



Ocular melanoma

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There are five types of ocular malignant melanomas. These neoplasms account for fewer than 0.5% of human malignancies [1]. The most common is primary uveal malignant melanoma, and it occurs with approximately one tenth the frequency of cutaneous melanoma; there are approximately six new cases per million per year in most western first-world countries [2]. In England, 13% of melanoma deaths are due to primary uveal melanomas [3]. Conjunctival melanomas have a frequency of between one twentieth and one fortieth of uveal melanomas [2]. In a Swedish study, the annual incidence of conjunctival melanomas was 0.024 per 100,000 [4]. In an American study of 4836 melanomas, 5.2% involved the ocular structures; of these 85% involved the uvea and 4.8% involved the conjunctiva [5]. Melanomas arising from the eyelid will not be discussed in this chapter, because they have an identical pathobiology to other cutaneous melanomas. The major difference is that surgical reconstruction of eyelid defects is more arcane than in many other body sites. Metastatic melanoma to the eye is rare; in order of frequency, it involves the orbit, retina, vitreous, iris, conjunctiva, and anterior chamber, and these entities will be briefly discussed at the end of the article. Even less common are two paraneoplastic syndromes. Melanoma-related retinopathy can produce a night blindness usually associated with metastatic disease. Rarely with metastatic tumors, diffuse pigmentation of the choroid can develop. Neither are true ocular tumors [6,7]. Primary orbital melanoma is exceedingly rare, often occurs in association with melanosis oculi, and will not be discussed.

Uveal, cutaneous, and conjunctival melanomas arise from the same cell type; however, they have distinctly different epidemiologies, molecular biologies, pathogenesis, and metastatic patterns. Unlike skin melanoma—which

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has a number of epidemiological causative associations, including patterns of sunlight exposure, the number of nevi on the skin, and hair color—in uveal melanoma there is a lesser correlation with these factors [8,9]. In uveal melanoma the most common genomic changes are monostomy of chromosome 3, increase in chromosome 8, and alterations on chromosome 6 [10–13]. As discussed elsewhere, the genomic changes in cutaneous melanoma are different, and unlike cutaneous melanoma, which can occur in a familial setting, there have been fewer than 60 reported cases of families with uveal malignant melanoma [14].

Although cutaneous and conjunctival melanomas usually have lymphatic spread, uveal melanoma has hematogenous metastases almost exclusively, and often initially presents with only liver involvement [15]. In contrast, conjunctival melanoma usually metastasizes to regional nodes. Iris melanomas rarely metastasize, but there have been a few cases of extraocular extension into the regional nodes.

Conjunctival melanomas

The origin of conjunctival melanomas is debated. Approximately 50% to 75% arise from areas of primary acquired melanosis, and the others arise either *de novo* or from nevi [16,17]. There is little definitive data on either the pathogenesis or molecular biology of conjunctival melanomas. My colleagues and I and other researchers have not found p53 abnormalities on histologic sections [18].

Conjunctival melanomas arise in the epithelium; most frequent simulating lesions do not (Fig. 1). The easiest test for a clinician is to put a drop of tetracaine in the conjunctiva and then try with a Q-tip to move the area of pigmentation. If the conjunctiva moves easily over the pigmented area it is not a conjunctival melanoma. When in doubt, a lesion should have an incisional biopsy.

Primary acquired melanosis (PAM) was first described by Reese many years ago [19]. It develops unilaterally in patients between the ages of 20

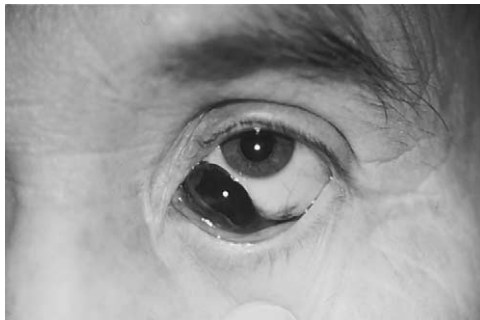


Fig. 1. Conjunctival melanomas arise from the epithelium.

and 50. Approximately 20% of cases undergo malignant degeneration. Folberg and others demonstrated that histologic examination of the basal layer of this proliferation was predictive: many of those cases with significant nuclear atypia underwent malignant change, whereas those that did not were unlikely to progress [20]. Benign and malignant conjunctival melanocytic proliferations are usually histologically straightforward to differentiate. There is an indeterminate group, however, that can be difficult to categorize, even by expert pathologists [21].

