once its proper positioning has been confirmed, the dummy plaque is removed, and the active plaque is placed in its position; the two Mersilene sutures are tied again but this time using permanent knots. The rectus muscle is then reattached to its insertion site; the suture can be tied with a loop knot with long ends or tied with a permanent suture. The advantage of a loop, adjustable suture is that the rectus muscle does not need to be re-sutured at the time of plaque removal. However, the longer ends of the adjustable suture can cause ocular irritation if not properly tucked under the conjunctiva. If the anterior portion of the plaque covers the rectus insertion site, then the sutures are passed through the superficial sclera near the limbus; it can be properly re-sutured to the insertion site after the completion of brachytherapy. Finally, the conjunctiva is closed over the plaque using an absorbable suture.

After completion of treatment, a second operation is performed to remove the plaque (3–7 days later). The con-

junctiva is gently reopened to allow for exposure of the anterior position of the plaque including the eyelets. The two Mersilene sutures are carefully lysed with Westcott scissors, being careful not to cause any traction or injury to the underlying sclera. Once the plaque is freely mobile, it is carefully removed from the scleral surface and given to the Rad Onc representative for inspection. The sclera should also be inspected for any unexpected findings such as a hematoma or dislodged seeds. The time of removal should be noted for the operative record. Again, it is critical to check the plaque for the correct number of seeds to ensure that none have become dislodged. A survey meter must also be passed over the eye and the patient to confirm complete removal of any radioactive seeds from the surgical site. If the rectus muscle had been disinserted, it is reattached to its insertion site. The conjunctiva is closed using absorbable sutures. Indirect ophthalmoscopy should also be performed at this point in the procedure to ensure that no unexpected events have occurred, such as inadvertent scleral perforation. Patients are typically seen in the first week after the removal of the plaque to ensure that healing is proceeding appropriately. The first post-brachytherapy ultrasound examination is performed at 3 months. Future follow-up exams are determined based on the clinical course.

Surgical Complications

Inadvertent perforation of the sclera may rarely occur, and as long as appropriate steps are taken, significant complications should not be observed. If the scleral perforation with the needle occurs outside the margins of the tumor, indirect ophthalmoscopy should be performed to determine if retinal perforation has occurred. If a retinal break is noted, then laser photocoagulation should be performed around the break in an attempt to seal it. If the scleral perforation has occurred within the margins of the tumor, then no other intervention is needed as long as the scleral defect is small and immediate brachytherapy will be performed over the site of perforation. If a small amount of subretinal fluid is present around the break, then cryotherapy is recommended to seal the retinal defect.

Brachytherapy Dose

The selection of dose is largely based upon empiric data. Based upon the pre-existing work, COMS chose a prescription dose of 100 Gy [99]. There have not been studies that systematically explore the optimal brachytherapy dose although some retrospective data supports the possibility of decreasing the dose [100]. Currently, a dose of 85 Gy is used; however this is not a decrease in prescribed dose but is related to a systematic error in the manner dose was calculated for ^{125}I before the mid-1990s [101]. For all intents and purposes, the 85 Gy that is currently prescribed is exactly the same as the 100 Gy used previously and should not be seen as a dose decrement.

Similarly, doses of charged particles and stereotactic radiation were chosen to mimic the dose of brachytherapy [102–104]. Accurate comparison of doses between different forms of radiation is a very difficult subject and far beyond the scope of this limited chapter. Unlike brachytherapy, studies examining dose de-escalation for proton therapy [105] and stereotactic therapy [106] are reported in the literature. These studies suggest that a substantial decrease in prescribed dose can result in similar rates of control for uveal melanoma and decreases the rate of complications.

Originally, brachytherapy use was confined to medium-sized uveal melanomas located posteriorly that spared the optic nerve. Entry in the COMS study required the tumor to be at least 2 mm from the optic nerve. This was required to ensure adequate dose to the tumor with margin. The COMS eye plaques did not have a notch or other adaptation to permit plaque placement close to the nerve. Some modern plaques have been designed with a notch so that this is no longer a restriction. Specialized brachytherapy applicators now allow for the treatment of challenging tumors with more precise techniques [107]. With experience and technical innovation, there are now few eyes that cannot be sparred by using radiation. Using these more advanced techniques, we were able to use a notched plaque in our patient to adequately cover the extent of tumor with only minimal impingement on the margin (Figs. 17.5 and 17.6). In fact, it is now acceptable to treat tumors up to T4e with brachytherapy as long as there is reason to believe that the treatment will result in successful salvage of the globe without unacceptable toxicity [108]. Enucleation is now mostly reserved for eyes that have little chance for salvage irrespective of the visual acuity that may result from treatment with radiation.

