Uveal Melanoma

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Introduction

The three main types of primary ocular melanoma are eyelid, conjunctival, and uveal melanoma, each fundamentally different from each other. Eyelid and conjunctival melanomas are external to the eye itself, while uveal melanoma refers strictly to intraocular melanomas. Eyelid melanomas can be considered essentially identical to cutaneous melanoma, as they both possess the same pathogenesis, genetic alterations, risk factors, and general principles of metastasis and treatment. The reader is referred to other sections of this book for further detailed discussion on cutaneous melanoma. The conjunctiva is the thin, clear external mucous membrane that covers the front of the eye, extending from the peripheral edge of the cornea (the corneal limbus) over the anterior sclera (termed the bulbar conjunctiva). It then loops back onto the posterior surface of the eyelids (termed the palpebral conjunctiva) (Fig. 16.1). While not identical to cutaneous melanoma, it is important to recognize that conjunctival melanoma has several features reminiscent of its cutaneous counterpart.

It is important to note that, when referring to "ocular melanoma," some sources will group together both conjunctival and uveal melanomas [1]. Occasionally, even periocular cutaneous melanoma is included when some sources discuss "eye melanomas." However, uveal (intraocular) melanoma is unique from both conjunctival and cutaneous melanoma in its clinical and molecular features as well as its risk factors, genetics, pathogenesis, metastatic behavior, and treatment [2–7]. Therefore, it is important to think of uveal melanoma as a separate entity from the other two [8]. This chapter focuses predominantly on primary uveal melanoma, which is 7.5–17.5 times more common than conjunctival melanoma [5, 9–12]. A brief discussion of conjunctival melanoma is found at the end of this chapter.

Basic Ocular Definitions (Fig. 16.1)

- *Uvea*: The pigmented layer of the eye, often referred to as the uveal tract. It is composed of three intraocular structures (choroid, ciliary body, and iris) that are morphologically and functionally distinct but contiguous with one another. Uveal melanoma arises from melanocytes within these three structures.
- *Choroid*: The pigmented vascular layer of the eye that lies between the retina and the sclera. It is the most posterior portion of the uvea.

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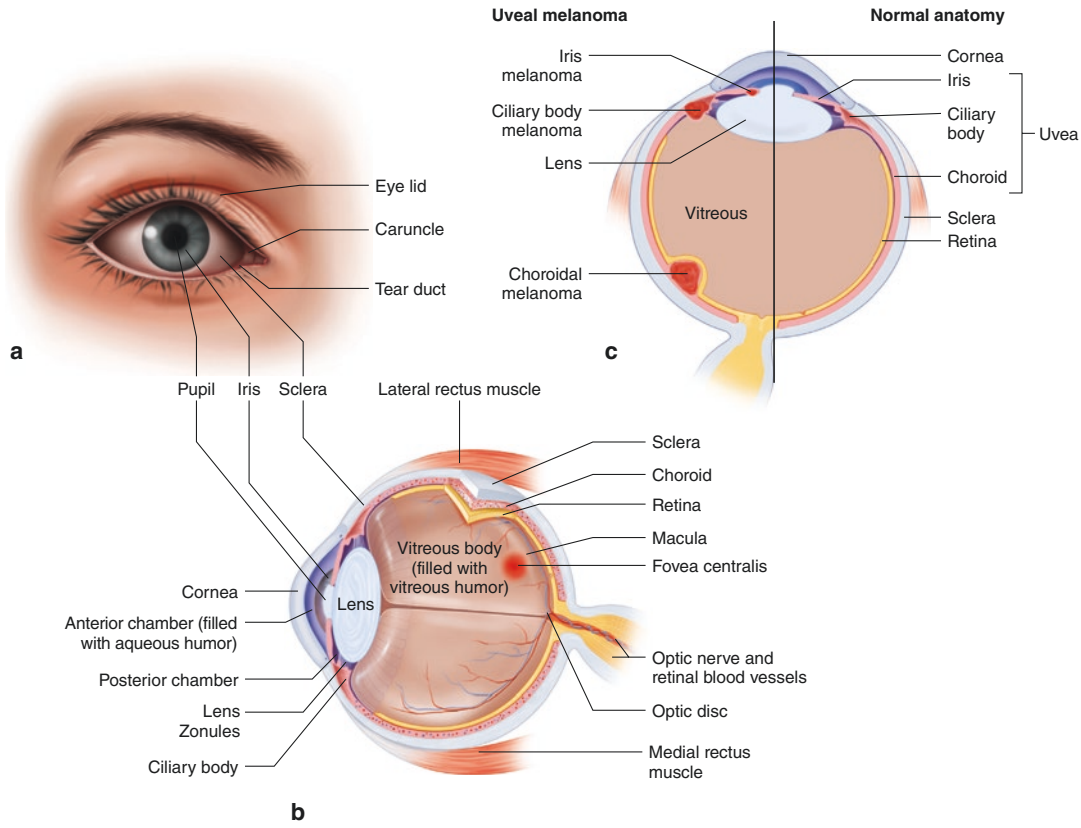

Fig. 16.1 Visual glossary of ocular anatomy. (**a**) External view with ocular surface and adnexal structures. (**b**) Sagittal cross section of the eye displaying intraocular anatomy. (**c**) Simplified cross section of the eye highlighting the normal uveal tract (on the *right*) and highlighting the location of the three locations of uveal melanoma (iris, ciliary body, and choroid) on the *left*

- *Ciliary body*: The pigmented vascular structure of the eye that connects the iris to the choroid. It consists of ciliary muscles (which alter the shape of the lens to allow the eye to focus on near objects) and ciliary processes (which produces the aqueous humor). It is the middle portion of the uvea.
- *Iris*: The thin circular pigmented structure that lies between the cornea and the lens. It has a dynamic aperture in the center that is known as the pupil. Eye color is defined by the color of one's iris. It is the most anterior portion of the uvea.
- *Aqueous humor*: The clear fluid produced by the ciliary body, which is composed primarily of water. It contains oxygen and nutrients that nourish the anterior structures of the eye, including the cornea.

Epidemiology

Uveal melanoma is the most common primary intraocular malignancy in adults [13] and is comprised of melanomas involving the choroid, ciliary body, and iris (Figs. 16.1, 16.2, and 16.3). Uveal melanoma represents 3–5% of all melanomas in the body, and the uvea is the second most common location, after the skin, from which primary melanomas arise [5, 14]. It is estimated that there are approximately 1,500–2,000 new cases of uveal melanoma diagnosed in the United States each year [5, 8], with the choroid accounting for 81–90% of these cases. Melanomas of the ciliary body are the second most common location for uveal melanomas and they comprise 5–8% of cases, while iris melanomas are the least common, representing only

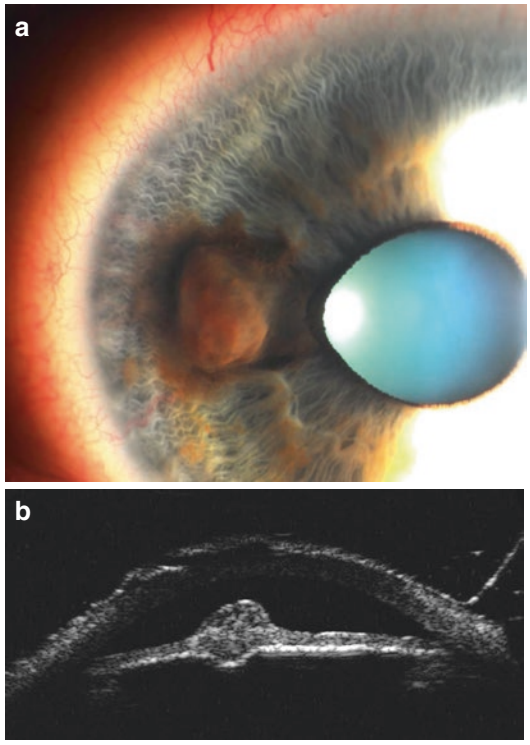

Fig. 16.2 Iris melanoma. (**a**) Anterior segment photographs of a small iris melanoma. (**b**) Ultrasound biomicroscopy (UBM) of the lesion seen in (**a**)

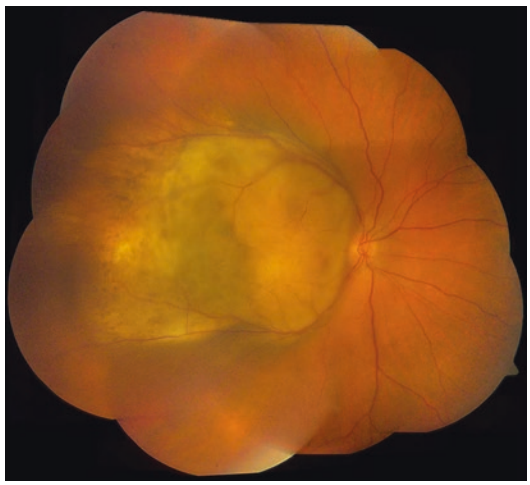

Fig. 16.3 Medium-sized amelanotic melanoma involving the macula and abutting the optic nerve (juxtapapillary)

3–5% of cases [9, 14, 15]. Infrequently, more than one site of the uveal tract may be involved, such as uveal melanomas that are large enough to involve both the iris and ciliary body (termed "iridociliary melanoma") or both the ciliary body and the choroid (termed "ciliochoroidal melanoma").

The annual incidence of uveal melanoma in the United States and Europe is 5–8 cases per million per year. Unlike cutaneous melanoma, where the incidence has been on the rise, the worldwide incidence of uveal melanoma has remained stable over the past several decades [5, 9, 10, 16]. Previously, a geographical trend in incidence change was identified, with the incidence of uveal melanoma observed to increase significantly with an increase in latitude of birth (4.91-fold increase from 20–22 degrees latitude to 47–48 degrees latitude) [17]. However, a further meta-analysis has shown that latitude of birth is not an independent risk factor for development of uveal melanoma. Rather, this trend reflects the genetic predisposition for uveal melanoma of populations living in these higher latitudes, with a higher incidence in countries having larger Scandinavian or Caucasian populations (higher latitude countries) and a lower incidence in East Asia and Africa (lower latitude countries) where there is a lower proportion of Scandinavian or Caucasian populations [5, 10, 18, 19].

Uveal melanoma primarily afflicts older Caucasian adults, with a peak age at diagnosis of 70–79 years, with men and women being equally affected [5]. However, uveal melanoma can occur over a wide age range, with diagnoses being reported anywhere from 6 to 100 years of age [14, 20, 21]. Caucasians represent 97.8% of cases in the United States, with a Caucasian-to-African-American ratio of 196:1 [5]. Population studies estimate the annual incidence of uveal melanoma, based on ethnicity, to be 4351 for Caucasian-non-Hispanics, 1154 for Hispanics, 875 for Asians, and 316 for Africans [22].

Risk Factors for Developing Uveal Melanoma

Several studies and meta-analyses have identified a variety of risk factors that put certain individuals at a higher risk for developing uveal melanoma. These risk factors include presence of light-colored irides, fair skin, cutaneous freckles, increased number of common cutaneous nevi, atypical cutaneous nevi, propensity to sunburn/inability to tan, iris nevi, ocular melanocytosis, dysplastic nevus syndrome, inactivating *BAP1* gene mutation, and welding as an occupation [18, 23–27]. In comparison, similar risk factors have been shown to be important in the development of cutaneous melanoma, including blonde or red hair, fair skin color, light eye color, skin freckling, presence of cutaneous nevi, and sensitivity to sunlight [28]. It has been shown that ultraviolet (UV) light/sunlight exposure is the most significant modifiable risk factor for cutaneous melanoma [29–31]. However, the effect of sunlight on the development of uveal melanoma has not been thoroughly identified as a major risk factor.

There is conflicting data from numerous studies which have investigated the role of UV/sunlight exposure in the development of uveal melanoma. For example, melanoma is more likely to arise within the posterior pole of the eye, where sunlight exposure is thought to be greatest. However, the preponderance of evidence suggests that UV light damage is not causative in the pathogenesis of posterior uveal (choroidal and ciliary body) melanoma [27, 32–34]. This is supported by the fact that the types of deoxyribonucleic acid (DNA) damage typically seen with UV light, such as C-to-T transitions, are not as commonly observed with uveal melanomas [35–39]. Similarly, genes mutated in cutaneous melanomas arising in sun-exposed or chronically sun-damaged skin, such as BRAF and NRAS, are not mutated in uveal melanoma (see Genetics section below) [40–42].

Genetics and Pathogenesis of Uveal Melanoma

Uveal melanoma harbors a relatively limited number of conserved genetic mutations, which are responsible for its oncogenesis and progression to metastatic disease [36–38, 43, 44]. This is in contrast to many other solid tumors, including cutaneous melanoma, which carry a much wider variety of pathogenic and passenger mutations. Chromosomal anomalies associated with uveal melanoma consist primarily of derangements in chromosomes 1, 3, 6, and 8 [45–50]. Further discussion of these chromosomal alterations and their implications for patient prognosis is given in detail later in this chapter. This section reviews the major genes and epigenetic modifications involved in the pathogenesis of uveal melanoma.