The management of conjunctival melanoma is usually surgical. In patients with flat conjunctival melanomas or PAM with atypia, several groups have tried topical agents such as Mitomycin C with generally good results, although there is a paucity of long-term data [22,23].

The optimum systemic evaluation of high-risk conjunctival melanoma patients is uncertain. Several groups have begun to perform sentinel node biopsies in the drainage area from a high-risk conjunctival melanoma; however, there is little data available [24,25]. Most relatively focal conjunctival melanomas are surgically resected with frozen section control of the margins and adjunctive cryotherapy of the base [2]. Relatively tight margins in the conjunctiva are obtained to preserve ocular function. In assessing horizontal margins the area of basillar material is significantly diminished, and hence a false negative examination of that dimension is possible; therefore patients are also treated with adjunctive cryotherapy. Most patients have not been treated with radiation, although various forms of this modality have been used, including both brachytherapy and external beams using protons, cobalt, or orthovoltage [2,26]. As a general rule, my colleagues and I have found that resection has been more useful. Although radiation can sterilize the lesion in cases of wide-field involvement of both inferior and superior bulbar and palpebral conjunctiva, all such eyes have been lost eventually due to treatment complications. After large tumor resections, mucosal grafts are usually necessary. In relatively smaller lesions, an autologous graft is obtained from the contralateral superior nasal conjunctival fornix. In the management of larger defects, either an autologous buccal membrane graft or an allogeneic amniotic graft has been used with good results [2].

Prognosis in conjunctival melanoma depends on tumor size, tumor location, cell type, complete tumor resection, lymphatic invasion, and mitotic rate [27]. Thicker tumors, more diffuse melanomas, and those that involve the fornices or the caruncle have a worse prognosis. As an example, in one study, patients with tumors that involved the eyelids or caruncle had over a twofold increase in mortality compared with patients with tumors that were localized to the globe [28]. Similarly, patients with mixed-cell melanomas had three times higher mortality than patients with spindle-cell melanomas, and lymphocytic invasion was associated with a fourfold increase in mortality rates. Overall, there is approximately a 20% five-year tumor-related mortality [4,28,29]. A recent study showed local recurrence rates of up to

50% at ten years. In a large series, Paridaens and coworkers showed that approximately 11% of patients developed lymph node involvement, 5% had an orbital recurrence, and 3% developed tumor in the sinuses [28].

In patients who have extensive involvement of the conjunctiva, especially intraocular orbital invasion or bulky forniceal involvement, exenteration is indicated (Fig. 2). The effect of exenteration on the natural history of conjunctival melanoma is unclear [30,31]. My coworkers and I have treated high-risk cases—which we define as thick lesions, lesions that involve the palpebral (eyelid) conjunctiva, or those which are diffuse—with high-dose interferon-2 alfa, although there are no definitive data on the use of this agent for high-risk conjunctival melanoma [32].

Uveal melanomas (choroid, ciliary body, and iris)

The initiating events for uveal melanoma remain uncertain. In uveal melanoma, contradictory results have been published on possible etiologic parameters, and no dominant environmental or workplace factors have been identified [8,32]. Fewer than 100 cases of familial uveal melanoma have been reported since Silcock's initial description in 1892 [33]. The absence of a strong familial clustering in uveal melanoma has precluded the kind of genetic linkage studies that were so helpful in defining the retinoblastoma gene locus [34,35].

Several groups have begun to identify these sequential genomic changes in uveal melanoma. Using comparative genomic hybridization (CGH), our group and others have demonstrated multiple genomic alterations in uveal melanoma, most commonly loss of chromosome 3 (monosomy of 3 or M3), loss of 6q, and an increase in chromosome 8q in the region of the *c-myc* gene [11,36–39]. Several investigators have demonstrated that loss of chromosome 3 is highly predictive of metastatic risk; it occurs relatively early in uveal melanoma development; and chromosome 8 increases appear to be



Fig. 2. The melanoma arose from primary acquired melanosis (PAM), involved the eyelid, eye, and orbit, and required exenteration. Most conjunctival melanomas can be treated with local excision.

a relatively late event [12,36,37,40–43]. In a study of 333 uveal melanomas, Tschentscher and colleagues found a subset of eight patients whose tumors had only partial deletions of chromosome 3 [42]. Two regions of the chromosome probably have tumor suppressor genes that have not been previously identified [42]. Parrella and colleagues observed that *c-myc* is amplified in many uveal melanomas, almost always in association with chromosome 3 loss, and not completely accounted for by 8q increase where that gene is encoded [40]. In the latter investigation, *c-myc* increase correlated with uveal melanoma dimensions, but there was insufficient length of follow-up to determine a correlation with survival [40]. Aalto and coworkers used CGH to analyze three types of uveal melanomas: specimens from enucleated uveal melanomas that did not metastasize; uveal melanomas that had metastasized; and metastatic deposits [36]. They noted that loss of chromosome 3, 6q, 1p, 13q, 8p, and 18 were associated with worse prognosis, as were gains in 8q, 1q, and 16p [36]. Other groups have noted similar prognostic correlations [44].