Treatment planning for brachytherapy is fundamentally based upon the findings at indirect ophthalmoscopy and ultrasound examination. Using these measurements, nearly any radiation oncology service can calculate and deliver the required treatment using the COMS technique. The prescription point is typically the dimensions of the tumor with an additional margin of approximately 2 mm. Typically, it is the height of the tumor that drives the prescription as base coverage can be addressed by altering the number of sources to ensure adequate coverage. It is important to be sure that the resultant isodose line covers the base of the tumor, again with an acceptable margin. Doses are typically between 70 and 100 Gy with a typical dose rate of approximately 0.6 Gy per hour. This results in typical implant

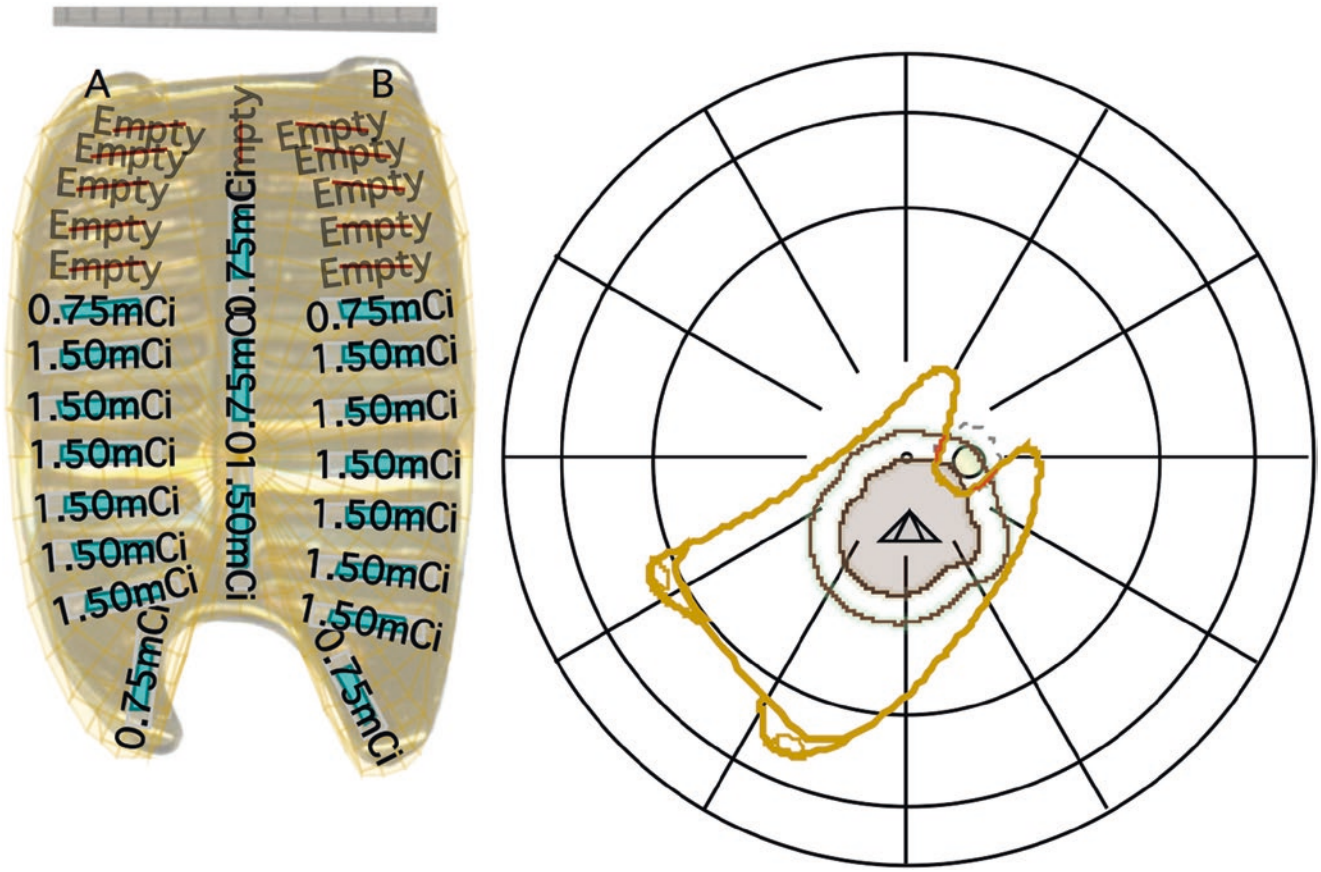

Fig. 17.5 Plaque model, loading, and placement for case study patient

Fig. 17.6 Eye Physics, LLC plaque for case patient placed on eye model. [Used with permission of Eye Physics, LLC]

duration of 5–7 days. Figure 17.7 shows the preplanning isodose lines superimposed on the fused imaging from our patient mentioned earlier. Figure 17.8 shows the dose area histogram of the tumor and various critical structures for our patient as well.

Treatments involving beta emitters can be a bit more variable. Since beta emitters (typically ^{106}Ru and ^{90}Sr) have a much longer half-life, these sources are typically reused over the course of several years. The length of time required to treat is then determined by the current activity of the source and the desired prescription. Treatment will be shorter for a new source and longer for an older one.

Since all forms of plaque brachytherapy are affixed to the globe, there is minimal difficulty ensuring adequate correction for motion. The plaque moves as a unit with the eye. However, there is great variability in the extent of treatment planning for plaque brachytherapy. Treatment planning can run from simple point source calculations on one of the standard COMS plaques to customized collimating plaques with highly accurate dose modeling supplemented by preoperative planning involving fusion of ultrasound, fundus photography, and fused CT/MRI images. The goal is to give