It is important to mention that the specific genetic variants underlying the development of uveal melanoma differ completely from those observed with cutaneous melanoma. The most commonly observed high-risk susceptibility genes associated with cutaneous melanoma include *CDKN2A*, *CDK4*, *MITF*, and *MC1R* [51]. Furthermore, cutaneous melanoma is typically driven by mitogen-activated protein kinase (*MAPK*) activating mutations in *BRAF* (40–50% of cases) and *NRAS* (10–25% of cases) or by loss-of-function mutations in the *NF1* gene (14% of cases) [52].

In contrast, uveal melanoma contains a more limited number of conserved mutations found almost exclusively in the *GNAQ*, *GNA11*, *SF3B1*, *EIF1AX*, and *BAP1* genes. Mutations in *GNAQ* and *GNA11* occur early and are found in approximately 83–91% of all primary uveal melanomas and are always mutually exclusive to one another [38, 43]. Mutations in *SF3B1*, *EIF1AX*, and *BAP1* are present, in addition to the early *GNAQ/GNA11* mutations. As with *GNAQ/GNA11*, mutations in *SF3B1*, *EIF1AX*, and *BAP1* are all also mutually exclusive from each other [37, 43, 53].

Uveal melanomas arise from uveal melanocytes. The timing of the major genetic mutational events that lead to melanocytic malignant transformation is largely predictable. Progression from uveal melanocyte to nevus is characterized by specific mutations in either *GNAQ* or *GNA11*, followed by a mutation in either *SF3B1* or *EIF1AX*. In turn, this causes a transformation from nevus to a "low-metastatic-risk" uveal melanoma. Alternatively, after the initial *GNAQ/GNA11* mutation, a uveal nevus may transform into a "high-metastatic-risk" uveal melanoma by acquiring a subsequent independent pathogenic derangement in the *BAP1* gene (Fig. 16.4).

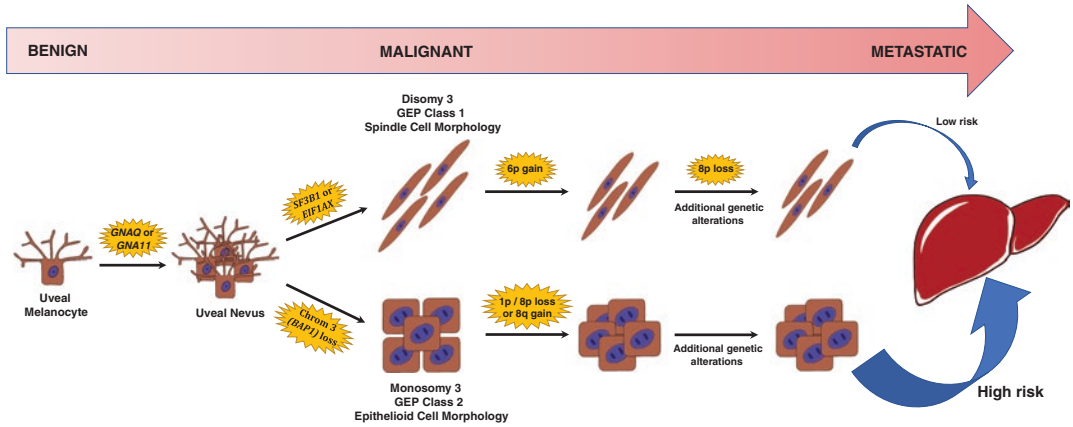

Fig. 16.4 Genetic pathway of uveal melanoma. The first step in the genetic development of a uveal melanoma starts with a uveal melanocyte acquiring a mutation in either *GNAQ* or *GNA11,* creating a uveal nevus. During melanomagenesis, the nevus then progresses along on one of the two mutually exclusive pathways. Some tumors will develop chromosome 3 loss (monosomy 3) with loss of *BAP1*, leading to a melanoma with high metastatic risk and Class 2 gene expression profile (GEP). Alternatively, tumors may instead acquire a mutation in either *SF3B1* or *EIF1AX*, leading to a melanoma with low metastatic risk and Class 1 GEP. After the initial genetic bifurcation, tumors may then acquire subsequent genetic derangements in chromosomes 1, 6, and 8, which are themselves independent modifiers of metastatic risk and patient mortality. Adapted with permission of Wiley

GNAQ and GNA11 Gene Mutations

GNAQ/11 each encodes for G protein-related alpha subunits of a larger cellular protein complex. Mutations in these genes are somatically acquired and almost exclusively occur within the GTPase catalytic domain at codon 209 in exon 5 [36, 38, 43]. Inactivating mutations at this site prevent hydrolysis of GTP, subsequently locking the mutated protein in its activated configuration and resulting in constitutive activation of many downstream pathways such as MEK/ERK. This causes YAP hypo-phosphorylation and nuclear localization, resulting in transcriptional activation of numerous cell cycle genes [36, 37, 54, 55]. Mutations in *GNAQ/11* lead to precursor uveal nevi, but alone are not sufficient to lead to melanoma. *GNAQ/11* mutations have been observed in nevi and melanomas at all stages of malignant progression, independent of other well-known oncogenic mutations. As such, *GNAQ/11* mutations represent the earliest genetic event in the pathogenesis from uveal melanocyte to melanoma [56].

BAP1 Gene Mutations

BRCA-1-associated protein-1 *(BAP1)* is located on chromosome 3p21. *BAP1* functions as a tumor-suppressor gene, and therefore requires functional loss of both copies of the gene in order to cause malignant transformation of a cell (i.e., a single functional copy of *BAP1* is adequate to maintain normal cellular function). The BAP1 protein is linked to many critical intracellular processes required for maintaining normal cellular function. Although its exact role in the oncogenesis of uveal melanoma remains unclear, it is certain that maintaining at least one functional copy of *BAP1* is critical for normal cellular growth, chromatin regulation, and DNA damage repair. Furthermore, it has been shown that reduction in BAP1 activity can result in regression of cellular differentiation of uveal melanoma cells, which is likely the underlying oncogenic driving force in cells with *BAP1* mutations [57].

There are two ways in which uveal melanocytes may develop total functional loss of *BAP1* (i.e., functional loss of both copies of *BAP1*). First, patients may carry a single mutant *BAP1* gene and then acquire a subsequent loss of the other, wild-type, *BAP1* gene via an inactivating mutation or total chromosome 3p21 loss, resulting in complete loss of cellular BAP1 function. Second, a uveal melanocyte may exhibit loss of *BAP1* heterozygosity by one parent cell, incorrectly contributing two mutant *BAP1* genes to a daughter cell during mitosis, creating isodisomy

(also known as uniparental disomy). By this mechanism, a melanocyte may acquire two copies of inactivated *BAP1* genes, and therefore exhibit complete loss of *BAP1* function [58]. Both genetic mutations and histone deacetylase enzymes have been shown to play a role in the inactivation of *BAP1*, with inactivating mutations observed in up to 84% of uveal melanomas that metastasize [59]. Genetic prognostication and metastatic disease are discussed later in this chapter.

SF3B1 Gene Mutations

The splicing factor 3B subunit 1 (*SF3B1*) gene encodes for a subunit of the splicing factor component of a larger intracellular spliceosome complex. This complex functions to splice precursor messenger ribonucleic acid (mRNA) into mature transcription products. The wild-type *SF3B1* gene product anchors the precursor mRNA onto the spliceosome complex, facilitating correct mRNA splicing. Mutations of the *SF3B1* gene can result in critical mRNA splicing errors that may result in downstream protein product dysfunction, cell cycle derangements, and ultimately melanomagenesis [60–62].

EIF1AX Gene Mutations

The eukaryotic translation initiation factor 1A, X-linked (*EIF1AX*) gene encodes for a protein involved in the translation of other intracellular proteins. Its exact mechanism of oncogenesis in uveal melanoma is not well understood at present. Mutations in the *EIF1AX* gene have been reported in up to 24% of primary uveal melanomas [63, 64].

Rb, p53, and PTEN Gene Mutations

In uveal melanomas, mutations in the retinoblastoma (*Rb*), phosphatase and tensin homolog (*PTEN*), and *p53* tumor-suppressor genes are exceedingly rare. However, most uveal melanomas exhibit some degree of inhibition of the Rb and p53 pathways, even in the presence of wild-type *Rb* and *p53* genes. This apparent loss of Rb and p53 activity is due to the overexpression of cyclin D1 and MDM2, respectively. Reduced Rb and p53 activity allows for disinhibited progression through the cell cycle and further malignant transformation [65–67].

The loss of *PTEN* activity has also been reported in a subset of uveal melanomas and is thought to result in increased downstream activity of PI3K/AKT signaling, which in turn activates many other downstream targets that lead to cellular proliferation [68]. In one study, up to 11% of uveal melanomas were found to have mutations in *PTEN*. Furthermore, there are other small studies suggesting that reduced patient survival may be associated with uveal melanomas containing *PTEN* mutations [68–73].

Epigenetics in Uveal Melanoma

Epigenetics is the study of mitotically inherited cellular influences that alter genetic function, but are not caused by direct DNA nucleotide alterations. Over the past two decades, it has become more apparent that these epigenetic factors play an important role in the modification of chromatin, resulting in dynamic alterations in the expression of DNA. It is now known that epigenetics plays an important role in the development of numerous pathologies and cancers, with several epigenetic mechanisms centrally involved in the malignant transformation and progression of melanoma.

The most notable epigenetic factors include DNA methylation and alterations of histones through acetylation or methylation. Collectively, this has been termed the "epigenome," and a "histone code" has been theorized. The histone code can be modified significantly by major regulators of transcription, such as polycomb group (PcG) proteins and histone-modifying enzymes (HMEs) such as histone acetyltransferases (HATs) or histone deacetylases (HDACs) [74].

Recently, Herlihy and colleagues showed that reduced expression levels of HMEs and PcG

proteins were associated with uveal melanoma harboring monosomy 3, with the gene expression profile (GEP) Class 2 [75], both of which are characteristics associated with increased metastatic risk. Currently, the role of epigenetics in the pathogenesis and treatment of uveal melanoma is still in its infancy. However, there have been some small studies elucidating potential future directions for utilizing epigenetic modification in the treatment of uveal melanoma [75, 76].

Summary of Genetic Pathogenesis of Uveal Melanoma

In summary, it is well known that the genetic pathway for uveal melanoma bifurcates at an early stage in its pathogenesis. The initial genetic alteration involves an early mutation in either GNAQ or GNA11. Mutations in GNAQ/11 result in the development of a uveal nevus, but a mutation in either of these genes alone is not fully sufficient for a uveal melanocyte to complete malignant transformation [36, 43, 53, 77]. After this initial mutation in either GNAQ or GNA11, the cell acquires another separate pathogenic mutation in either *SF3B1 or EIF1AX* (leading to melanoma with a lower metastatic risk) or *BAP1* (leading to melanoma with a high metastatic risk). Each of these mutations is mutually exclusive to the others [63], and this bifurcation results in two mutually exclusive and genetically distinct uveal melanoma subtypes (Fig. 16.4) [36, 45, 78].

Evaluation and Diagnosis of Primary Uveal Melanoma

Uveal melanoma arises from uveal melanocytes, and may either develop from a long-standing choroidal nevus or arise de novo, without progressing from a precursor nevus. However, there is no data documenting the proportion of melanomas that arise from nevus vs. de novo. In fact, the overwhelming majority of published literature only reports rates of growth and transformation of uveal nevi into melanomas, with only two case reports documenting truly de novo choroidal melanomagenesis [79, 80]. Additionally, it is reasonable to assume that some larger reports of nevi progression may actually include melanoma variants that arose de novo but were initially misclassified. Consequently, it is difficult to establish an accurate incidence of malignant transformation from nevus vs. incidence of de novo melanomagenesis. Given the lack of documentation of uveal melanomas arising de novo, experts believe that the overwhelming majority of melanomas evolve along a continuum between benign uveal nevus and melanoma, analogous to cutaneous nevi and melanoma [81, 82].

Diagnosis of Primary Uveal Melanoma

The diagnosis of uveal melanoma is determined by the clinical judgment of the evaluating ophthalmologist, and is based on patient presentation with a detailed physical examination using biomicroscopy and ophthalmoscopy. Adjuvant diagnostic imaging techniques may be used as well to look for the presence of high-risk features, suggesting uveal melanoma over a benign nevus. Studies have shown that the rarity of uveal melanoma may play a role in the correct diagnosis (i.e., differentiating a melanoma from a nevus) being missed by comprehensive ophthalmologists who may only observe this disease a few times during their career. In fact, it is estimated that a comprehensive ophthalmologist practicing in the United States will see one new case of uveal melanoma per decade of practice [20, 83]. Consequently, given uveal melanoma's high rate of metastasis and mortality [84–87], along with its evolution along a continuum from benign to malignant, careful ophthalmologic examination by a trained and experienced clinician remains critical.