Several other gene abnormalities have been noted in uveal melanoma, but their importance, and their timing in relation to the onset of oncogenesis is uncertain. Initiating genetic events are unknown; it is doubtful that monosomy of chromosome 3 is a very early alteration in most melanomas. In familial breast cancer patients with the *BRCA2* gene on chromosome 13q12-13, there have been several reports of an increased incidence of uveal melanoma; however, the role of this gene in ocular melanoma development is unclear [45–47].

In uveal melanoma, although the retinoblastoma (*Rb*) gene product is usually normal, several factors that perturbate that system are not (Fig. 3). In familial cutaneous melanoma there are alterations on chromosome 9p21, which codes p16, a cyclin kinase inhibitor. This was noted in 24% of uveal melanoma specimens [35]. Alterations in p16 are relatively frequent in a number of malignancies, and several groups have shown alterations in uveal melanomas, including inactivation by methylation of the CpG island in the p16 promoter region [35,48]. Inactivation of p16 results in increased cyclin D levels that promote cell cycling, and this has been noted in uveal melanoma [34]. Similarly, alterations in the retinoblastoma gene-related family member, *Rb2/p130*, have correlated with survival in some uveal melanoma studies as well as in other malignancies [49]. A number of cyclin kinase inhibitors are altered in uveal melanoma cells, including p21, p16, and p27 [50]. These cyclin-dependent kinase inhibitory proteins are upregulated by TGF- β , and the receptor for this latter factor has been shown to be lost in some uveal melanomas [51].

Either mutational errors in p53 or alterations in its pathway are almost universal in malignancy. My coworkers and I and others have shown that p53 was not mutated in most uveal melanomas [52,53]. The p53 system is abnormally perturbed in uveal melanoma by increased expression of

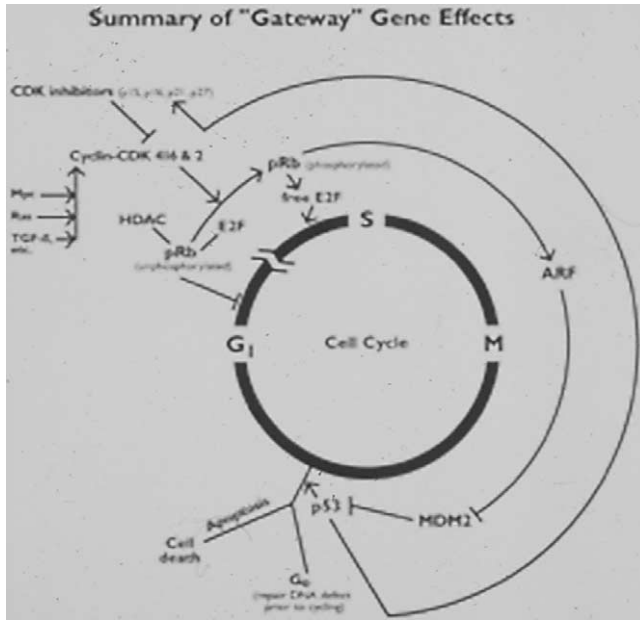


Fig. 3. Uveal melanomas have been shown to have a number of perturbations of normal cell-cycle control pathways.

MDM2, which degrades p53; some groups have shown a correlation with increased MDM2 expression in uveal melanoma and decreased survival [34,54]. Both c-myc and Bcl-2 factors that can impact the p53 pathway have also been shown to be altered in uveal melanoma [55].

Angiogenic factors and their inhibitors have been demonstrated in uveal melanoma [55–58]. Complex intramelanoma vascular patterns are associated with poor prognosis, but our understanding of these alterations has been limited [59]. Hess and colleagues observed in three-dimensional tissue culture matrixes that more malignant uveal melanoma cells express protein tyrosine kinases, especially EphA2, that allow tumor cells to mimic vascular endothelium to build these unusual channels. Blockage of these PTKs inhibited that process [60]. Further investigations by this group on “vasculogenic mimicry” by aggressive uveal melanoma cells have shown that these tumors express higher levels of a basement membrane component Ln-5 as well as several proteases: MMP1, 2, 9, and 14 [61].