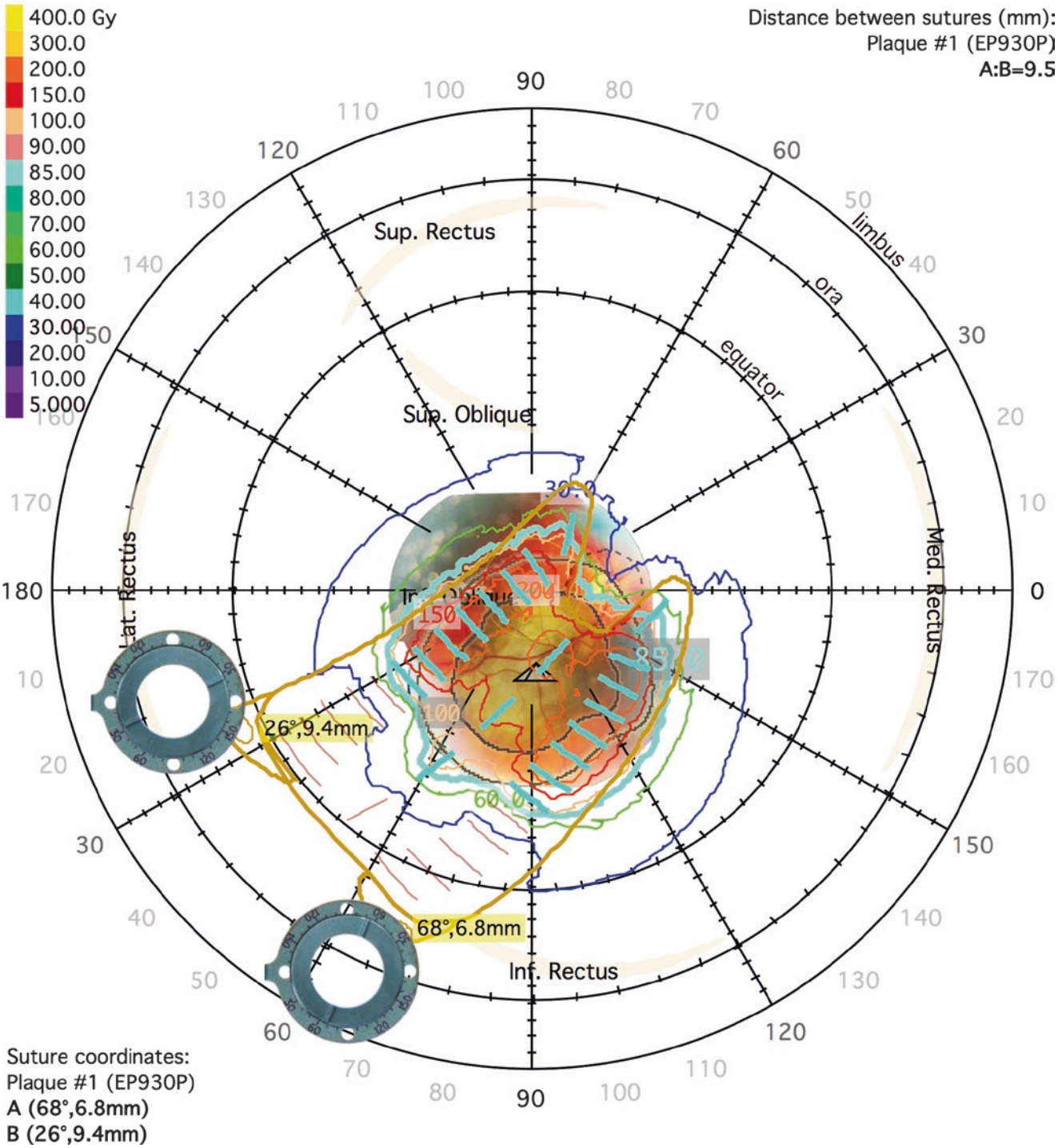

Fig. 17.7 Tumor and normal structure contours with isodose overlay for case study patient

adequate dose to control the tumor while minimizing the dose to adjacent critical structures. The more advanced planning and treatment delivery systems allow for significant dose reduction to normal structures (Fig. 17.9) and a more streamlined procedure in the operating room, but do not allow for modification of the device during the procedure [107]. The main advantage to the advanced plaque delivery systems over traditional COMS style plaques is the increased collimation obtained by the slotted metal plaque construction (Fig. 17.10). There are no randomized trials addressing the superiority of one technique over the other, but the American Brachytherapy Society assigns level 1 importance to attempts at reducing dose to normal structures and so would favor the more advanced plaque designs [108].