Differential Diagnosis of Uveal Melanomas

There are numerous other benign and malignant neoplasms of the retina, the outer lying retina

pigment epithelium (RPE) and choroid, all of which can mimic the appearance of ciliary body or choroidal melanoma on physical exam. The differential diagnosis of a solitary, pigmented lesion includes uveal melanoma, choroidal nevus, melanocytoma, congenital hypertrophy of the RPE (CHRPE), hemorrhage in the subretinal or suprachoroidal space, and metastatic cutaneous melanoma. The differential diagnosis of a solitary amelanotic lesion includes amelanotic uveal melanoma, choroidal hemangioma, metastatic choroidal tumors, solitary choroidal granuloma (from sarcoidosis or tuberculosis), posterior scleritis, and prominent vortex ampulla [88]. The differential diagnosis of pigmented melanocytic iris lesions includes iris nevus, iris melanoma, primary iris cyst, essential iris atrophy, iris foreign body, peripheral anterior synechiae, iris metastasis, leiomyoma, melanocytoma, and other rare entities [89].

Delays in Early Diagnosis of Primary Uveal Melanoma

Despite the high mortality rate associated with metastatic disease, studies have not conclusively shown that early diagnosis and treatment of primary uveal melanoma have an impact upon improving a patient's survival. However, there are numerous studies demonstrating that early diagnosis prevents disease-related morbidity by reducing the rate of enucleation (removal of the entire eye) and increasing the rate of eye-sparing treatment with radiotherapy. Enucleation rates for delayed diagnoses are 44–52%, compared to the 17–29% for cases without diagnostic delays [20, 87, 90]. Several reports show that diagnostic delays result from an initial misdiagnosis in 23–42% of cases. Diagnostic delays are associated with a significant delay in the onset of treatment, with an average time to treatment of 6.6 months for cases with diagnostic delays compared to 4.2 weeks for cases without delays [20, 90]. Cited reasons include tumors located in areas difficult to observe on exam (such as in the anterior choroid or ciliary body), the presence of media opacities (such as cataracts) that may obstruct the view, and the presence of other ocular pathologies that may incorrectly explain visual symptoms which are actually caused by the melanoma [83, 90].

Patient Presentation

Large, prospective studies have shown that 69–72% of patients with uveal melanoma present symptomatically. The most common presenting symptom is blurry vision, occurring in 37.8% of symptomatic patients, followed by photopsias (flashes of lights) in 8.6%, floaters in 7.0%, visual field loss in 6.1%, visible tumor in 3.1%, and pain in 2.4%. Larger tumors are more likely to present with some of these symptoms due to secondary effects from the tumor, such as associated serous retinal detachment which may cause reduced vision, visual field deficits, and photopsias [20, 90]. On the other hand, 28–31% of patients present completely asymptomatic and are diagnosed on routine ophthalmic screening exams. Rarely, a long-standing blind eye or an eye with a very dense cataract may harbor an occult uveal melanoma. Therefore, eye care providers must routinely and thoroughly evaluate eyes with a poor view to the posterior pole (e.g., due to dense cataracts, diseased corneas, or phthisis bulbi) with ocular ultrasonography, in order to monitor for the development of an occult tumor [91].

Clinical Features of Ciliary Body and Choroidal Melanomas

Melanomas of the ciliary body and choroid typically present as a solitary, elevated, pigmented, or amelanotic lesion. Ciliary body and choroidal melanomas are typically dome shaped (Figs. 16.2 and 16.5) with 60% of choroidal melanomas being located within 3 mm of the optic disc or fovea. There may be clumps of overlying orange pigment, due to collection of lipofuscin associated with the melanoma (Fig. 16.6). In some cases, serous fluid may leak from the tumor and

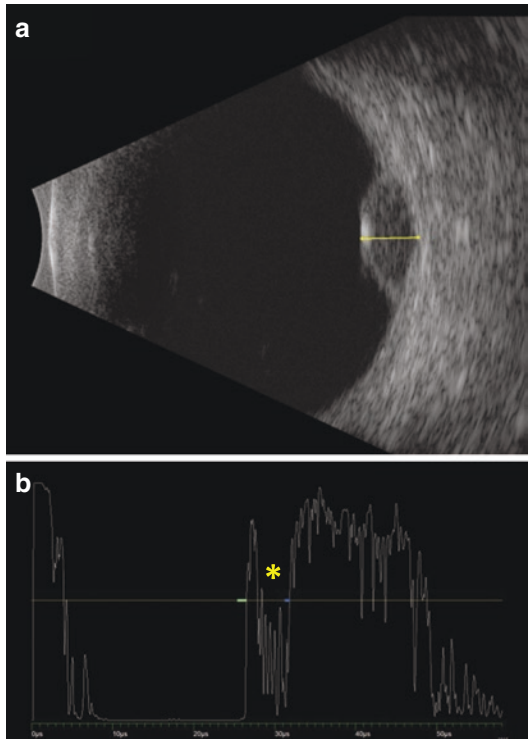

Fig. 16.5 Choroidal melanoma ultrasonography. (**a**) B-scan ultrasonography of choroidal melanoma, demonstrating the characteristic dome shape, and acoustic hollowness. (**b**) The corresponding A-scan ultrasonography of the same melanoma, displaying low-medium internal reflectivity (*yellow asterisk*) with vascular spikes

collect underneath the retina, causing an associated serous retinal detachment or subretinal hemorrhage (Fig. 16.6).

Large ciliary body and choroidal melanomas are often easy for the trained ophthalmologist to diagnose on physical exam, based on the presence of high-risk clinical features that distinguish them from smaller benign nevi. However, the distinction between small- and medium-sized nevi versus melanomas can be difficult, with adjuvant imaging modalities quite useful as an aid in making the correct diagnosis. Such imaging modalities include fundus photography, ophthalmic ultrasonography, ultrasound biomicroscopy (UBM), optical coherence tomography (OCT), fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green (ICG), and magnetic resonance imaging (MRI).

Anterior Segment and Fundus Photography

Anterior segment and fundus photography employ the use of a specialized camera attached to a biomicroscope with a light source. This camera is used to capture high-resolution photographs of the anterior segment (iris, cornea, conjunctiva, and sclera) and fundus (the back of the inside of the eye) (Figs. 16.2, 16.3, 16.6, and 16.8). Fundus photography is mainly used for monitoring and documenting any change in the pigmentation and borders uveal nevi, melanomas, and other suspicious lesions requiring monitoring for growth. Fundus photography allows for lesions to be documented and compared over time. Any documented change or growth of a nevus may represent malignant transformation, necessitating treatment.

Ophthalmic Ultrasonography

Ophthalmic ultrasonography (USG) is the single most valuable diagnostic tool available to the experienced clinician to aid in diagnosis, monitoring, and documenting growth for uveal melanoma. Serial USG measurements are used to monitor for any change in tumor dimensions over time, with an increasing basal diameter or apical height highly suggestive of malignant transformation and growth [8, 92, 93]. Additionally, USG is indispensable for accurately evaluating lesions through retinal detachments and dense media opacities that would otherwise obstruct the examiner's direct view of the lesion in question. Clinicians utilize both B-scan and A-scan USG to accurately evaluate lesions suspicious for the diagnosis of melanoma (Figs. 16.5 and 16.7).

Traditional USG B-scans use a 10 MHz transducer that provides a resolution of 300–400 μm, and is used to reliably define the tumor extent, shape, and dimensional measurements. Typical features of choroidal and ciliary body melanomas on B-scan USG include a dome or mushroom shape, apical height >3 mm, choroidal excavation, acoustic hollowness, and posterior shadowing

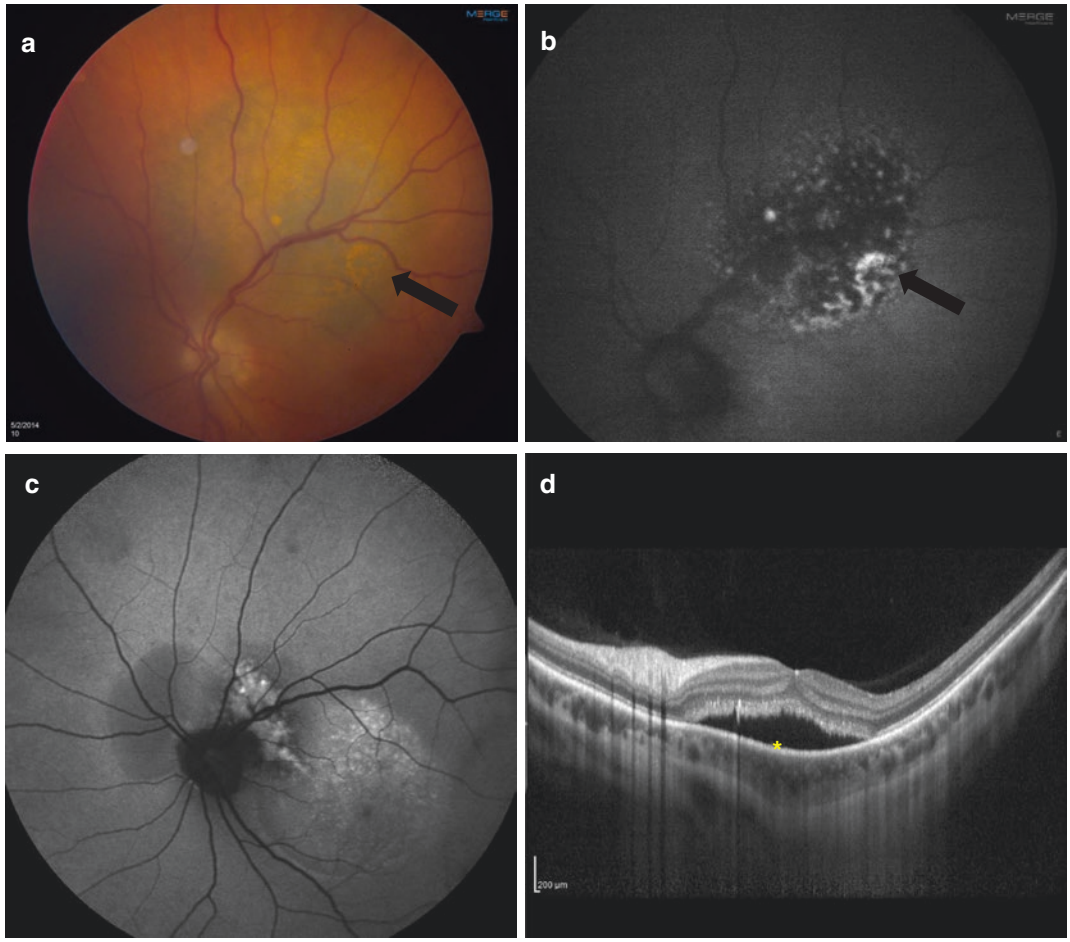

Fig. 16.6 (**a**) Color fundus photography of a choroidal melanoma with several high-risk features, including the presence of orange pigment (*arrow*) and juxtapapillary location abutting the optic nerve head. (**b**) Fundus autofluorescence of the choroidal melanoma displayed in (**a**), demonstrating hyper-autofluorescence (*arrow*) corresponding to the orange pigment seen on the fundus photograph. (**c**) Another fundus autofluorescence of a different choroidal melanoma, also displaying some hyper-autofluorescence of orange pigment and subtle subretinal fluid. (**d**) Spectral domain optical coherence tomography (OCT) of the choroidal melanoma displayed in (**c**). This OCT highlights the presence of subretinal fluid (*asterisk*)

(Figs. 16.5 and 16.7) [94]. Mushroom shape on USG (Fig. 16.7) is nearly pathognomonic for choroidal melanoma [95], which occurs as a result of melanoma extension through Bruch's membrane (the innermost layer separating the choroid from the retina). Another concerning feature on USG is the presence of an apical height >3 mm, as these lesions are very likely to be melanoma [8, 93]. In addition to B-scan USG, there are characteristic features on A-scan that are highly suggestive of the diagnosis of uveal melanoma. The classic acoustic features of uveal melanoma seen on A-scan USG include homogenous, low-to-medium internal reflectivity, solid consistency with no "after movement," and echographic signs of vascularity, such as fast vertical flickering A-scan spikes (Fig. 16.5) [96].

