Chapter 15
Management of Uveal Melanoma

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Abstract About 3% of all melanomas are of ocular origin; of these, 85% are uveal. Uveal melanomas are rare, with standardized incidence rates ranging from approximately 2 to 8 cases per 1 million people in the United States and Europe. The typical presentation of uveal melanoma depends on the site of origin: choroid, iris, or ciliary body. About 80–90% of all uveal melanomas develop in the posterior choroid. Uveal melanoma is typically a clinical rather than a pathologic diagnosis. Currently, several options are available for the management of uveal melanoma, including observation, transpupillary thermotherapy, brachytherapy, stereotactic radiotherapy, proton radiotherapy, and tumor resection.

15.1 Epidemiology

About 3% of all melanomas are of ocular origin; of these, 85% are uveal, and the majority are choroidal. Uveal melanomas are rare, with standardized incidence rates ranging from approximately 2 to 8 cases per 1 million people in the United States and Europe. Mean age at diagnosis is approximately 60 years, with the incidence rate increasing to age 70. Risk factors for development of uveal melanoma include history of choroidal nevi, ipsilateral nevus of Ota, and atypical mole syndrome. Weak correlations have suggested sunlight exposure as a possible causative agent. Welders and metal workers have also been reported as having a slightly higher incidence of uveal melanoma, possibly due to ultraviolet light exposure [1].

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15.2 Clinical Features

The typical presentation of uveal melanoma depends on the site of origin: choroid, iris, or ciliary body. About 80–90% of all uveal melanomas develop in the posterior choroid. Patients with these tumors generally present with complaints of blurred vision or floaters. Occasionally, pain, inflammation, or double vision is noted. Metamorphopsia (distortion of vision) and photopsias (flashing lights) are not uncommon symptoms and may be associated with an exudative retinal detachment [2, 3].

Iris melanomas are generally smaller at diagnosis than those of the choroid. Iris melanomas can grow in a circumscribed or diffuse pattern. The circumscribed type can vary in color and invade the anterior chamber, ciliary body, or posterior chamber. Diffuse iris melanomas can infiltrate the iris stroma, causing pupillary distortion.

Ciliary body melanoma can develop as a circumscribed or annular type. The circumscribed type is often brown and can invade the anterior chamber, causing elevated intraocular pressure. In contrast, the annular type grows around the ciliary body in a ring-type fashion. Ciliary body melanoma may be initially misdiagnosed as open-angle glaucoma because of the difficulty in visualizing a distinct mass [3, 4].

As the uvea has no intrinsic lymphatic drainage, metastasis occurs by hematogenous dissemination. Ciliary body melanomas can invade anteriorly toward the sclerocorneal limbus. Posteriorly located tumors can spread via the vortex veins or ciliary arteries, or they can have frank invasion past the sclera. Large peripapillary tumors can invade the optic nerve and adjacent meninges. The liver is the primary site of distant metastasis, followed by the skin and lung; brain metastasis rarely occurs [3].

15.3 Diagnosis

Uveal melanoma is typically a clinical rather than a pathologic diagnosis. A 20–40% misdiagnosis rate has been reported in historical series following enucleation. Yet with recent advances, this has been reduced to less than 1%. As is the case with any malignancy, a thorough systematic history should be obtained.

An external ocular examination should be performed to evaluate for dilated episcleral vessels or pigmented nodules suggestive of extraocular extension. Slit-lamp evaluation can reveal bulging of the iris, a distinct iris or ciliary body mass, cataract, or subluxation of lens. Indirect ophthalmoscopy can demonstrate details regarding tumor color, size, and configuration. Features such as drusen, subretinal fluid, retinal pigment epithelial changes, and orange pigment are important prognostic indicators that should be documented [5].

Gonioscopy should be performed for all tumors in the anterior segment. Fluorescein angiography can demonstrate pinpoint hyperfluorescence or a distinct

"second" choroidal vasculature [6]. Echography should be performed in all cases and is the single most important noninvasive test. Typical ultrasonographic features of choroidal melanomas on B-scan echography include an internal acoustic quiet zone, choroidal excavation, and orbital shadowing (Fig. 15.1a). A-scan echography demonstrates low internal reflectivity with an angle kappa (Fig. 15.1b) [7, 8]. In rare cases in which these noninvasive techniques do not establish the diagnosis, tissue biopsy can be performed via an ab externo or ab interno approach.