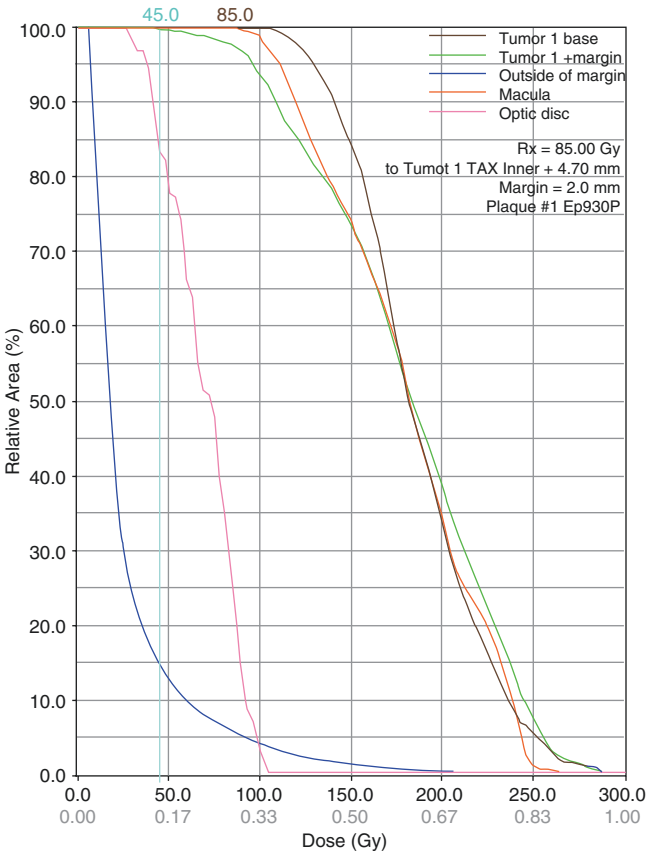

Fig. 17.8 Dose area histograms for case study patient

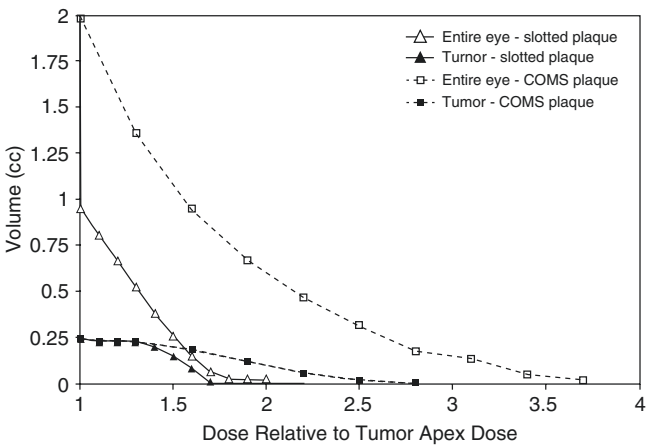

Fig. 17.9 Dose volume histograms for COMS plaque versus advanced collimated plaque treating identical tumors. [Reprinted from Astrahan MA, Luxton G, Pu Q, Petrovich Z. Conformal episcleral plaque therapy. International Journal of Radiation Oncology Biology Physics. 1997;39:505–19. With permission from Elsevier]

Charged Particle Radiation

At the same time that brachytherapy was beginning to be used, other institutions evaluated the use of charged particle

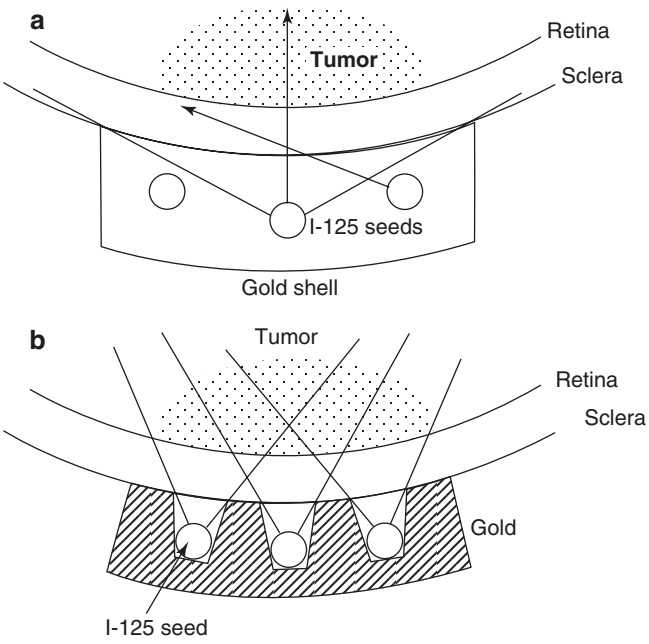

Fig. 17.10 Effect of slotted plaque construction on collimation (**b**) of photons when compared to traditional COMS style plaque (**a**). [Reprinted from Astrahan MA, Luxton G, Pu Q, Petrovich Z. Conformal episcleral plaque therapy. International Journal of Radiation Oncology Biology Physics. 1997;39:505–19. With permission from Elsevier]

external beam irradiation in the management of uveal melanoma. Most often, this was done with proton beam radiation although helium ions have been evaluated as well [102, 109]. Charged particle radiation uses the Bragg peak to help confine the radiation to the targeted area. In short, the Bragg peak limits the effective range of the beam so that there is essentially no exit beam at any point past the physical location of the peak. The only prospective randomized trial, conducted by UCSF, compared brachytherapy with charged particle therapy in the form of helium ions. This study favored charged particle therapy for control [110]; however complication rates were significantly higher with charged particle treatment [111] especially in the anterior segment of the eye. Modern series with more advanced plaque techniques report control rates superior to COMS or the UCSF study reported above [112]. Proton beam radiation, although not supported by a study similar to COMS, nonetheless benefits from the COMS study based upon the assumption that similar rates of local control will, likewise, achieve similar rates of overall survival and distant metastasis.