Ultrasound Biomicroscopy

Ultrasound biomicroscopy (UBM) is a separate ultrasonography technique that is used primarily to evaluate the anterior segment of the eye,

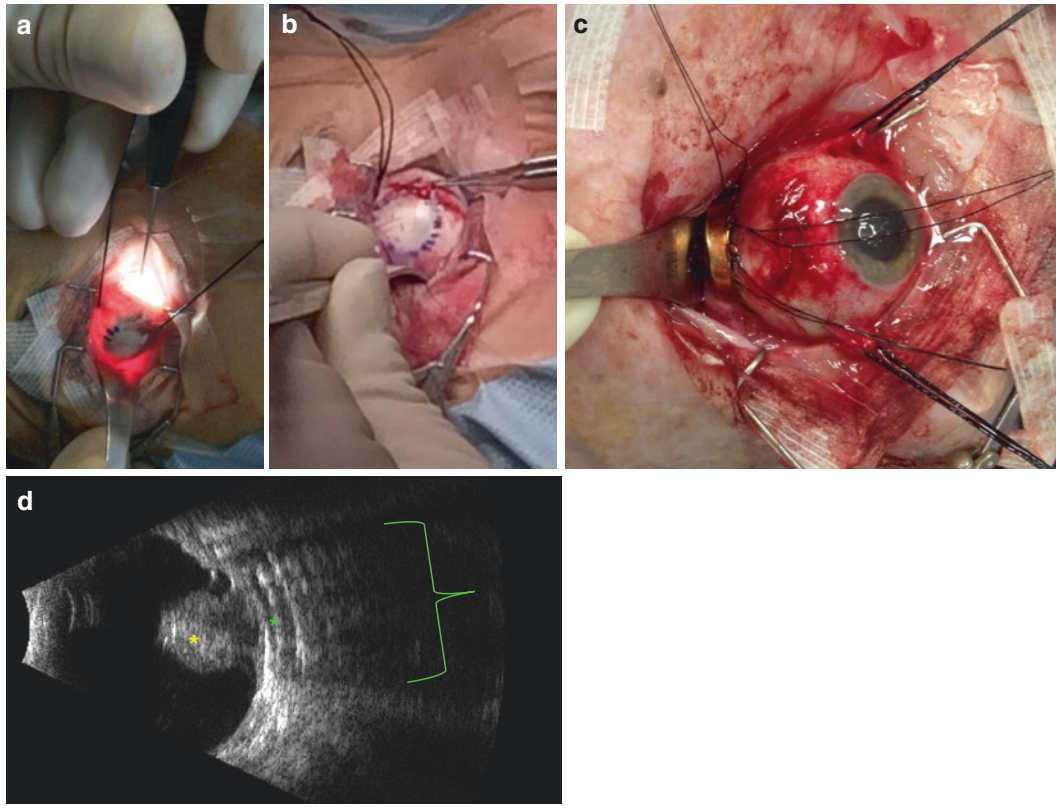

Fig. 16.7 Radioactive brachytherapy plaque placement. (**a**) Traction sutures have been placed around the superior and inferior rectus muscles and the eye has been rotated. The lateral rectus muscle has been disinserted to allow better access to the underlying tumor. A light is shined into the eye in this photo, transilluminating the melanoma on the surface of the overlying sclera. (**b**) This transillumination shadow is then marked to delineate the borders of the tumor. The radioactive plaque is sewn to the sclera to cover the previously marked tumor borders. (**c**) The gold plaque shell can be seen on the left side of the eye. (**d**) Intraoperative ultrasound showing a mushroom-shaped choroidal melanoma (*yellow asterisk*) and the correctly placed brachytherapy plaque (*green asterisk*) with acoustic shadowing posterior (*green bracket*) to the plaque

including the iris, ciliary body, anterior chamber, and cornea. Compared to conventional ophthalmic A-scan and B-scan ultrasonography, UBM uses a higher frequency transducer (35–100 MHz) to capture anterior segment images with a higher resolution approaching 20–60 μm [97]. While standard B-scan ultrasonography of the eye is useful for evaluation of posterior choroidal melanomas, UBM's higher resolution is better for imaging smaller uveal melanomas of the ciliary body and iris. UBM improves on the axial and lateral resolution of conventional B-scan imaging by a factor of ten, and its imaging penetrates up to 4 mm, which is sufficient to image most ciliary body and iris melanomas [98]. Due to its superior resolution and penetration over USG, UBM demonstrates superior accuracy in acquiring dimensional measurements and localization of uveal melanomas involving the ciliary body and peripheral iris (Fig. 16.2) [99].

Fundus Autofluorescence

Fundus autofluorescence (FAF) is a noninvasive retinal imaging modality that provides a density map of lipofuscin, the predominant fluorophore in the retinal pigment epithelium (RPE). Fluorophores are naturally occurring molecules that absorb light of a particular wavelength, and

then emit (autofluoresce) light of a distinctly separate wavelength. Classically, FAF utilizes blue light to excite the lipofuscin, and then collects the subsequent fluorescent emissions to form a brightness map that reflects the distribution of lipofuscin located in the RPE. The RPE is the pigmented, outermost layer of cells that lines the retina, serving multiple functions to support and nourish the retina photoreceptors. In clinical practice, FAF is used as a reliable noninvasive method to estimate the viability of the RPE [100].

For choroidal melanomas, FAF is used to assess the health of the overlying RPE, which may demonstrate characteristics that differentiate choroidal nevus from melanoma [101]. FAF features associated with choroidal nevus include overlying hypo-autofluorescence (56% of cases), homogenous hyper-autofluorescence (25% of cases), or iso-autofluorescence (19% of cases). Hypo-autofluorescence on FAF is a sign that is suggestive of chronic RPE atrophy associated with the underlying lesion. Signs of chronicity are more likely to represent a benign nevus over melanoma. Such chronic changes indicate that a particular lesion has been present for an extended time period that is long enough for these changes to manifest. Therefore, chronic changes are indirect signs of slow or minimal growth, which is the major characteristic of a nevus.

Contrasting FAF of nevi, choroidal melanomas are more likely to demonstrate distinct hyper-autofluorescence that corresponds directly to intrinsic lipofuscin deposition (seen as orange pigmentary deposits on physical exam) (Fig. 16.6). While the absence of this FAF feature does not rule out the diagnosis of melanoma, its presence suggests malignancy. Thus, the diagnostic utility of FAF in uveal melanoma is most beneficial for potentially highlighting subtle lipofuscin aggregates (orange pigmentation) of uveal melanomas that may be missed on the clinical exam alone [101–103]. Some researchers have demonstrated quantification of FAF images using imaging software to quantify the amount of autofluorescence and differentiate between clinically benign and malignant choroidal melanocytic lesions [104].

Optical Coherence Tomography

Optical coherence tomography (OCT) is both a noncontact and noninvasive ophthalmic imaging technique commonly used in ophthalmology. It is utilized to quickly and accurately visualize in vivo cross-sectional images of ocular tissues in a wide variety of diseases. Modern OCTs are capable of producing high-definition images with a resolution of up to 5 μm. This technique uses the interference patterns of laser light that is shined onto, and reflected from, the ocular tissue to create high-definition cross-sectional images of the cornea, iris, ciliary body, retina, and choroid. OCT is not regularly employed as a diagnostic tool for uveal melanomas, as it has shown limited use for evaluating lesions >3 mm in thickness or lesions with heavy pigmentation [105, 106]. However, when utilized, OCT is primarily used to confirm the presence of subtle subretinal fluid associated with uveal melanoma and which may be missed on clinical exam alone (Fig. 16.6). Other less common roles of OCT for uveal melanoma include obtaining dimensional measurements of small tumors and differentiating congenital hypertrophy of the retina pigment epithelium (CHRPE) from choroidal melanoma.

Fluorescein Angiography

Fluorescein angiography (FA) is a relatively more invasive chorioretinal vascular imaging technique that involves injecting a fluorescent dye into the patient's bloodstream. While the dye circulates through the retinal and choroidal vasculature in the back of the eye, serial fundus images are captured. FA is not routinely used to evaluate or monitor uveal nevi/melanomas, as it has limited ability to distinguish between the two and there is no pathognomonic FA characteristic for either of these lesions. However, it is important to note that FA can demonstrate a "dual-circulation" pattern in up to 61% of choroidal melanomas, which is a sign of secondary choroidal vascularization in tumors that have broken through Bruch's membrane beneath the RPE [107].

Indocyanine Green Angiography

Indocyanine green angiography (ICGA) is an ophthalmic imaging technique that is used to evaluate the choroidal vasculature, but has a limited role for evaluating uveal melanomas. ICGA is similar to FA, in that it involves the injection of a dye into the patient's bloodstream, with subsequent serial imaging of the ocular fundus while the dye circulates through the choroidal blood vessels. However, ICGA is better for imaging the choroid, utilizing near-infrared light, which penetrates the RPE to activate the indocyanine green dye in the choroidal vessels. These features allow for ICGA to evaluate the integrity of the choroidal vascular system.

While ICGA may demonstrate hypocyanescence of uveal melanomas, this finding is not reliably characteristic and its role in the diagnosis, evaluation, and monitoring of uveal melanoma remains rare and limited. ICGA may be most useful in distinguishing choroidal melanoma from choroidal hemangiomas if this distinction is not apparent to the clinician on physical exam, as the choroidal vessel patterns differ between these two entities [108]. There are previous studies suggesting that ICGA may be capable of detecting prognostically significant microvasculature patterns (such as closed vascular loops that are only seen on histopathological biopsy evaluations) [109, 110]. However, these studies have not been validated and this imaging modality continues to have limited utility in the evaluation of uveal melanoma.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are rarely used for the evaluation of primary uveal melanomas. Uveal melanomas may be seen as hyperdense on CT imaging and may demonstrate mild-to-moderate enhancement with contrast dye. With MRI, they appear hyper-intense on T1-weighted images and hypo-intense on T2-weighted images [88]. While large melanomas can be seen on both imaging modalities, with MRI able to demonstrate extrascleral extension in rare cases of larger tumors [111], the role of CT and MRI for primary uveal melanomas remains limited. The principal role of CT and MRI in uveal melanoma is for monitoring the development of systemic metastatic spread of the disease, rather than for imaging the primary tumor itself. In usual practice, CT and MRI of the orbit are only used when treatments such as stereotactic radiosurgery are being planned (see treatment section below), or if optic nerve invasion is suspected.

Monitoring Uveal Melanoma Over Time

Imaging modalities are not only useful for aiding in the correct diagnosis on initial evaluation, but also invaluable for serially following suspicious lesions that may not have the typical features of melanoma. Of the previously mentioned modalities, B-scan ultrasonography and fundus photography are the most useful and most regularly utilized methods for monitoring growth and change in appearance over time. Any documentation of rapid growth would be indicative of malignancy and therefore indicate urgent treatment. The appearance of new subretinal fluid is likewise worrisome for malignant transformation.

Clinical Features of Iris Melanomas

Iris melanomas may be well circumscribed (90%) (Fig. 16.2) or diffuse (10%) and are much less common than ciliary body or choroidal melanoma. Due to their anterior and more visible location in the front of the eye, iris melanomas are diagnosed an average of 10–20 years earlier than their ciliary body and choroidal counterparts [88, 112]. In most cases, iris melanomas are noticed due to a change in iris color (iris heterochromia) or pupil distortions (corectopia). Iris melanomas are most commonly located in the

inferior quadrant of the iris (45% of cases) and may be associated with pupillary border abnormalities, secondary glaucoma, ectropion uveae (posterior iris pulled forward through the pupillary margin), hyphema (bleeding in the anterior chamber), and extraocular extension [88, 112–114]. Evaluation of iris melanoma includes exam with the slit lamp, gonioscopy (evaluation of the anterior chamber angle and trabecular meshwork), photos, and UBM. Occasionally, anterior segment OCT can be helpful, but in general UBM is superior to OCT in assessing iris melanomas. This is because UBM penetrates deeper into the tumor, allowing better characterization of the posterior border of the iris tumor and therefore more accurate measurements compared to OCT [115].

Lesion Characteristics Associated with High Risk for Malignancy, Growth, and Metastasis

In addition to differentiating uveal melanocytic lesions (nevi and melanomas) from other entities on the differential diagnosis, the ophthalmologist is often called upon to determine if a uveal melanocytic lesion is benign (nevus) or malignant (melanoma). At the extremes, when lesions are either very small or very large, the diagnosis of nevus or melanoma (respectively) is straightforward. However, it can be difficult to differentiate a small melanoma from a large or an atypical nevus. In this indeterminate range, there are certain ophthalmoscopic and imaging features that are associated with subsequent growth, serving as indicators that a particular lesion represents a small melanoma rather than a nevus.

Analogous to the ABCDEs of cutaneous melanoma, ophthalmologists look for specific clinical features that portend a higher risk of malignancy and active growth. These high-risk clinical features are remembered by the mnemonic, "To Find Small Ocular Melanomas Using Helpful Hints" (TFSOMUHH) [92, 116–118]. These features are used to distinguish benign uveal nevi from small melanomas and include

- T—Tumor **T**hickness >2 mm
- F—Subretinal **F**luid
- S—**S**ymptoms
- O—**O**range pigment
- M—**M**argin of tumor within 3 mm of the optic disc
- UH—**U**ltrasound **H**ollowness
- H—*Absence* of **H**alo

Although not included in the mnemonic, the *absence* of yellow drusen deposits (a sign of chronicity) is also a risk factor for growth.

The median hazards ratio for lesions with 1–2 of the above features is 3; for 3–4 features is 5; for 5–6 features is 9; and for all 7 features is 21 [92, 116–118]. It is important to note that *the presence of three or more of the above features conveys a >50% risk of active growth* (i.e., melanoma).