Baseline testing should include liver function tests and chest and liver imaging (generally a computed tomography of the chest and abdomen with contrast) to rule out distant metastasis. Magnetic resonance imaging of the brain and orbit can be helpful in identifying intraocular features consistent with melanoma (Fig. 15.2).
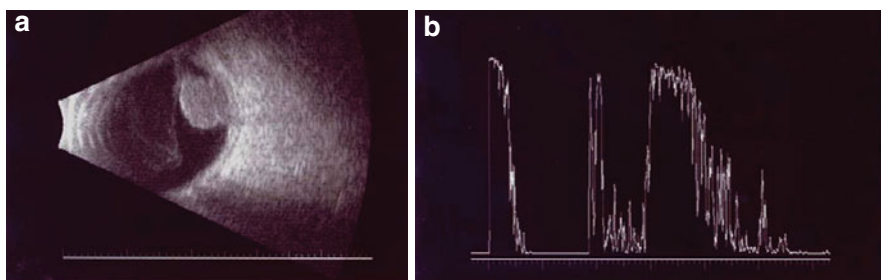
Fig. 15.1 Ultrasonography demonstrates the features of a mass consistent with left-sided cilio-choroidal melanoma. (**a**) The first scan is a B-scan sonogram with a collar-button appearance. (**b**) The second scan is an A-scan sonogram with low internal reflectivity
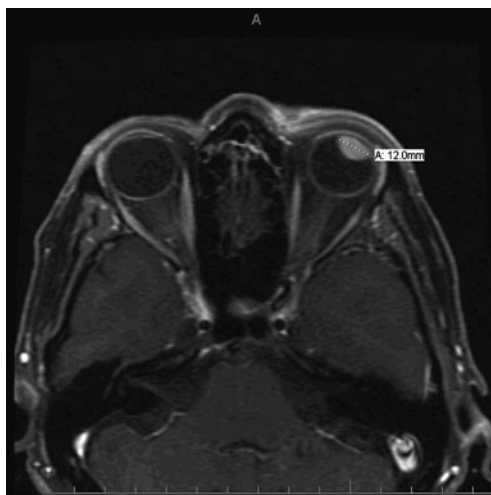
Fig. 15.2 Magnetic resonance imaging showing an intraocular melanoma, left eye

15.4 Staging and Prognostic Factors

Currently, the staging process is less than ideal for uveal melanoma. Accurate use of the American Joint Committee on Cancer TNM staging system requires pathologic diagnosis, which is often not obtained in uveal melanoma cases since most are treated with brachytherapy. No widely accepted staging system is used for most iris melanomas.

In patients with uveal melanoma, prognostic factors for patient survival differ from prognostic factors for eye and vision preservation. The most important feature predicting mortality in uveal melanoma is largest basal diameter. Other factors correlating with increased morbidity include extrascleral extension, diffuse presentation, older age, male gender, rapid growth, and recurrence after treatment. Pathologic features in enucleated specimens indicative of poor prognosis include a large number of mitotic figures per high-power field or high Ki-67; a high number of tumor-infiltrating lymphocytes; and periodic acid Schiff identification of vasculogenic mimicry patterns. Fine-needle biopsy for tissue prognostication is currently undergoing scientific testing in a number of centers. Fluorescence in situ hybridization studies have suggested molecular abnormalities associated with chromosomes 1, 3, 6, and 8. Monosomy 3 strongly correlates with metastatic disease. Gene expression profiling using microarray analysis suggests that uveal melanomas can be divided into two groups. "Class 1" tumors (low grade) are thought to have a much lower risk of distant metastasis than "class 2" tumors (high grade) [9–13].

15.5 Background Studies

Historically, enucleation was considered the only acceptable method of managing uveal melanomas. In the late 1970s, this practice was brought into question by suggestions that enucleation might expedite metastasis by promoting intraoperative seeding of tumor cells (Zimmerman's hypothesis) [14]. To evaluate this hypothesis, the Collaborative Ocular Melanoma Study (COMS) was organized in 1986. This was a multicenter effort with 43 participating centers in the United States and Canada. The COMS investigators conducted several studies, including two randomized trials and an observational study; in addition to reports on these studies, several technical papers have been published on the basis of the COMS results [15–17].

The observational study evaluated risk factors for growth of small melanomas (less than 3.0 mm in apical height) [18]. A total of 204 patients were enrolled and 188 were observed. On multivariate analysis, tumor characteristics associated with greater likelihood of growth included the presence of orange pigment, tumor thickness of at least 2 mm, and largest basal diameter of at least 12 mm [19].