Cell-cell adhesion molecules and proteases are central components in both invasion and metastases. Preliminary investigations on both integrins and proteases in uveal melanoma have been reported [62–64]. The type IV collagenase MMP2 was shown to be correlated with poorer survival in uveal melanoma patients in one study, and MMP9 was associated with more malignant cell type and worse survival in another investigation [62–65].

A third study showed that more malignant epithelioid melanomas, as compared with spindle-cell melanomas, were more likely to express the laminin-binding alpha 6 beta 1 integrin, although follow-up was too short and numbers too small in this patient cohort to be certain if this finding has prognostic significance [62].

Similar to cutaneous melanomas, uveal melanoma occurs more commonly in light-skinned patients with red or blond hair and blue or green irises [66]. The average age at diagnosis of uveal melanoma is in the sixth or seventh decade; fewer than 1% of patients are under age 20 [67]. Most (~80%) uveal melanomas involve the choroid, a vascular support layer posterior to the ciliary body and between the retina and sclera. The ciliary body supports the lens; ciliary body melanomas account for approximately 10% of cases and the iris is involved in approximately 5% of uveal melanomas.

Iris melanoma

Most iris melanocytic proliferations are benign and do not require intervention [68,69]. In definite melanomas that arise and remain solely in the iris, there is less than 2% long-term, tumor-related mortality [2]. Iris tumors are usually diagnosed because of either abnormal pigment or distortion of the pupil. Almost all the metastatic events associated with iris melanomas occur in three settings: (1) when the tumor causes increased intraocular pressure, an ophthalmologist is unaware of the etiology of the glaucoma, filters the patient, and inadvertently spreads the tumor; (2) cases of ciliary body melanomas with some iris involvement; or (3) diffuse uveal melanomas that are mistakenly thought to be isolated iris tumors [68,70].

The management of iris pigmented tumors is straightforward [2]. Smaller lesions that grow, are intensely vascular, or that involve the ciliary body, are resected (iridocyclectomy). In most of these surgical cases (under four clock hours in size), good vision is obtained and recurrences are rare. In tumors that encircle the iris (ring melanoma) and produce increased pressure due to tumor infiltration of the filtering angle, the eye is removed.

Choroidal (posterior and ciliochoroidal) melanoma

The origin of uveal melanomas, either new or from degeneration of an existing nevus, is uncertain. Malignant degeneration of a choroidal nevus is estimated to occur in approximately 1 per 5000 cases [71]. A higher risk group are lesions that my coworkers and I have termed “choroidal neviomas” (indeterminate pigmented choroidal tumors) [72,73]. We believe these lesions are analogous to a hyperplastic breast nodule. These tumors are larger than the average choroidal nevus (over 6 mm in diameter and greater than 1 mm in thickness) (Fig. 4). Previously we and others have demonstrated risk factors for growth in these lesions, including the presence of symptoms produced by the lesion and characteristic findings on physical

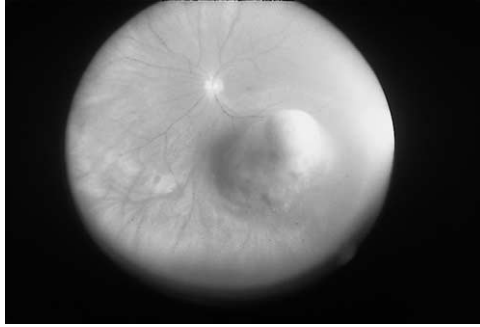


Fig. 4. Posterior choroidal melanoma. Approximately 80% of such lesions are pigmented. Tumors over 6 mm thick often break through the Bruch's membrane layer of the retina and form a collar button- or mushroom-shaped tumor, which is almost pathognomonic for a uveal melanoma. As the tumors expand, most develop an associative exudative retinal detachment. (See also Color Plate 1.)

examination (lipofuscin and exudative subretinal fluid), as well as ancillary test parameters, including homogeneity on ultrasound and “hot spots” on fluorescein angiography [72,74,75] (Fig. 5). In most centers, low-risk choroidal nevoma patients are followed, because such stable lesions have no metastatic events. In nevasomas that grow, if the patient is treated quickly there is less than a 3% incidence of a tumor-related mortality [72,74,75].