Small uveal melanomas are defined as 3 mm or less in diameter, with this cutoff chosen based upon calculations of tumor doubling time and the associated likelihood of metastatic conversion. Despite the classification as "small," these tumors still portend a very real risk for metastasis and mortality for the patient. For example, it has been theorized that the average size of uveal melanoma at the time of metastasis is 3 mm in basal diameter and 1.5 mm in thickness (a small melanoma) [119, 120]. Furthermore, it is estimated that micrometastatic seeds have already developed approximately 5 years prior to the initial diagnosis or treatment of the primary melanoma [119]. On the other hand, small nevi have a <1% chance for malignant transformation and pose minimal risk for vision loss or death [121]. Thus, it is imperative for the ophthalmologist to scrutinize each choroidal nevus for the presence of any high-risk features that may suggest a diagnosis of uveal melanoma over nevus [81].

Clinical features that are more consistent with a benign choroidal nevus include the presence of drusen (yellow subretinal deposits of lipids and proteins), RPE changes, and presence of a hypopigmented halo surrounding the lesion (Fig. 16.8). These features represent secondary signs of chronicity. When drusen, a halo, or RPE changes are associated with a melanocytic lesion less than

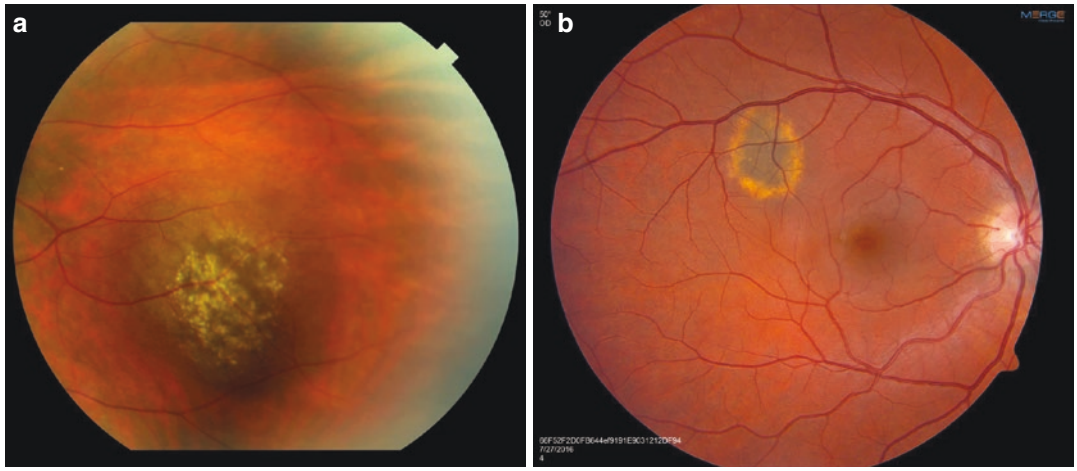

Fig. 16.8 Benign choroidal nevi. (**a**) Benign nevus with overlying yellow drusen and lack of other high-risk malignant features. (**b**) Benign choroidal nevus of the superior macula with a reassuring halo, suggesting a diagnosis of nevus rather than melanoma

3 mm in thickness, it can generally be assumed that the lesion has been present for years without significant growth, strongly supporting a diagnosis of benign nevus. However, nevus malignant transformation is still possible in the future. Therefore, these lesions must be monitored over time for any changes in appearance, presence of any TFSOMUHH features, or any documented growth in dimensions [92, 116–118].

It is important to remember that the *sine qua non* of uveal melanoma malignant transformation is increasing basal diameter or apical height observed over serial measurements. It is recommended, and considered the standard of practice, to follow patients with uveal nevi regularly, typically reexamining small nevi every 6 months initially, followed annually afterwards if the lesion remains stable. Monitoring must be performed by a qualified eye care provider for life [31]. The authors have treated patients who experienced obvious evidence of tumor growth and malignant transformation of uveal melanocytic lesions that had previously been stable over the course of >26 years of observation (including photographic evidence of stability going back several decades). Thus, it must be impressed upon patients the importance of continued monitoring even of those lesions that have been stable for a long time.

Clinical and Histopathologic Characteristics Associated with an Increased Risk of Metastasis

Uveal melanoma location, size, histopathology, and genetics have all been shown to impact risk for metastasis and patient survival [87]. Tumor location and size are readily evaluated in the outpatient clinical setting with tumor histopathology and genetic evaluation both requiring surgical biopsy in the operating room. In this section, we discuss how tumor size, location, and histopathology relate to patient prognosis. The genetics of uveal melanoma and how it relates to prognosis will be discussed later in this chapter.

Tumor Location

Ciliary body involvement of uveal melanoma is a clinical feature associated with a poorer prognosis when compared to iris or choroidal location. Relative to iris and choroid locations, ciliary body involvement has been associated with accelerated growth and an increased risk for development of metastasis within the first 3 years after diagnosis. However, the risk for metastasis after 3 years diminishes to that equal of tumors without ciliary body involvement [49, 122–124].

It is thought that contraction of the ciliary body muscles leads to increased mechanical progression of tumor cells through the adjacent ciliary blood vessels. However, anterior tumors (i.e., tumors involving the ciliary body) typically are not discovered until they are large enough to become symptomatic. It is plausible that ciliary body location may be a surrogate for late disease presentation, explaining the observed increased metastatic risk [87, 123].

On the other hand, iris melanomas have a much lower rate of metastasis when compared to their choroidal and ciliary body counterparts [124]. As previously discussed, these tumors are often easily visible to the naked eye, and are picked up early both by physicians and by patients themselves. Thus, this earlier detection may be at least partly responsible for the lower rate of metastasis [124].

Tumor Size

When ophthalmologists discuss uveal melanomas, they describe them in terms of relative sizes, such as small, medium, and large. As defined by the Collaborative Ocular Melanoma Study (COMS) [118, 125–128], these sizes are standardized, and convey increasingly higher risk for metastasis and mortality with increasing size.

- Small uveal melanomas: <3 mm height, <10 mm diameter
- Medium uveal melanomas: 3–8 mm height, <16 mm diameter
- Large uveal melanomas: >8 mm height or >15 mm diameter

Increasing basal diameter and thickness are risk factors associated with increased metastasis and mortality, even after treatment with enucleation [129, 130]. As tumor thickness increases, so does the 3-, 5-, and 10-year mortality rate [93]. Since this is true even among eyes that underwent enucleation, this observation obviates the question as to whether metastasis occurred in the setting of unsuccessful local therapy, given that enucleation always achieves local tumor control (except in cases of extraocular extension of tumor at presentation).

High-Metastatic-Risk Histopathologic Features of Uveal Melanoma

There are three main histopathologic features associated with a poorer prognosis for patients with uveal melanoma: higher proportion of epithelioid cells, higher mitotic activity, and presence of closed vascular loops. Uveal melanomas arise from uveal melanocytes and are comprised of two major cell types, spindle-shaped cells and epithelioid cells (or a mixture of both spindle and epithelioid cells). On histopathologic evaluation, an increasing proportion of epithelioid-type cells is associated with a progressively worse prognosis [124]. This proportion is calculated by counting the number of epithelioid cells per high-power field [87], with the 10-year mortality of 5× higher in patients with >0.5 epithelioid cells per high-power field [123].

High mitotic activity is another histopathological feature associated with higher rates of metastasis and mortality for patients with uveal melanoma. Mitotic activity is measured by the number of mitotic cells seen per high-power field. In a study of 217 uveal melanomas, McLean and colleagues found that mitotic activity was a prognostic feature that is independent of tumor size. McLean's group also found that the 6-year mortality rate was 3.6-fold higher with uveal melanoma demonstrating high mitotic activity compared to those with low activity [131].

The third major high-risk histopathologic feature of uveal melanoma is the presence of closed vascular loops. These loops represent the intrinsic dual-vascular circulation of uveal melanomas. The presence of these closed vascular loops has been shown to correlate with a markedly reduced overall patient survival from 90 to 50%, even after treatment [109].

It is important to note that all three of the preceding findings can only be readily discerned if the eye is enucleated, whereas the vast majority of eyes are treated with globe-conserving therapies.

Fine-Needle Aspiration Biopsy of Uveal Melanoma

Uveal melanoma biopsies are performed using fine-needle aspiration (FNA), as excisional biopsy is often not possible without blinding the patient or removing the eye completely. While endoresection has been reported either as primary therapy or in conjunction with radiotherapy, it is not currently standard-of-care treatment for posterior (ciliary body or choroidal) uveal melanoma. It should be stressed that FNA biopsies require a skilled and experienced vitreoretinal or ocular oncology specialist in collaboration with an experienced cytopathologist. The major role of FNA biopsy of uveal melanomas is for prognostication, and is rarely required for the purpose of making the correct diagnosis.

As previously discussed, the diagnosis of uveal melanoma is ultimately a clinical one, based upon the physical examination and clinical judgment of as-experienced ophthalmologist. In fact, the COMS reported a >99% diagnostic accuracy for patients who had the typical high-risk features of uveal melanoma [118, 132, 133]. Furthermore, FNA biopsy is of limited utility in differentiating melanoma from a nevus, as even melanoma cells can have benign-appearing nuclear morphology [134, 135]. Even in the hands of very experienced ocular cytopathologists, FNA biopsies may not be able to unequivocally differentiate benign nevus from melanoma [135, 136]. However, there may be rare situations in which the diagnosis is uncertain and diagnostic biopsies may be helpful, such as with amelanotic lesions without typical melanoma features, within eyes that have media opacity (such as vitreous hemorrhage) or in differentiating between a primary choroidal melanoma versus a metastasis [134, 136, 137]. Studies have shown that diagnostic biopsy with FNA can be safely used to assist in the diagnosis of iris melanoma in small suspicious melanocytic lesions. In 100 consecutive biopsies with FNA, Shields et al. demonstrated that an adequate sample could be obtained with minimal complications in 99% of cases [138].

Biopsy with FNA plays a much more significant role in prognostication. While FNA is rarely performed for diagnostic purposes, it is very commonly performed to obtain genetic material to aid with patient metastatic stratification and prognosis. Prognostic biopsies are useful for assessing high-risk genetic features and obtaining a specific gene expression profile (GEP) on uveal melanoma [139–141]. Uveal melanoma genetics and its relation to tumor behavior and prognosis are discussed in further detail later in this chapter.

Staging of Uveal Melanomas

During the evaluation of uveal melanoma, the ophthalmologist may use clinical features to stage the tumor and provide prognostic data for patients. However, molecular analysis of the tumor has largely surpassed and replaced the prognostication based upon clinical features alone. In general, staging is performed using the COMS staging criteria, which divides tumors into small, medium, and large categories (see previous section on Clinical and Histopathology Characteristics Associated with Metastatic Uveal Melanoma). Additionally, as with cutaneous melanomas, the American Joint Commission on Cancer (AJCC) has specific staging criteria for uveal melanoma as well [142].

AJCC Staging of Uveal Melanomas

The AJCC uses clinical (rather than genetic) characteristics to classify ciliary body and choroidal melanomas on a T1 through T4 grading scale, based on tumor basal diameter, thickness, involvement of ciliary body, and degree of extraocular extension [142–145]. For iris melanoma, the AJCC staging includes specific criteria based on tumor size, location, clock hours of iris involvement, extension into the ciliary body or choroid, features of secondary glaucoma, and extraocular extension [142, 145]. Shields et al. conducted a retrospective review of 7731 patients with posterior uveal melanoma and found that

patients had a twofold increase in risk for both metastasis and death with each increase in AJCC classification from T1 through T4 [143]. While the AJCC system has been shown to be predictive, the COMS classification system is more widely used.

Systemic Evaluation

The overall long-term metastatic rate for primary uveal melanoma is ~50%, with a 15-year mortality rate that is similar at about 50% [85, 86, 146]. Thus, the systemic evaluation of uveal melanoma is directed primarily at detecting metastatic disease. Unlike cutaneous melanoma, metastatic spread of uveal melanoma is hematogenous, involving the liver in more than 90% of cases, with the second most common site of metastasis being the lungs [5, 16, 125–127, 130, 147]. Central nervous system (CNS) metastasis from uveal melanoma is extraordinarily rare, to the point that the brain is not even included in standard staging imaging. Systemic evaluation for metastatic disease includes measuring serum transaminases (AST, ALT, and GGT) to evaluate for hepatocyte structural compromise that may result from liver metastases, as well as liver ultrasonography, CT, or MRI [148]. Chest plain-film radiographs (CXR) have a poor sensitivity and are rarely able to demonstrate lung metastases without liver involvement seen first [148].

Monitoring for metastatic spread is highly individualized and based on a patient's metastatic risk. Patients with GEP Class 1B or Class 2 uveal melanomas (i.e., tumors with relatively higher metastatic risk) are generally monitored every 6 months with multiphasic contrasted CT of the abdomen, with or without CT imaging of the chest. Patients with GEP Class 1A tumors are typically monitored less frequently with CT imaging, or are monitored at the same 6-month interval but without radiation-based imaging modalities (such as with liver ultrasonography).