Stereotactic External Radiation

There is also a third technique, namely, stereotactic radiation. This is an outgrowth of similar work on other central nervous system tumors. In short, multiple beams can deliver conven-

tional photon irradiation so that the dose is accurately placed at the target and demonstrates very rapid fall off in all other directions. Most forms of stereotactic radiation rigidly affix a treatment apparatus to the target and use this apparatus to guide the series of beams in a very tightly conformal manner that is highly accurate. Stereotactic radiation uses multiple beams to emulate what the Bragg peak does for charged particle therapy or what the inverse square law does for brachytherapy.

Treatment planning and prescription for external beam treatments employing charged particles or stereotactic techniques will necessarily involve the planning system for the device chosen. With charged particles, fiducial markers are typically placed to help with treatment alignment. With stereotactic techniques, some form of motion management is required. Motion management can vary from rigid fixation using various surgical apparatus to motion detection using various systems to follow visual fixation on a target [113–116]. For protons, typical doses have been in the range of 50–70 CGE (cobalt gray equivalent) usually delivered over five fractions [105]. For single faction stereotactic treatment, the range of doses is 25–50 Gy to the tumor margin [106]. As would be expected, treatment with lower doses is associated with lower rates of complication.

Radiation Complications

Many critical structures lie close to one another within the eye, and, as a consequence, the complications experienced are not only related to dose but also related to anatomic position of the tumor with regard to these critical structures. Endpoints such as visual acuity are multifactorial in determination and can be related to damage to the nerve, macula, lens, or retina. Typical classes of complications are radiation retinopathy, glaucoma (including neovascular glaucoma), optic neuritis, keratitis, and iris neovascularization. As expected, there are wide ranges seen in reported complications both from brachytherapy and charged particle treatment [102, 117]. Table 17.2 summarizes the reported complication rates throughout the literature. Tumors that are in the anterior segment or adjacent to it also carry an increased risk of complications [118]. Depending upon beam placement, charged particle therapy may carry an increased risk of anterior chamber complications even when treating a posteriorly located tumor [111].

Table 17.2 Summarized radiotherapy complication rates by technique

Complication	Charged particle [109]	Brachytherapy [117]
Glaucoma (unspecified)	17–29%	6–11%
Rubeosis	13%	4–23%
Neovascular glaucoma	12%	2–45%
Maculopathy	67%	13–52%
Cataract	32–68%	8–83%
Keratitis	12%	4%
Retinopathy	28%	10–63%
Optic neuropathy	8%	0–46%

Case Presentation

A 27-year-old white male was diagnosed with a retinal detachment, possibly secondary to a mass, 4 days prior and referred in for evaluation. He has no significant past medical history and no significant family history.

Physical examination reveals vision to be finger counting only in his right eye and normal visual acuity in his left. Intraocular pressures were normal bilaterally. Indirect ophthalmoscopy revealed a pigmented lesion in the right eye involving the macula and adjacent to the optic disc. The lesion was located inferotemporally extending from approximately 6 o'clock to approximately 9 o'clock (Fig. 17.11). The lesion was associated with orange pigment and subretinal fluid. B-mode ultrasound measured the lesion to be 8.4 mm by 8.5 mm with a height of 3.1 mm. He subsequently underwent thin-section computed tomography of the orbits as well as computed tomography of the chest, abdomen, and pelvis. All studies were negative for metastatic disease. He was referred for treatment with episcleral plaque