Typically, uveal melanomas are diagnosed in symptomatic patients with a clinical characteristic pattern. Ciliary body tumors often produce a “sentinel” episcleral vessel, and may distort the lens and vision. Posterior uveal melanomas often present with decreased vision from one or more of four mechanisms: (1) a large tumor produces an exudative retinal detachment that can decrease the vision, contract the visual field or both; (2) a tumor under the macular may mechanically distort the retina and alter vision; (3) a large peripheral lesion can actually block a portion of the visual field; or (4) less commonly, a tumor can produce sufficient hemorrhage to

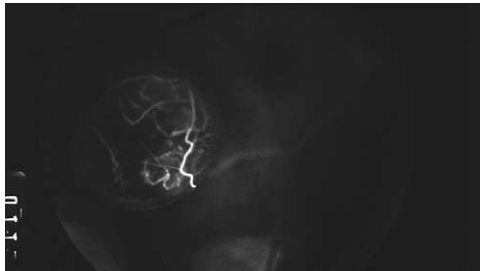


Fig. 5. Fluorescein angiography of choroidal melanomas shows intrinsic tumor vessels, which have been termed a “second circulation.”

decrease visual acuity. A clinical examination, in expert hands, has approximately 91% to 96% accuracy [76,77]. Patients with presumed uveal melanomas have a diagnostic evaluation that also includes fluorescein angiography and ultrasound studies (Fig. 6A,B). In difficult cases, fine-needle aspiration biopsy can be performed; we noted no significant adverse effects in eyes that had fine-needle aspiration biopsy as compared with those who did not (Fig. 7A,B) [76,78]. In expert ophthalmic oncology centers, the overall accuracy is over 99% in tumors that require intervention; accuracy would probably be much lower in very small lesions that did not require intervention [2,76].

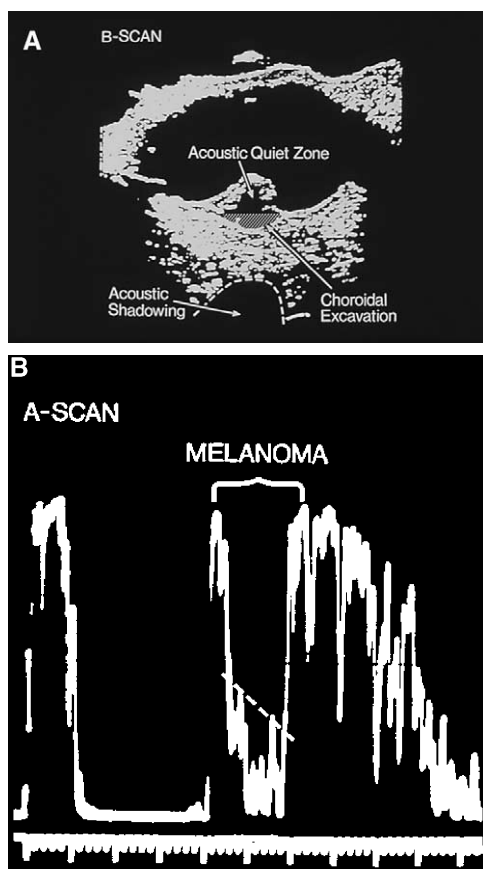


Fig. 6. Combination of B- and A-scan ultrasonography has approximately 95% accuracy in choroidal melanoma diagnosing. In lesions less than 3 mm in thickness the accuracy is less. (A) The B-scan typically has an internal quiet zone, choroidal excavation, and orbital shadowing. (B) On A-scan the tumor has low to medium reflectivity (as compared with the anterior retinal and posterior scleral spike). The scleral spike is sharp (in contrast to a metastasis, which has a stepwise climbing pattern). During the actual performance of the test there are spontaneous pulsations visible in the tumor.

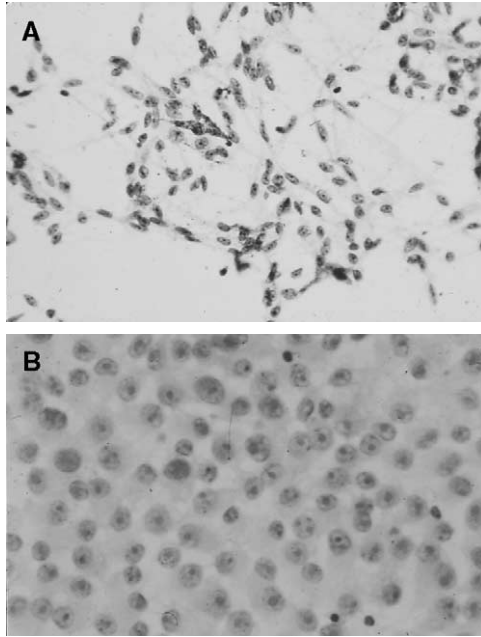


Fig. 7. (A) Fine-needle aspiration biopsy demonstrates a spindle-cell melanoma. (B) Fine-needle aspiration biopsy demonstrates an epithelioid melanoma, which has a worse prognosis than a spindle-cell tumor.