This is primarily due to the desire to balance the benefit of surveillance imaging with the risk of additional repeat radiation exposure in the setting of lower risk GEP Class 1A uveal melanomas [87]. There is some data on the use of serum monoclonal antibody screening with melanoma-associated antigen (MAA). However, there are no studies that definitively support the clinical utility of serum MAA in detecting subclinical metastases [149].

Treatment of Primary Uveal Melanoma

Historically, all uveal melanomas were treated by removing the entire eye (a procedure called enucleation). Enucleation was performed in order to remove the tumor *in toto* in an attempt to prevent metastatic spread and death. This traditional treatment paradigm was challenged in the 1970s by Zimmerman et al., who theorized that surgical enucleation may actually worsen prognosis by physically promoting liberation of tumor cells and hematogenous dissemination during the act of enucleating the eye. Thus, the "Zimmerman hypothesis" was born, emphasizing the concern that traditional enucleation may increase rates of metastasis [150, 151].

Inspired by Zimmerman's provocative challenge to the traditional standard of treatment, the multicenter COMS investigational group was formed, and ultimately disproved Zimmerman's theory [125, 130, 147, 152]. Furthermore, the COMS showed that enucleation of the eye had no benefit over conservative eye-preserving radiotherapy in relation to metastatic rate and mortality for small- and medium-sized melanomas. In fact, radiotherapy maintained the same metastatic and mortality rate as enucleation for these tumors while adding the benefit of significantly reduced morbidity and preservation of vision over enucleation [118, 125–128, 130, 147].

As a result of the COMS, the treatment paradigm has shifted from enucleation to preservation of both the eye and maintained vision through the use of focal radiotherapy whenever possible. Today, radioactive plaque brachytherapy is the most commonly used treatment for COMS small- and medium-size tumors. Enucleation is now reserved for COMS large-size tumors not amenable to radiotherapy, where

radiotherapy would lead to excessive ocular and adnexal morbidity and significant vision loss. Furthermore, enucleation is also reserved as a secondary treatment for tumors that recur following initial treatment with radiotherapy, or for eyes that have become blind and painful from neovascular glaucoma or other complications after radiotherapy [2, 4, 5, 87].

Treatment of Ciliary Body and Choroidal Melanomas

Radioactive Plaque Brachytherapy

Radioactive plaque brachytherapy remains the most commonly used treatment for ciliary body and choroidal melanomas <10 mm in apical height [2, 4, 5]. The prefix "brachy" is derived from the Greek word meaning "short range." Therefore, the moniker "brachytherapy" refers to the short distance between the source of radiation and the target treatment tissue. Brachytherapy for uveal melanoma consists of placing radioactive isotopes (most commonly iodine-125 (^{125}I), ruthenium-106 (^{106}Ru), and palladium-103 (^{103}Pd)) [4, 153] that release ionizing X-ray radiation that is then absorbed by the nearby tissues, breaking DNA bonds and leading to tumor cell death. Presently, in the United States, the most common radioactive brachytherapy plaques for uveal melanoma use ^{125}I, while ^{106}Ru is popular in Europe [154].

Radioactive plaque brachytherapy is performed in the operating room with the patient under general anesthesia (Fig. 16.7). An incision is created in the conjunctiva (called a peritomy) that overlies the ciliary body or choroidal melanoma. The eye is then rotated and a light is shined into the eye through the pupil. This creates transillumination of the sclera from the light inside the eye, with the tumor casting a shadow on the sclera. This shadow is then marked on the scleral surface, delineating the borders of the tumor. In some small or lightly pigmented tumors, the borders may be better delineated using binocular indirect ophthalmoscopy with scleral indentation and marking by the surgeon.

Once the tumor's base is outlined on the scleral surface, a clear-centered plaque is centered over the marked borders, to ensure that the actual radioactive plaque will fit appropriately and adequately. This plaque has the same dimensions and the same eyelet positions as the radioactive plaque, and appropriate eyelet locations are marked on the scleral surface. Sutures are preplaced at these eyelet markings. A nonradioactive "dummy" plaque is then temporarily sutured into position using these pre-placed eyelet sutures. Intraoperative ultrasonography can be used to ensure that the plaque is centered and completely covers the intended treatment area of the tumor. The dummy plaque is then removed and replaced by the radioactive plaque and intraoperative ultrasonography is again used to ensure appropriate plaque placement with adequate tumor coverage (Fig. 16.7).

The use of intraoperative ultrasonography has been shown to improve plaque placement rates and to reduce treatment failure rates from geographic miss to near 0% [4, 155]. Furthermore, the use of a nonradioactive "dummy" plaque for the initial tumor localization reduces the overall radiation exposure to the surgeon, as any adjustments to plaque location can be made with the nonradioactive "dummy" plaque [156]. Most radioactive brachytherapy plaques are designed to emit focal low levels of radiation at a rate of 0.6–1.2 Gy/h over a period of 5–7 days [153]. A team-based approach is key for the successful treatment and dose planning for the patient. The most appropriate dose rate should be based on the detailed evaluation and collaboration of both the ocular oncologist and radiation oncologist [157]. Plaque brachytherapy is best suited for the treatment of COMS small- to medium-sized melanomas, but can lead to scleral melt and necrosis when used for thicker tumors. This is because of the higher radiation dose exposed to the scleral bed of larger melanomas. Other radiation modalities should be considered for larger tumors [3, 4].

The advantage of treating with plaque brachytherapy is that the plaques can be made in a variety of shapes and sizes to fit varying tumors and tumor locations, such as notched plaques used for tumors adjacent to the optic nerve. The therapeutic advantage of plaque brachytherapy is that the radiation dose distribution follows an inverse

square law with the radiation dose dropping off exponentially with increasing distance from the plaque. This means that ocular and adnexal structures farther away from the melanoma will receive exponentially less radiation than the target melanoma. Another therapeutic advantage is that the gold plaque shell shields the orbit and adjacent ocular tissue from unwanted exposure to radiation [4, 158].

Charged Particle Therapy

Particle beam radiation therapy (PBT) is an effective treatment option for primary uveal melanomas, and is sometimes referred to as external beam particle therapy (EBPT). Both protons and charged helium ions have been used in the treatment for uveal melanoma, with proton beam being the most widely studied and widely used charged particle [159–165]. The biologic effect of protons and helium ions does not significantly differ from that of the X-rays emitted with radioactive brachytherapy. Similar to brachytherapy, charged particles interact with the planetary electrons of target tissues, causing electron excitation and ionization of atoms within the tumor. Additionally, protons interact with atomic nuclei, dislodging other heavy particles that then go on to incite additional therapeutic damage to adjacent tumor cells. The ultimate target is tumor DNA molecules, leading to DNA damage and strand break, followed by mitotic crisis and apoptosis.

Proton beam radiotherapy is more useful than traditional external beam radiotherapy for uveal melanomas, requiring more precise localization of radiation to the target area. This is especially true with tumors located adjacent to critical structures that require sparing of radiation. Proton beam therapy takes advantage of a phenomenon known as the Bragg peak effect, which allows for high-radiation dose deposition within the targeted melanoma, followed by abruptly diminishing dosages directly behind the tumor, limiting unwanted radiation to posterior tissues such as the brain. Therefore, PBT is a useful alternative to brachytherapy for treating tumors that would otherwise be difficult to treat with plaques, such as melanomas abutting or surrounding the optic nerve [154, 158, 166].

Prior to irradiation with charged particles, the patient is taken to the operating room where the globe is transilluminated and the tumor borders are marked on the scleral surface. Next, nonferromagnetic tantalum clips are sewn to the sclera over the surface markings, delineating the borders of the base of the tumor. This serves to outline the base of the tumor and localize the target treatment zone. Next, the patient is taken to the cyclotron (the source of the charged particles) and the beam is aimed at the patient's eye in line with the tumor. For most uveal melanomas, the patient is typically given 50–70 cobalt gray equivalents (CGE) divided into five fractions [4, 167].

The major limitation of charged particle therapy with proton beam is the cost associated with creating centers with cyclotrons capable of delivering this treatment. As a result, these treatment centers are rare and the patient cost for this therapy can be prohibitive. Proton therapy has not been widely adopted because of these reasons and because there is a lack of evidence to demonstrate an advantage of PBT over more cost-effective treatments such as plaque brachytherapy for uveal melanoma [4].

External Beam Radiotherapy

External beam radiotherapy (EBRT) refers to the use of an external source to create photons of ionizing X-rays or gamma rays that are then focused and directed at the target tissue. The external source for EBRT is most often a linear accelerator. For the treatment of uveal melanoma, the main form of EBRT in use today is stereotactic radiosurgery (SRS), which is a technique that most often refers to high-precision, gamma-based or X-ray-based photon therapy. SRS occurs with the patient inside a CT scanner and utilizes 3-dimensional tumor localization, with radiation beams cross-firing from multiple directions precisely onto the targeted tumor. The high degree of precision allows for the delivery of very high doses of radiation to the tumor with minimal collateral damage to noninvolved adjacent ocular tissues.

Traditionally, EBRT is performed by first immobilizing (paralyzing) the treatment eye with retrobulbar anesthesia. Sometimes the eye is

further immobilized by placing horizontal rectus muscle stay sutures to firmly position the eye in a specific orientation. Alternatively, a fixation point target can be provided, with patients instructed to maintain fixation on this target, thus "immobilizing" their own eye. A stereotactic frame is then applied to the patient's head and MRI or CT imaging is utilized with the head frame to precisely localize the tumor within the eye. The head frame also serves to immobilize the patient's head.

While the patient's head and eye are adequately immobilized, radiation is then precisely delivered to the tumor, either as a single dose or with fractionation. SRS is useful for patients with large melanomas who do not want enucleation, although it has been used for small- medium-sized melanomas as well [168]. It can also be useful for posterior uveal melanoma or melanomas that are adjacent to the optic nerve, similar to the advantage of charged particle irradiation. Thus, SRS may be capable of treating certain tumors for which brachytherapy treatment may not be possible, or in which brachytherapy may give too large a dose to the scleral bed [4]. Studies have shown that gamma-based SRS does not compromise survival when compared to enucleation [169]. However, there is no proven survival benefit to any one radiotherapy technique over the others [170–173].

Transpupillary Thermotherapy

Transpupillary thermotherapy (TTT) is a noninvasive treatment modality that utilizes infrared diode laser light at a wavelength of 810 nm, shined through a dilated pupil onto the choroidal melanoma. As the laser light is absorbed by the pigmented tumor cells, the temperature of the tumor increases to 45–60°F, causing thermal obliteration of the tumor's vascular supply and subsequent tumor necrosis [174]. TTT is limited to the treatment of only COMS small-sized choroidal melanomas, as TTT only penetrates to a maximum depth of 4 mm [174]. TTT is most efficacious when used with heavily pigmented small tumors, as the absorption of the diode laser increases with increasing pigmentation. Conversely, TTT is not a good choice for treatment of medium- to large-sized tumors or amelanotic tumors. However, for small heavily pigmented choroidal tumors, TTT has the benefit of causing immediate tumor necrosis with less damage to surrounding normal ocular tissues compared to methods of radiotherapy [174]. However, TTT alone has fallen out of favor as a primary treatment for uveal melanoma. The majority of the time, TTT is used as an adjuvant to consolidate treatment at the tumor edges following radiotherapy.

Treatment of Primary Iris Melanomas

Small (<3 mm basal diameter) iris melanocytic lesions suspicious for nevus vs. melanoma in an otherwise asymptomatic patient can be monitored for growth with periodic slit lamp exams and photography. However, once there is documented growth, these lesions are presumed to be melanoma and require urgent treatment with either radioactive plaque brachytherapy or PBT. Surgical excision may be utilized in very select cases. Enucleation is rarely used for iris melanomas and is reserved for special cases of large diffuse iris melanomas in eyes with poor vision potential or in cases with recurrence of melanoma [33, 88].

Radiotherapy for Iris Melanomas

Radioactive plaque brachytherapy and PBT are the current preferred treatment modalities for iris melanomas. These modalities provide the greatest relative benefit over surgical excision in tumors with extensive tumor seeding and in nonresectable iris tumors. Both plaque brachytherapy and PBT have been shown to achieve local control in 92% of cases [175–177]. For a detailed discussion on plaque brachytherapy and PBT see the section above on the treatment of ciliary body and choroidal melanomas.

Surgical Excision of Iris Melanomas

While surgical excision of choroidal melanomas is generally not possible without blinding or enucleating the eye, there is a limited role for the excision of melanomas localized to the iris. For these tumors, surgical excision involves removal

of the entire tumor by removing the part of the iris (partial iridectomy) housing the tumor. If the iris melanoma also involves the anterior chamber angle, then the surgeon must remove a portion of the trabecular meshwork as well (iridotrabeculectomy). For iris melanomas with ciliary body extension, a portion of the iris and ciliary body must be removed at the time of tumor excision (iridocyclectomy) [88, 112]. Because these are large and invasive procedures that sometimes are associated with high ocular morbidity, radiotherapy has now become the primary treatment modality in most cases.