One of the randomized clinical trials was conducted for medium-sized choroidal melanomas (2.5–10 mm in apical height and no more than 16 mm in largest basal

diameter); patients were randomized to receive either enucleation or iodine-125 plaque brachytherapy [20]. Patients with tumors touching the optic disc or primarily in the ciliary body were excluded. A total of 1317 patients were randomized, and 12-year follow-up data showed no difference in melanoma-related morbidity between the two treatment arms. Visual loss secondary to brachytherapy correlated with tumor thickness, tumor proximity to the foveal avascular zone, and a history of diabetes. Visual loss was significant, with 43% of patients progressing to an acuity of 20/200 (legal blindness) within 3 years. The contralateral eye, however, was not affected by treatment. Patients with recurrence after brachytherapy were treated with enucleation for salvage; about 10% of patients who underwent enucleation had recurrence at 5 years [21]. A quality-of-life study was performed on 209 of the 1317 patients and found that visual acuity in patients who received brachytherapy was greater than that in patients who underwent enucleation until about 3–5 years after treatment [22].

In the second randomized trial, a total of 1003 patients with large tumors (greater than 10 mm in apical height or 16 mm in largest basal diameter) were randomized to enucleation with or without presurgical radiotherapy consisting of 20 Gy in five fractions [23]. This study was designed to address concerns regarding the possibility of tumor seeding during enucleation and the potential benefit of pre-enucleation radiotherapy. On 10-year follow-up, no difference was noticed in melanoma-related mortality, and neither harm nor benefit was ascribed to pre-enucleation radiotherapy [23].

In both of the randomized COMS trials—for medium and large choroidal melanoma—annual screening after treatment included liver function tests and chest radiography. The use of liver function tests to identify distant metastasis had a sensitivity of 15% and specificity of 92%; thus, the COMS authors recommended annual liver imaging. Liver echography and computed tomography are the most common methods of liver imaging, but some centers advocate the use of routine positron emission tomography scans.

15.6 Overview of Management

Currently, several options for the management of uveal melanoma are available, including observation, transpupillary thermotherapy, brachytherapy, stereotactic radiotherapy, charged-particle radiotherapy, and tumor resection. A choice between these modalities depends on tumor size, location, and growth pattern and the condition of the patient. The goal of vision and organ preservation should be balanced with that of tumor control. Asymptomatic tumors that are less than 10 mm in basal diameter and less than 2.5 mm in thickness may be reasonable candidates for observation. Medium-sized uveal melanomas generally receive brachytherapy but may be amenable to charged-particle radiotherapy or resection. Larger tumors are often treated by enucleation [14, 19].

15.7 Brachytherapy

The concept of treating uveal melanoma with brachytherapy began in the 1930s when Sir Foster Moore inserted radon 222 seeds directly into a choroidal melanoma. This technique was later changed to use of episcleral cobalt 60 and then to ruthenium 106 and iodine 125 eye plaques. Iodine 125 was used in the COMS protocol and is a practical isotope because low-energy photon radiation allows for shielding with 1 mm of lead, reducing dose to hospital personnel. Iodine 125's half-life of 59 days allows for re-use of the seeds [24]. The plaque is shielded with gold, and the iodine 125 seeds are set in a template. These plaques can be customized to fit specific tumor locations, e.g., a notch can be placed to fit around the optic nerve. Plaques are available in various sizes ranging from 12 to 22 mm in diameter with multiple suture holes (Fig. 15.3) [24].

**Fig. 15.3** An 18-mm iodine 125 plaque with 21 seeds

Ruthenium 106 is used at some institutions in Europe and has been used at our institution, but it is no longer commercially available in the United States. It is a beta emitter with a steeper dose gradient than iodine 125, allowing for lower dose delivery to surrounding structures. The half-life of ruthenium 106 is about 1 year, allowing for re-use of the plaque. This source is generally used for tumors with apical height of less than 5 mm. These plaques are thinner than the COMS iodine 125 plaques, making surgical placement easier and more comfortable for the patient.