Several newer techniques have also been described, including more advanced positron emission tomography (PET), PET-computed tomography (CT) scans, and doppler imaging [79–81]. Our experience has been that these investigative techniques, although consistently helpful in the diagnosis of melanoma in large, obvious tumors, have not shown utility in diagnosing smaller, diagnostically-challenging lesions. Doppler has also been shown to document vascular changes in irradiated melanomas [80].

Historically, over 20% of eyes enucleated with a clinical diagnosis of a uveal melanoma contained a simulating lesion on histologic examination [2]. Unfortunately, in ophthalmic oncology centers with only limited exposure to these types of patients, that diagnostic error rate is still approximately 9% [82]. Fortunately, in major centers the diagnostic error rate is under 1% [77]. A recent collaborative National Eye Institute-sponsored melanoma trial, which required an obvious melanoma for inclusion in this study, found a less than 1% diagnostic error rate [83]. Obviously, if one evaluates cases that consist of only classic large melanomas at inception, the error rate should be small.

There have been several different classifications of tumor size [2]. All are relatively arbitrary and were mainly promulgated to establish entry criteria for randomized therapy trials, before the widespread availability of powerful microcomputer-based statistical programs that allowed multivariate analysis.

Tumors less than 3 mm in thickness and less than 10 mm in diameter have a very low tumor-related mortality; in most series this has been under 5% at five years [72]. As tumors get larger (with diameter being more important than thickness for its association with survival), cross the equator to involve the anterior portion of the globe, occur in older patients, have localized extrascleral extension, have a more malignant cell type, have a higher growth fraction (mitotic activity etc), or undergo genomic alterations (especially loss of chromosome 3), there is a cumulative increased incidence of metastatic disease [2]. The interactions between most of these parameters at a molecular level remain to be determined.

The management of uveal melanomas depends on the patient's general health; the tumor's location, size, and configuration, and ancillary features (subretinal fluid, retinal invasion, hemorrhage); and the clinician's expertise.

As mentioned above, many indeterminate choroidal pigmented lesions (nevomas) can be safely watched. My colleagues and I and others have created statistical models that accurately delineate the risk of such a tumor growing and producing metastatic disease [72,74,75]. Nevomas that do not grow have had no metastatic events. These are lesions that are under 10 mm in diameter and under 3 mm in height, that do not have exudative detachment, and that usually do not have high-risk growth features such as orange pigment, symptoms related to tumor, exudative retinal detachment, or ultrasound and fluorescein changes associated with growth.

Small growing tumors or indeterminate tumors with a high probability of growth (<10 mm diameter, <3.5 mm thickness) that are distant from visually vital structures (optic nerve or fovea) are often treated with newer laser modalities. Several groups have used an 810 nm laser with long-duration (1 minute), large-diameter overlapping spots (>3000 micra) to induce hyperthermia to treat smaller tumors [84–86]. This technique has shown good results in a number of settings, although its mechanism of action is uncertain. In contrast with hyperthermia treatment studies in other body sites, it is very difficult to do multiple thermal-couple monitoring of intraocular tumor temperature with acceptable morbidity. Therefore, although the term “transpupillary thermotherapy” has been used to characterize this technique, because the appropriate basic science data is unavailable I prefer to term it “laser-induced hyperthermia,” with the warning that its mechanism of tumor cytotoxicity is undoubtedly both coagulative as well as hyperthermic. The long-term efficacy of this laser-induced hyperthermia is uncertain. Older photocoagulation and laser treatment modalities had at least a 10% incidence of late failure, and we suspect a similar figure will be noted with this technique, although the failure is higher in tumors contiguous to the optic nerve [2,85]. There is approximately a 35% incidence of visually damaging complications in most series [2]. Nevertheless, in some cases, especially if the tumor is thin, in the posterior pole, and away from the optic nerve and fovea, the lesion can be treated on an outpatient basis, without ionizing radiation, and with good control and often retention of good vision. In tumors over

3.5 mm in thickness, penetration is incomplete and the use of this modality alone is probably contraindicated.