Control Rates for Treatment of Primary Uveal Melanoma

Radioactive Plaque Brachytherapy

Local control rates for radioactive plaque brachytherapy are excellent, with rates that approach 90–95% [160, 178, 179]. The Mayo Clinic has published data on its control rates and complication rates with the use of ^{125}I plaque brachytherapy, demonstrating a favorable recurrence rate of 8% and a posttreatment enucleation rate of 8%. It also demonstrated that 22% of patients maintained a visual acuity of better than 20/40 after brachytherapy [180].

Charged Particle Therapy

Proton beam therapy has shown similarly favorable results as brachytherapy, with recurrence rates of 2–4% and secondary enucleation rates of 7–11%. Additionally, up to 44% of patients treated with PBT have been shown to maintain visual acuity of better than 20/40 [159, 164, 172, 181–183]. The Curie Institute-Orsay Proton Therapy Center has published its data from more than 20 years of experience treating uveal melanomas with PBT. It has shown a 5-year survival rate of 99%, a 5-year metastatic-free survival rate of 81%, and a 5-year overall survival rate of 79% [159]. There are other smaller studies that have demonstrated similar results, confirming that PBT does not compromise patient survival when compared to enucleation [184, 185].

External Beam Radiotherapy

Study results for the control rates of EBRT have also been similar to those of brachytherapy and PBT. EBRT has demonstrated a 5-year uveal melanoma control rate of 94% and a secondary enucleation rate of 2.4–14%, with 14–33% of patients maintaining a visual acuity of better than 20/200 [168, 171, 186–188]. Other smaller studies have corroborated these results [169, 189–191].

Transpupillary Thermotherapy

Recurrence of choroidal melanoma after treatment with TTT ranges from 9 to 12%, with a direct correlation between tumor recurrence and number of high-risk features present (i.e., features predictive of tumor growth—TFSOMUHH) [174, 192]. Therefore, TTT is less preferable for tumors having multiple high-risk characteristics of the TFSOMUHH. TTT is best used as an adjuvant treatment to enhance local control after plaque brachytherapy. There is no difference in visual acuity outcomes with adjuvant TTT compared to brachytherapy alone [193].

Side Effects and Complications of Treatment

Radiotherapy and Charged Particle Therapy

The acute side effects of all radiotherapy modalities, including radioactive plaque brachytherapy, charged particle therapy, and various forms of EBRT, result in acute local intraocular inflammation and irritation of the conjunctiva and sclera. Acute inflammation is short-lived and less concerning than the long-term side effects. The most significant side effects from radiation therapy are typically delayed and increase over time after treatment. The most common delayed side effects

include radiation-induced retinopathy, choroidopathy, optic neuropathy, retinal neovascularization, intraretinal microangiopathy, chorioretinal atrophy, vitreous hemorrhage, cataract formation, iris neovascularization, and neovascular glaucoma, and symptomatic dry eyes (keratoconjunctivitis sicca). Less common side effects of radiotherapy include retinal detachment and scleral melt [165, 178, 179, 194, 195]. Development of secondary malignancy after treatment with radiotherapy is extremely rare with all these modalities. This is due to the sparing of unnecessary radiation exposure to the surrounding healthy ocular and adnexal tissues. The most common cause of vision loss after radiotherapy for uveal melanoma is radiation retinopathy and optic neuropathy, which both progressively worsen over time after treatment. The most common side effect necessitating enucleation after radiotherapy is neovascular glaucoma [154, 159].

Transpupillary Thermotherapy

Although it is the least invasive treatment modality, TTT is not without its own unique side effects and complications. The most common side effects of TTT include development of vitreoretinal traction (44% of cases), branch retinal vein occlusion (26–41% of cases), branch retinal artery occlusion (12% of cases), cystoid macular edema (9–23% of cases), epiretinal membrane (23% of cases), and vitreous hemorrhage (10% of cases). Other rare long-term complications include retinal neovascularization, chorioretinal scarring, retinal detachment, optic nerve atrophy, optic disc edema, and cataract formation [174, 192]. In addition, since TTT destroys the overlying retina, treatment of macular or juxtapapillary tumors can lead to immediate vision loss.

Prognostic Characteristics and Genetic Testing

Because metastatic disease carries a very high risk of mortality for patients with primary uveal melanoma [130], there has been a significant amount of effort directed towards elucidating the clinicopathologic features that are most closely associated with the overall risk of metastasis. As previously discussed, clinicopathologic characteristics were traditionally used to classify uveal melanomas into high- and low-risk categories for development of metastatic disease and death. However, chromosomal analysis and genetic testing have proven to be much more reliable prognostic tools and are the mainstay of prognostic classification at the present time.

Chromosomal Abnormalities

Uveal melanoma is associated with several genetic and epigenetic derangements that are tightly linked to the risk for metastasis and patient mortality. Chromosomal anomalies that provide prognostic value for patients with uveal melanoma include derangements of chromosomes 1, 3, 6, and 8 [45–47]. A gain in chromosome 6p is associated with a relatively good prognosis compared to other chromosomal derangements. The chromosomal anomalies shown to be strongly linked to poorer prognosis (increased mortality from uveal melanoma) include loss of chromosome 3, loss of chromosome 1p, and gain of chromosome 8q. Complete or partial loss of chromosome 3 is the most significant prognostic alteration in uveal melanoma, with monosomy 3 being highly associated with a significantly increased risk for metastatic disease and decreased patient survival [45, 47, 139, 140, 196, 197].

The presence of chromosome 3 loss or 8q gain each correlates with high-risk clinicopathologic features, including increasing tumor basal diameter, ciliary body involvement, presence of epithelioid cell type, high mitotic index, and closed vascular loops [198]. The presence of either chromosome 1p loss or 8q gain in combination with loss of chromosome 3 has an additive effect on the risk of metastasis and death. Specifically, a large study by Damato et al. demonstrated that the 10-year disease-specific mortality for uveal melanomas was 0% for melanomas without chromosome 3 loss, 55% for melanomas having

chromosome 3 loss without 8q gain, and 71% for melanomas with concurrent chromosome 3 loss and 8q gain [198].

These chromosomal derangements were initially discovered using standard karyotyping methods [47] and have been validated by other genetic studies, including gene expression profiling (GEP) and multiplex ligation-dependent probe amplification (MLPA), among others. GEP and MLPA are quick and inexpensive commercially available tests that have become the gold standard of prognostication for uveal melanoma, used to reliably and accurately stratify patients into groups of low and high risk for metastasis and death [45, 140, 198].

Gene Expression Profiling

Gene expression profiling (GEP) is a technique that allows for the measurement of the activity of thousands of genes at once, allowing the clinician to discern the global transcriptome of the sample tissue. GEP can be used for rapid detection of the up- or downregulation of select genes. It can be performed even on a very tiny amount of tumor tissue obtained via FNA biopsies. Once the tumor sample is obtained, mRNA is then converted to cDNA and subsequently hybridized to gene chips. Microarray analysis is then performed using these gene chips to quantify the relative upregulation or downregulation of specific genes. For uveal melanomas, tissue samples are typically obtained by FNA biopsy at the time of radioactive brachytherapy plaque placement or immediately after enucleation of the eye [44].

GEP for uveal melanoma was first introduced by Harbour et al. in 2004 and has since been shown to accurately and reliably classify uveal melanomas into two distinct classes (Class 1 and Class 2) with tremendous prognostic utility in accurately predicting metastatic risk and patient mortality [139, 199]. The current technique for GEP of uveal melanoma has evolved into a 15-gene PCR-based assay that reliably segregates tumors into relatively good and poor prognostic classes. The present GEP assay quantifies the expression patterns of 12 class-discriminating genes and 3 control genes. This assay has been validated in a large multicenter prospective clinical trial, correctly classifying uveal melanomas in 97.2% of cases [199]. GEP testing is presently commercially available, providing the treating physician with accurate prognostic information regarding the patient's risk for metastasis and mortality [63, 140].

GEP Class 1 tumors have a low metastatic risk and are associated with gains in chromosome 6p and 8q. These tumor cells closely resemble normal uveal melanocytes or low-grade uveal melanomas and are further subdivided into GEP Class 1A and Class 1B, with Class 1A carrying a 0–2% 5-year metastatic risk and Class 2B carrying a 21% 5-year risk for metastasis. GEP Class 2B tumors also carry an additional increased risk of developing late metastases [63, 78, 139, 200].

GEP Class 2 uveal melanomas resemble primitive stem cells and represent higher grade uveal melanomas. They have more aneuploidy and are most often associated with the loss of chromosome 3, chromosome 1p, and chromosome 8p. These tumors are strongly associated with inactivating mutations of *BAP1*, located on chromosome 3p21. GEP Class 2 melanomas are considered to be very-high-risk tumors, carrying a 72% 5-year risk for metastasis [63, 200].

A limitation of GEP is the potential for limited classification accuracy in small uveal melanomas, which may have genetic heterogeneity within the tumor itself. Augsburger et al. demonstrated a discordance of GEP classification in 11.3% of tumors when biopsy sampling was performed at different sites within a single tumor. They also showed a correlation between tumor height and degree of GEP discordance. Thicker tumors tended to show less discordance, compared to a higher level of intratumoral heterogeneity in thinner tumors. This study demonstrated the risk of prognostic misclassification if GEP is performed on a single-site FNA biopsy. Augsburger et al. suggested considering GEP testing on two separate biopsy sites to reduce this risk [201].

Preferentially Expressed Antigen in Melanoma

To further increase the prognostic accuracy of GEP, a genome-wide analysis was performed, to identify other biomarkers that were altered in patients with uveal melanoma. In this effort, Field et al. discovered that mRNA expression of the cancer-testis antigen, preferentially expressed antigen in melanoma (PRAME), was a biomarker for metastasis of uveal melanoma, independent of either GEP Class 1 or GEP Class 2 profiles [202]. The mechanism by which PRAME expression relates to uveal melanoma progression to metastatic disease is not fully understood. PRAME testing for uveal melanoma is commercially available in conjunction with standard GEP testing.

Multiplex Ligation-Dependent Probe Amplification

Multiplex ligation-dependent probe amplification (MLPA) was first described in 2002 by Schouten et al. as a novel technique with the ability to detect relative quantities of up to 40 different DNA sequences within a single test [203]. With this technique, uveal melanoma DNA is obtained from FNA biopsy, denatured, and then mixed with DNA probes that target specific select genes on chromosomes 1p, 3, 6, and 8. The probes then hybridize to the target DNA sequence, and are amplified using PCR. Lastly, the amplified selected sequences are separated and identified by electrophoresis. The separated products are then quantified to determine the relative expression of each gene product [203, 204].

In 2007, Coupland and colleagues at the Liverpool Ocular Oncology Centre created a novel technique for assessing known chromosomal derangements in uveal melanomas. Coupland's group replaced traditional FISH testing for uveal melanoma with an MLPA reaction that targeted 38 loci across chromosomes 1p, 3, 6, and 8 [45, 204]. Using this novel technique, their group was able to show that MLPA can detect gain or loss of a much larger number of multiple chromosome segments (as many as 50 targets) in one single reaction, and with higher resolution than traditional FISH [203, 204]. Unlike GEP, which is marketed as a stand-alone assay for uveal melanoma prognostication, MLPA is intended to be used in conjunction with other uveal melanoma clinical and clinicopathologic features to provide prognostic utility. In this way, MLPA has been shown to provide similar prognostic accuracy as GEP. MLPA is also presently commercially available [198].

Use of Clinicopathologic Features with Genetic Tests

As previously mentioned, clinicopathologic features alone were traditionally used to stratify patients into high and low risk for metastatic disease and disease-related death. Recently, however, modern genetic and molecular testing techniques (such as GEP and MLPA) have proven to be far superior to clinicopathologic features alone in predicting metastasis and mortality [45, 140, 198, 202, 204, 205]. Still, there is data supporting the role of clinicopathologic features in conjunction with MLPA to improve prognostic accuracy and reliability, and therefore there is a nomogram for predicting metastasis which includes both MLPA and clinical tumor characteristics. In addition, there is recent evidence to suggest that there may be utility in combining tumor characteristics such as largest basal diameter with GEP results to improve prognostic accuracy [141, 198].

Uveal Melanoma Metastases

Unlike metastatic spread of melanomas of the skin, conjunctiva, and eyelids, which is primarily lymphatic, metastatic spread of primary uveal melanoma is hematogenous with a strong predilection for the liver. Once metastatic disease develops, it is uniformly fatal, with a 1-year survival rate of 13% and a 5-year survival rate

approaching 0% (mean survival is ~6 months) [16, 206–209]. The most common sites for metastasis are the liver (91%), lung (26%), bone (18%), skin (12%), and lymph nodes (11%). Uveal melanoma does not metastasize to the brain, except for the rare, late-stage presentation of direct extension of the primary to the brain via the optic nerve, or perhaps in very rare patients with widespread metastatic disease [86, 126]. Thus, the presence of brain melanoma metastases from an unknown primary source should not routinely necessitate a dilated ophthalmologic examination to rule out uveal melanoma. Furthermore, patients with a history of primary uveal melanoma who later develop brain melanoma metastases should be evaluated for a second primary melanoma outside the eye that might be the origin of the brain metastasis.