Treatment planning begins with indirect ophthalmoscopy and ocular ultrasonography to delineate the location and exact dimensions of the tumor. The plaque size is chosen to give a 2–3 mm margin around the tumor base. As per the COMS protocol, dosing is based on the apical height measured from the scleral surface. A total dose of 85 Gy is prescribed to the apex of the tumor if the tumor apical height is greater than 5 mm; a total dose of 85 mm is prescribed to 5-mm height if the apical height is 5 mm or less. Because of the sharp dose gradient of the brachytherapy system, the

apex is the prescription point and the area of minimum tumor dose. As such, much of the tumor actually receives more than the prescribed dose. Total dose rates should fall between 42.5 and 106 cGy/h. The use of a three-dimensional treatment planning system allows for decreased dose to be delivered to critical structures while ensuring dose delivery to the tumor by collimation of individual seeds [24].

Placement of the plaque is done in the operating room. The ophthalmologist transilluminates the globe and outlines the tumor shadow on the sclera. A dummy plaque is then placed over the marking, and loose sutures are placed in the suture holes. With the radiation oncologist present, the dummy plaque is removed, replaced by the radioactive plaque, and fastened in place with the sutures. A lead shield is placed over the affected eye as a safety precaution. The plaque is left in place for a number days, after which the patient is taken back to the operating room for removal of the plaque (Fig. 15.4).

This treatment is well tolerated in the short term. Late effects include dry eye, retinopathy, glaucoma, maculopathy, and scleral necrosis, depending on the proximity of the tumor and the radiation dose to adjacent structures. A significant percentage of patients develop radiation retinopathy. In a large review, poor long-term visual acuity was found to be associated with tumor location less than 5 mm from the fovea, age greater than 60 years, and use of cobalt 60 plaques [25].
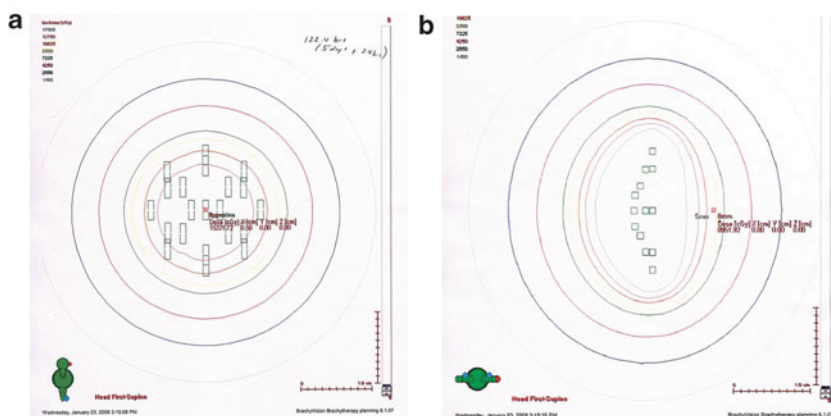
Fig. 15.4 Dose distribution of iodine 125; 85 Gy prescribed to apical height of 8.3 mm

15.8 Charged-Particle Radiotherapy

Proton radiotherapy offers the potential to deliver a homogenous and conformal dose to tumors, particularly those located close to critical structures such as the macula or optic disc. The physical properties of protons are such that stopping power is great, allowing for a high-dose deposition in the desired location with no exit dose. Restrictions related to tumor size or location are less than those

with brachytherapy. The use of charged particles in treatment of uveal melanoma began in 1975, and about 20 institutions around the world have employed this approach [24].

Treatment planning is similar to the typical evaluation for uveal melanoma, with the addition of surgical tumor localization. Patients undergo intraoperative transillumination, and the base of the tumor is marked by suturing radio-opaque tantalum rings to the sclera around the tumor. Tumor and eye dimensions are entered into the treatment planning computer, and an aperture is designed for the proton beam that approximates the shape of the tumor with a 3-mm lateral margin. Doses to critical structures are calculated in the treatment plan made by the computer but assessed by the MD. During treatment, patients are immobilized, and the eye is aligned on a flashing light; the eye is monitored for movement. Lid retraction is used to reduce treatment of the eyelid. The standard dose is 60–70 cobalt Gy equivalents in four to five fractions [24].

Several extensive series of uveal melanoma patients treated with proton radiotherapy have been published. Neovascular glaucoma was the most common cause of subsequent enucleation and was more prominent in patients with larger tumor volumes [25]. Other complications included radiation maculopathy and papillopathy, which was greater among patients with tumors close to the optic disc. Vision loss was associated with dose to the macula of greater than 35 cobalt Gy equivalents, larger apical height, and a history of diabetes. Local tumor control is excellent with protons. Comparison of complication and survival rates between proton and plaque treatment is difficult since many patients are referred to proton centers because of larger tumor size or tumor location close to the optic disc or macula [26–30].