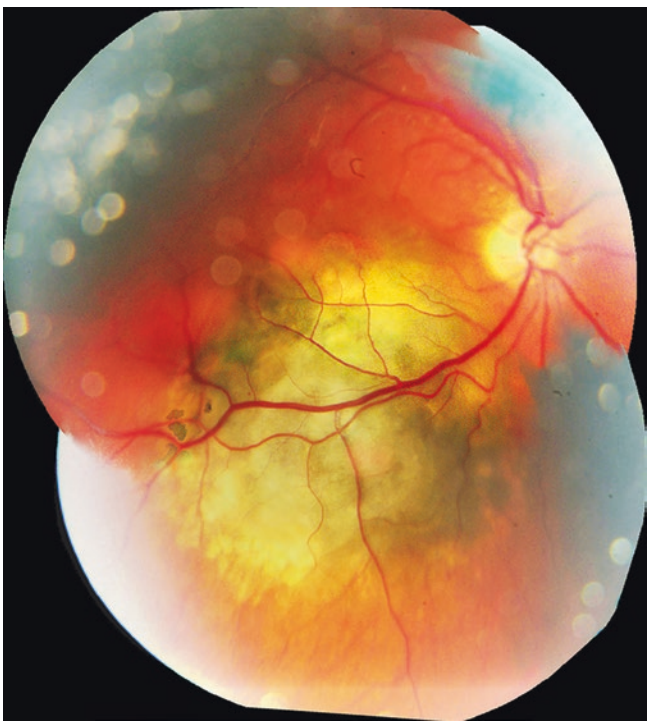

Fig. 17.11 Fundus photo of case study patient

brachytherapy with a clinical diagnosis of choroidal melanoma of the right eye.

Summary

UM is an uncommon disease whose management has been significantly impacted by the well-conducted COMS prospective trial. Treatment has progressed to such an extent that salvage of the eye is now a realistic possibility in all but the most advanced cases. Advances in molecular genetics have identified several subtypes of tumor with markedly different prognostic expectations but has yet to impact decisions on disease management. There are many surgical and radiotherapeutic options in the management of this disease, but episcleral plaque brachytherapy remains the mainstay of treatment at this time.

Self-Assessment Questions

1. Which of the following is not a commonly used criterion to diagnose uveal melanoma?
   A. Appearance on indirect ophthalmoscopy
   B. Findings on B-mode ultrasound
   C. Biopsy
   D. Growth rate on serial observation

2. In the COMS study of medium-sized choroidal melanomas, patients were excluded for entry if their tumor was within 2 mm of the optic disc. Why was this an exclusion criterion?
   A. It was not possible to adequately cover the tumor volume with a COMS style plaque due to obstruction from the optic nerve.
   B. There would be unacceptable morbidity from damage to the optic nerve.
   C. There would be unacceptable toxicity from damage to the macula.
   D. Tumors in close approximation to the optic nerve are not surgically accessible.

3. All of the following radiotherapy techniques have been used to manage uveal melanoma except one. Which has not been successfully employed to manage uveal melanoma?
   A. Episcleral plaque brachytherapy
   B. IMRT
   C. Stereotactic radiotherapy
   D. Charged particle treatment

4. What is the approximate expected overall survival at 10 years for a melanoma measuring 12 × 8 mm with a height of 9 mm which does not involve the ciliary body or manifest extra-scleral extension?
   A. 95%
   B. 85%
   C. 75%
   D. 50%

5. All of the following isotopes used in the management of uveal melanoma by episcleral plaque brachytherapy are commonly used except one. Which isotope is no longer commonly used to treat uveal melanoma?
   A. ^{125}I
   B. ^{106}Ru
   C. ^{90}Sr
   D. ^{60}Co

Answers

1. Answer: C. Biopsy is not a commonly used criterion although it can be used to help with prognostication. Both indirect ophthalmoscopy and findings on B-mode ultrasound are commonly used to diagnose uveal melanomas. Small lesions of indeterminate nature can be followed for growth on serial observation.
2. A. Tumors within 2 mm of the optic disc could not be properly covered by a COMS style plaque because of interference from the optic nerve. There were no constraints upon visual acuity toxicity in the COMS trial. There is no difficulty with surgically accessing the posterior globe.
3. B. Plaque brachytherapy, stereotactic radiation, and charged particle treatment have all been proven effective in the management of this disease. IMRT without the special immobilization and rapid fall off of the other techniques lacks the precision to treat this disease.
4. B. This tumor would stage as a T2a N0 M0 Stage IIA choroidal melanoma. The correct overall survival would be 85% at 10 years according to the AJCC staging system.
5. D. All listed isotopes have been used to treat uveal melanoma. The soft photon emitter iodine remains the most common isotope in the United States, while Europe still frequently employs ruthenium or strontium beta emitters. Although cobalt was classically used, the high energy photons proved problematic when attempting to shield the orbital adnexa, and so it is no longer used.

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