Historically, enucleation (eye removal) was the treatment of uveal melanomas. Many investigators who have extensive experience with alternative eye-salvage treatments have noted that the survival rate was at least as good with those options [2,87–89]. Most experienced American ophthalmic oncologists did not participate in the COMS (Collaborative Ocular Melanoma Study) that compared I¹²⁵ brachytherapy with enucleation and the effect of low dose rate pre-enucleation radiation [2,87–89]. The COMS investigators noted no difference in survival between enucleated and I¹²⁵ brachytherapy-irradiated eyes with mainly choroidal melanomas <16 mm in diameter and <10 mm in thickness, generally >2 mm distal to the optic nerve [90]. One important caveat should be stressed. We and others have previously shown that survival with alternative, eye salvage techniques equals enucleation as long as there is good tumor control. If a patient receives radiation for an eye melanoma and the tumor does not respond, there is a significantly increased risk of metastatic disease compared with those who have a good treatment response [91–93].

Several radiation options have been used to treat melanoma since the first attempts with implanted radon seeds in 1929 [2]. The earliest relatively large experience used cobalt-60 brachytherapy, a relatively penetrant gamma emitter. A major problem with cobalt radioactive plaques was that, due to its relatively strong gamma radiation, there was a significant incidence of visually destructive radiation vasculopathy. In the early 1970s, a group in Boston and our group in San Francisco began using charged-particle radiation [2]. There were several potential advantages with these approaches: (1) these charged particle beams, because of the inherent Bragg peak, could be more tightly focused and thus possibly less likely to induce visually destructive radiation retinopathy; (2) there was perhaps increased radiation efficacy against a melanoma, especially with heavier charged particles; and (3) there was no radiation delivered to the surgical team. The data with the charged particles in experienced centers have shown that approximately 98% of irradiated cases have local control, although there is an individual institutional learning curve [94–97]. Overall, at five years approximately 90% of eyes treated with these techniques are salvaged. Survival and metastatic risks mirror prior enucleation data (important risk factors are patient age, tumor diameter, intraocular location of melanoma, localized extraocular extension, cell type, and genomic changes) [2].

In most centers the major cause of eye loss after charged particle radiation was radiation-induced morbidity, especially neovascular glaucoma [98]. My coworkers and I demonstrated that the percentage of the anterior ocular segment (cornea, iris, filtration angle, and lens) in the entrance beam was a major risk factor for eye loss, and by adapting techniques to decrease its exposure we have diminished the incidence of neovascular glaucoma from 30% to approximately 6% [98,99].

Particle radiation has been effective in retention of the eye; however, it has complications. Unfortunately, as we have learned both from molecular biology and clinical studies, eyes with progressively larger tumors are more likely to have a poor visual outcome. As an example, a tumor 8 mm thick is roughly tenfold more likely to cause severe visual loss than one less than 5 mm thick [94]. Other factors associated with poor visual outcome after particle radiation include tumor proximity to the optic nerve and the fovea (≤ 3 mm), older age of patients, and poor pretherapy vision. Overall, approximately 35% of patients who are treated with uveal melanomas using charged particle radiation retain excellent vision [2,97].

Several different brachytherapy approaches have been used to treat uveal melanomas. In the United States, most current treatment has been done with I^{125} brachytherapy [96,100]. My coworkers and I performed a prospectively randomized, dynamically balanced study comparing helium ions with I^{125} plaques in a group of approximately 200 patients [95]. This study was more inclusive than some recent investigations; uveal melanomas in all locations < 15 mm in diameter and < 10 mm thick were randomized [95]. We noted a statistically significantly better control rate with the charged particles as compared with the I^{125} plaques. In addition, uveal melanomas treated with I^{125} plaques have approximately a 2% per year late incidence of treatment failure [101]. This latter finding is not surprising, given some of the brachytherapy data for prostate carcinoma. In contrast, late failures after particle radiation are distinctly uncommon.

In Europe, ruthenium plaques have been used to treat most uveal melanoma [89,102]. Ruthenium is mainly a beta emitter, and we have tended to use it much less frequently in the United States because it does not have adequate coverage, especially for thicker tumors, and potential confusion with multiple isotope use limits any potential advantage over iodine-125. Other brachytherapy options, including radioactive gold and palladium-103, have also been reported in small series [103,104].

Technical consideration has a large impact on uveal melanoma radiation results. Problems with plaque fabrication as well as dose rate have a major affect on local intraocular tumor control [105,106].