15.9 Surgical Techniques

15.9.1 Uveal Resection

Depending on the size and location of the tumor, uveal resection can be a good treatment option for globe salvage. Small iris and ciliary body tumors (less than 4 clock hours) can be safely resected by iridectomy or iridocyclectomy techniques. Some surgeons advocate hypotensive anesthesia to reduce the risk of expulsive hemorrhage. The main complications are iris coloboma and lens instability from ciliary body excision. Visually, this can lead to photophobia and polyopia. Transscleral resection of choroidal tumors was popularized in the late 1970s and 1980s; however, given the high percentage of scleral invasion in many uveal melanomas, there is concern about inadequate resection with such procedures [31]. As a result, some centers routinely treat patients with adjuvant plaque brachytherapy at the time of resection [31, 32]. This approach (uveal resection) also exposes the patient to the possibility of expulsive hemorrhage and the risk of orbital tumor seeding.

15.9.2 Enucleation

Primary enucleation is typically used with large uveal melanomas that involve greater than one-half of the globe. Integrated implants, such as hydroxyapatite and Medpor, are generally implanted and provide excellent cosmesis with good ocular motility. When local extraocular extension is present, a modified enucleation can be performed with excision of the overlying tissue removed en bloc with the globe. Exenteration is rarely indicated but can provide good local control in cases of diffuse orbital involvement.

15.9.3 Transpupillary Thermotherapy

Transpupillary thermotherapy involves a low-energy diode laser that heats the tumor and surrounding choroid to 45–60°C. The laser is generally administered in multiple sessions. As a primary treatment modality, this technique is recognized as being associated with a risk of local recurrence, especially for thicker tumors and tumors that overhang the optic nerve. Transpupillary thermotherapy is increasingly used as an adjuvant modality following plaque brachytherapy (also referred to as "sandwich" therapy, which is brachytherapy followed by thermotherapy). Significant visual field loss can occur in the area treated; other complications include extrascleral extension, hemorrhage, and vascular occlusion [33].

15.9.4 Pathologic Assessment

An enucleation specimen is the most common tissue specimen obtained for pathologic evaluation. The intact globe is received fresh from the operating room when tissue is harvested for research purposes and/or tissue banking. Initial pathologic assessment of the specimen includes three-dimensional measurements of the globe and the length of the attached optic nerve. Also, the iris is examined for any deformity or gross involvement by the tumor. Each external component of the eye and anterior chamber is evaluated, and any abnormalities are documented. Samples of the vortex veins, located in the posterior portion of each quadrant, should be obtained for histologic examination. The entire extraocular portion of each vein is removed, and its location is noted (Fig. 15.5). A compound microscope may be used for gross assessment of ocular specimens, as needed.

Transillumination is used to locate the intraocular mass. When a light is held directly proximal to the pupil or sclera, light is transmitted into the vitreous, which glows through the sclera when the normal ocular structures are in place. A shadow, when noted, is marked on the sclera with a colored pencil, and its location is noted relative to its distance from the limbus, optic nerve, and region involved (i.e., 11:00 to 2:00) (Fig. 15.6). The basal dimensions of the tumor are also noted. Although the

Fig. 15.5 Histologic sampling of the extraocular portions of the vortex veins, which exit the globe posteriorly in each quadrant, is recommended