As previously discussed, the overall long-term rate of metastasis for primary uveal melanoma is ~50%, and results in a 15-year mortality rate that approaches 40–50% [85, 86, 146]. Despite significant advances in the treatment of primary uveal melanoma with good local tumor control rates, the 5-year survival rate remains 72–84% [5, 206, 208, 210]. This observed reduced 5-year survival is largely the result of the high rate of metastasis, even despite successful treatment of the primary. For example, although rates of local ocular tumor control exceed 90% with radiotherapy, approximately half of these treated patients will develop metastases extending out to decades following the initial diagnosis [16, 208, 211]. This trend is observed even in patients who receive early treatment with enucleation (complete removal of the eye and tumor) and is presumably due to the presence of previously disseminated micrometastatic disease at the time of treatment for the primary intraocular tumor [87, 212].

Uveal melanoma is a disease that affects primarily older aged individuals who, because of their advanced age, likely have other numerous systemic comorbidities (such as pulmonary and cardiovascular disease) that also carry their own mortality risk for this age group. However, 20 years after treatment of primary uveal melanoma, even in this advanced-age cohort, the number one cause of death is related to uveal melanoma metastatic disease [213]. This evidence, along with the observation of metastatic disease decades after enucleation, suggests that micrometastatic seeds spread to the liver early in the life of the primary tumor and then lie dormant for decades before overt active metastatic disease develops [120, 212, 214]. In fact, these dormant micrometastases have been directly observed in the livers of patients with a history of uveal melanoma and who have died of an unrelated event [212, 215]. Survival after diagnosis of metastatic disease is generally 2–9 months [143]. Even though the majority of metastases develop within the first 5 years after initial diagnosis, metastatic disease remains the most common overall cause of death in uveal melanoma patients for up to 20 years after the initial diagnosis has been made [127, 213].

Treatment of Metastatic Uveal Melanoma

Presently, there is no good data to demonstrate any significant benefit from adjuvant chemotherapy, immunotherapy, radiotherapy, or surgical therapy in reducing the rate of development of metastatic disease [3, 216–221]. Treatment of metastatic disease has been explored with numerous and diverse treatment modalities, including systemic chemotherapy, immunotherapy, hepatic arterial chemotherapy, hepatic artery chemoembolization, regional immunotherapy, and surgical metastasectomy. To date, results of these treatment modalities have shown only modest metastatic tumor response and limited survival benefit [3, 126, 145, 209, 216–220, 222–231].

Given that the majority of patients with metastatic disease present with diffuse liver involvement, surgical resection is generally not a viable treatment. Surgical resection may be considered only in very select cases where patients present with only a few, localized, and easily accessible hepatic lesions. Survival results from focal resection still remain modest at best [3]. It is important to note that although MEK, BRAF, and KIT inhibitors have been transformative for the treatment of cutaneous melanoma, these treatments

do not appear to be nearly as effective for the treatment of either primary or metastatic uveal melanoma [36, 37, 43, 53, 232]. Similarly, while immunotherapy appears transformative for the field of metastatic cutaneous melanoma, most metastatic uveal melanomas do not appear to respond to these treatments [221, 233–240].

Surveillance for Development of Metastatic Disease

Although radiographically or clinically apparent metastases are only found in 3% of patients with uveal melanoma at the time of diagnosis [241, 242], everyone agrees that all patients with a new diagnosis of uveal melanoma should undergo systemic staging with imaging [243–245]. This generally consists of CT, MRI, or PET-CT imaging of the chest and abdomen. Due to the very low incidence of CNS metastases from uveal melanoma, the CNS is generally not imaged [241, 243–245]. Beyond this, there is controversy surrounding the role and utility of subsequent surveillance imaging for metastases. While everyone agrees that the risk of developing subsequent metastases is high, there is a difference of opinions regarding the utility of potentially identifying metastases earlier through surveillance imaging when there are no effective treatments for those metastases.

While there is evidence that surveillance imaging leads to prolonged survival following the identification of metastases, this is felt to largely represent lead-time bias, while actual patient survival is not extended [246]. In general, most ocular oncologists do recommend systemic surveillance imaging for metastases, because there are many clinical trials into which patients without end-stage disease could enroll, and because a certain small fraction of patients will respond to one or another class of currently available treatments. This surveillance imaging generally consists of CT or MRI imaging of the liver, with or without CT imaging of the chest [243, 244, 247]. Abdominal ultrasound, in experienced hands, has been shown to be an effective screening modality for the liver, in nonobese patients, and has the benefit of avoiding additional radiation exposure to the patient [248]. Any additional benefit of liver function tests in patients undergoing an imaging-based screening regimen is unclear [148]. As treatments for metastatic uveal melanoma improve, the importance of surveillance imaging will increase.

Association with Systemic Disease

Uveal melanoma is largely an isolated and independent disease for the overwhelming majority of patients. In contrast to cutaneous melanoma, uveal melanoma presents with a positive family history of uveal melanoma only 1.6% of the time [249–251]. However, there are a few other notable diseases and syndromes that are known to be associated with an increased risk for uveal melanoma. These include *BAP1* cancer syndrome, dysplastic nevus syndrome, xeroderma pigmentosum, and oculodermal melanocytosis (Nevus of Ota) [250, 252–254]. The *BAP1* cancer syndrome is associated with an increased risk for development of numerous malignancies, including uveal melanoma, cutaneous melanoma, cutaneous basal cell carcinoma, malignant mesothelioma, clear cell renal cell cancer, abnormal skin lesions termed "melanocytic BAP1-mutated atypical intradermal tumors" (MBAITs), breast cancer, cholangiocarcinoma, non-small-cell lung adenocarcinoma, meningioma, and neuroendocrine carcinoma [253].

Thus, a patient with cutaneous melanoma without any of these other *BAP1*-associated malignancies is unlikely to have any significant difference from the general population regarding the risk for developing uveal melanoma. Therefore, ophthalmic uveal melanoma screening examinations are not typically warranted for patients with simple, isolated cutaneous melanoma in the absence of a cancer syndrome. Even patients with a family history of cutaneous melanoma do not have an increased risk for uveal melanoma unless the cutaneous melanoma is associated with a cancer predisposition syndrome like *BAP1* cancer syndrome, dysplastic nevus syndrome, or xeroderma pigmentosum

[250, 253–255]. Alternatively, patients with uveal melanoma have an 11% increased risk for developing other secondary malignancies such as renal cell carcinoma or cutaneous melanoma. This increased risk is thought to be attributable to germline *BAP1* mutations [256].

Conjunctival Melanoma

The conjunctiva is the thin, clear mucous membrane that is external to the eye and covers the front portions of the sclera, extending from the peripheral edge of the cornea to the eyelid fornix and then looping back onto the posterior surface of the eyelids (Fig. 16.1). Conjunctival melanomas may arise from a conjunctival nevus, primary acquired melanosis (PAM) of the conjunctiva, or de novo [257]. Conjunctival melanomas are rare and have an incidence of 0.2–0.5 per million Caucasians [12]. In fact, uveal melanoma is 7.5 to 17.5 times more common than conjunctival melanoma [5, 9–12]. However, conjunctival melanoma represents 52–53% of all malignant conjunctival tumors [258, 259].

As previously mentioned, it is important to understand that conjunctival melanoma is not intraocular, and is therefore quite different from uveal melanoma. In fact, conjunctival melanoma has many more characteristics and features in common with cutaneous melanoma, including genetics, sun exposure as a risk factor, treatment approach, and propensity for lymphatic spread [6, 13, 28, 260–263]. For example, like cutaneous melanoma, the incidence of conjunctival melanoma in the United States has doubled over the past 50 years from 0.27 to 0.54 per million. Like cutaneous melanoma, this rise is thought to be attributable to increasing UV light exposure [11, 12]. Staging for cutaneous melanoma is via the TNM staging criteria similar to cutaneous melanoma [142].

Treatment of Conjunctival Melanomas

While treatment for primary uveal melanoma is primarily with radiotherapy, conjunctival melanoma is largely a surgical disease, much like its cutaneous counterpart [2–6]. In the past, conjunctival melanomas were treated with extreme measures, such as exenteration (complete removal of the eyeball along with the surrounding orbital fat, extraocular muscles, nerves, and eyelids), because these tumors were thought to be extremely invasive [264]. However, in 1996, Norregaard et al. demonstrated that there was no significant difference in tumor recurrence or patient survival between aggressive exenteration and conservative surgical excision [261]. The results from Norregaard's study dramatically changed the treatment paradigm and conservative treatment is now the mainstay for most conjunctival melanomas [260].

Today, techniques for limited (but complete) excision of the visible tumor with a wide local margin have been widely published. Adjuvant topical chemotherapy with mitomycin C eye drops is commonly used. Excisional biopsy of the melanoma is performed in the operating room with wide surgical margins, employing a no-touch technique, in which the tumor itself is never touched with the surgical instruments, to prevent spread to uninvolved tissues. Alcohol may be used to assist in removing any corneal epithelium that may be involved. Next, a double-freeze-thaw cryotherapy technique is applied to the edges of the limbus and conjunctiva that were excised. Recurrence is then monitored with serial examinations and photography, and periodic surveillance map biopsies of the conjunctiva may be performed if there is concern for recurrence [260, 265].

Recurrence Rates for Conjunctival Melanoma

Despite optimal surgical treatment with acceptable negative surgical margins and negative repeat map biopsies, the prognosis is highly variable and somewhat unpredictable, with significant rates of recurrence and metastases [266]. Recent published recurrence rates are 26% at 5 years, 51% at 10 years, and 65% at 15 years. Metastases are seen in up to 26% of patients at 10 years after treatment. Similar to cutaneous melanoma, the most frequent sites of metastasis for

conjunctival melanoma are the regional lymph nodes, with subsequent progression to the brain, liver, and lung. Death from metastatic conjunctival melanoma has been reported to be 13% at 8 years after the initial diagnosis [267].

Areas of Future Study

Over the past several decades, our understanding of the genetics, pathophysiology, risk factors, and prognostic features of uveal melanoma has greatly improved. We understand how uveal melanomas develop from a melanocyte to a benign nevus to a malignant melanoma. Our treatment paradigm has shifted from complete removal of the eye (enucleation) to eye- and vision-sparing treatment with radiotherapy [4]. However, despite excellent local treatment control rates, our ability to prevent or treat metastases is very poor. Once metastases develop, there are currently no good treatment options and patient mortality is nearly 100% at 5 years [207–209].

Furthermore, with the development of genetic prognostication for uveal melanoma, we are now equipped to accurately predict which patients will develop metastatic disease. We also understand that micrometastatic spread to the liver happens very early in the primary disease state, with long periods of micrometastatic dormancy. However, we do not understand how these undetectable micrometastases stay dormant, nor why they ultimately may reactivate, causing overt metastatic disease. Further studies are needed to fully elucidate the pathophysiology of this process and to develop therapies to prevent this reactivation or treat the metastatic tumors once they form.

A potential novel treatment modality on the horizon may utilize epigenetic regulation of genes to treat both primary and metastatic uveal melanoma. The term epigenetics refers to mitotically inherited factors that alter genetic expression but are not caused by direct changes in the primary DNA sequence [268]. Over the past two decades, it has been shown that epigenetics plays an important role in a multitude of diseases and cancers. Epigenetic mechanisms are responsible for producing dynamic modifications of chromatin structure, resulting in relatively more or less compaction of DNA. Ultimately, epigenetic mechanisms produce fluent alterations in gene expression. Relatively recently, the mechanisms underlying a number of epigenetic alterations have been elucidated, including DNA methylation and histone modification through acetylation or methylation. As a result of these discoveries, the terms “epigenome” and “histone code” have been coined [269].

Recent studies have demonstrated strong evidence that aberrant histone modifications play a critical role in the oncogenesis of several malignancies, and prognostic outcomes have been associated with changes in the global cellular patterns of histone modifications in these malignancies [270–273]. It has been shown that the histone code can be altered by modifications to major regulators of transcription, such as the polycomb group (PcG) of proteins and histone-modifying enzymes (HMEs) such as histone acetyltransferases (HATs) or histone deacetylases (HDACs) [74, 274].

In 2015, Herlihy et al. showed that monosomy 3 and GEP Class 2 uveal melanomas are associated with reduced expression levels of several HMEs and PcG proteins [75]. Furthermore, Landreville et al. have shown that histone deacetylase (HDAC) inhibitors can reverse uveal melanoma cellular morphology into a more differentiated state and inhibit growth of these malignant cells in vivo [75, 76]. Future treatments for primary and metastatic uveal melanoma may therefore focus on harnessing the epigenetic regulation of the aberrant genes associated with this disease. Although initial results are intriguing, more studies are needed to better explore and validate these strategies as potential future treatment options.

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