Posterior view
1-4. Vortex veins in each quadrant
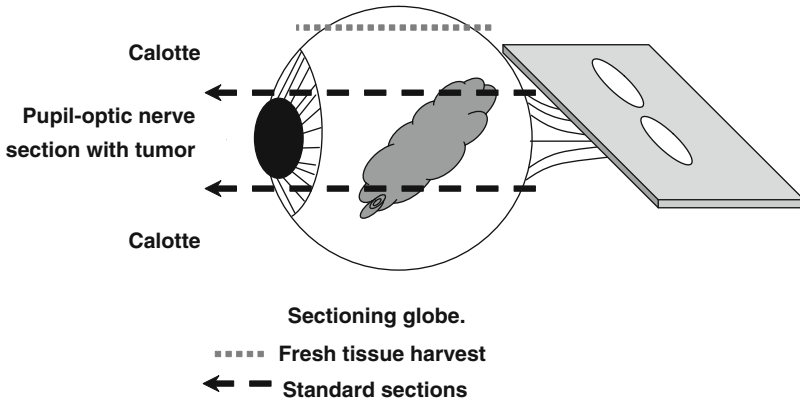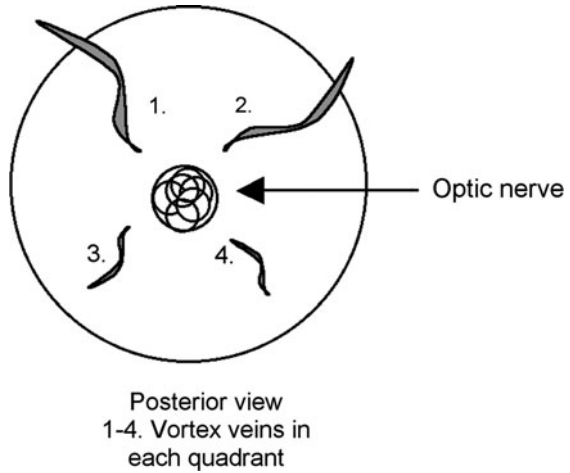
Fig. 15.6 Once the tumor base is located using transillumination, the globe is oriented with the tumor in the plane of the optic nerve and pupil and transected directly above the optic nerve to the edge of the pupil, as shown

shadow may correspond directly to the mass, retinal detachment can also cause a shadow that may obscure the exact size and location of the tumor.

Optimal sectioning of the tumor, following fixation in 10% buffered formalin, is generally achieved when the pupil and optic nerve are seen in cross section along with the tumor (Fig. 15.6) [34]. Horizontal, vertical, or oblique sectioning of the globe can be used to obtain this orientation.

If fresh tissue is to be harvested prior to fixation, a window or flap is opened adjacent to the tumor in the same plane from which the main tissue sections will be taken (Fig. 15.6). Normal retina and choroid are removed from the scleral flap. The tumor is then incised, using a sterile scalpel blade parallel to the window, and removed with forceps. No more than one-third of any tumor should be harvested to

ensure the integrity of the specimen for histologic diagnosis. Also, tissue harvesting should be avoided when the tumor is small or flat or when it is poorly visualized.

15.9.5 Histologic Examination

Histologic parameters include the initial determination that the lesion is a melanoma [35]. Among the primary intraocular tumors, uveal melanoma is the most common [36]. Uveal melanomas arise most commonly in the choroidal space and less frequently in the ciliary body and iris [35]. Large choroidal melanomas may involve adjacent structures, and any such involvement is noted in the pathologic report. Both the largest tumor dimension and tumor cell types (epithelioid, spindle, or mixed), which are important predictors of outcome, are documented [37, 38]. The growth pattern of a thin, diffuse, spreading melanoma should be documented, and additional hematoxylin and eosin-stained levels of the tumor should be examined, as this growth pattern portends a higher risk of extraocular extension and high risk of metastatic potential (25% at 5 years) despite its flatness [38, 39]. Multiple hematoxylin and eosin-stained levels are examined to check for invasion of the sclera directly or around nerves and vessels and exclude extraocular tumor extension, which would warrant additional therapy. Likewise, involvement of the optic nerve, optic nerve margin, or meninges must be assessed [40].

Unlike retinoblastomas, uveal melanomas generally do not spread via the optic nerve; however, they are more likely than retinoblastomas to invade the vortex veins [38]. Thus, both the vortex veins as they course through the sclera and the extraocular portions of the vortex veins are sampled and assessed [34].

Additional intratumoral factors—including complex vascular loops (which are optimally visualized for evaluation by a periodic acid Schiff stain) and mitotic figures (number of mitoses per 10 high-power fields)—may provide additional prognostic information [40, 41]. The final pathologic report includes both the findings on gross assessment and the pathologic parameters of the uveal melanoma, which facilitates determination of mortality risk for patients with this disease.

15.10 Conclusion

The past two decades have seen significant advances in the ocular treatment of uveal melanomas. Large prospective randomized trials, such as the COMS, have demonstrated the efficacy and benefits of globe-salvaging approaches, such as plaque brachytherapy. Charged-particle radiotherapy has also become an accepted standard of care, particularly for tumors adjacent to critical ocular structures such as the disc and macula. Unfortunately, these advances in treatment of the primary tumor have not been accompanied by advances in treatment for distant metastatic disease, for which limited effective therapy exists. The next decade is likely to see further research in gene expression and identification of specific tumors with high

metastatic potential. Those tumors should be targeted with adjuvant therapies to treat and prevent extraocular recurrence and reduce patient morbidity.

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