Several newer teletherapy approaches have been reported using either a gamma knife or a variant of intensity modulated conformal therapy [107–110]. A high incidence of complications, especially neovascular glaucoma, has occurred, particularly with the former technique [108]. The optimum single fraction dose with a gamma knife is uncertain [108]. A group in Vienna has used up to three fractions with a 98% local control rate [110]. Others have noted a 90% to 98% control rate. The focusability available with these approaches does not achieve that observed with proton or helium ion delivery systems [2,107,109].

The molecular basis of uveal melanoma radiation efficacy is uncertain. P16 alterations, which have been demonstrated in eye melanoma, are associated with altered radiation sensitivity [111]. Alterations in p53

expression may also be important in uveal melanoma radiation affect [111,112].

Surgical resection of uveal melanomas has been attempted since the early part of the twentieth century. Until the development of modern surgical techniques for choroidal or ciliary body melanomas the operation was quite risky (Fig. 8). Even today there are only a few ophthalmic oncology centers that have shown excellent results [113]. The indications for these techniques vary. Our experience has suggested that for most posterior tumors, especially those less than 8 mm in thickness, radiation is a better option. In addition, because most uveal melanoma patients are rather elderly and some have age-associated cardiovascular problems, the performance of these operations, which require hypotensive anesthesia, can be problematic. In patients with melanomas tumors over 8 mm thick, however, eye wall resection usually produces better ocular results than radiation in expert hands [113,114]. We noted that approximately 75% of all eyes operated on with these techniques were salvaged, and about half retained 20/40 or better vision. Larger, more posterior tumors had a poor visual outcome, with only about a third retaining excellent vision [113].

Enucleation is indicated in several settings: (1) in a patient who after being informed of the diagnosis requests this operation; (2) in a patient with a tumor involving over 40% of ocular volume—almost no eyes with such tumors retain functionality after alternative therapy; (3) after treatment with an alternative modality that has failed; and (4) in patients with significant ocular neovascularization before any therapy.

Any patient considered for enucleation should have a metastatic evaluation before consideration of this approach. The mean survival in patients with symptomatic uveal melanoma metastases is less than six months [15]. Similarly, removal of an eye should not be considered if there is any doubt regarding the diagnosis.

In the late 1970s, my coworkers and I and others hypothesized that pre-enucleation, low-dose (20 Gy) fractionated radiation might decrease

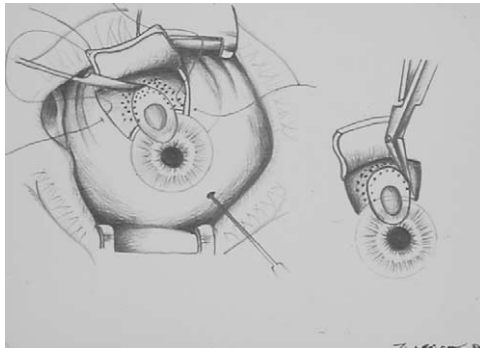


Fig. 8. A schematic representation of an eyewall resection.

tumor-related mortality if the trauma of enucleation was important in tumor dissemination. In a small series we reported in the 1980s, we observed that this approach did not appear beneficial and we stopped those studies. Others reported similar findings [2,115]. The National Eye Institute-sponsored COMS study, which used the above treatment paradigm as the basis of a national, prospective, randomized trial, was completed two years ago [116]. The researchers noted, as we did, that there was no beneficial effect with pre-enucleation radiation as compared with enucleation alone [116].

Exenteration is rarely used in uveal melanomas unless there is diffuse involvement of the orbit and the patient has no metastatic disease. Patients with focal extraocular extension are usually treated either with enucleation plus a sector tenectomy, surgical resection of the entire tumor en bloc, or radiation of both the intra- and extraocular portions of the tumor.

The metastatic pattern of uveal melanoma is often distinct from that of the cutaneous form of the disease. Approximately 90% of uveal melanoma patients die with liver metastases [15]. Almost 60% of patients will initially present with symptoms referable to hepatic metastases. Approximately 25% will have subcutaneous metastases; less commonly, eye melanomas can involve other structures, including bone, pleura, lung parenchyma, and even myocardium. The conventional metastatic evaluation of uveal melanoma patients includes a physical examination, chest radiograph, and liver function tests, with a gamma glutamyl transpeptidase (GGT) and a lactate dehydrogenase (LDH) being the most sensitive assays. The relative utility of serum liver function tests as compared with abdominal ultrasound or abdominal/chest CT is uncertain [117,118]. Most studies have shown CT or ultrasound to be more sensitive than serum liver function tests, but occasionally we have seen the inverse results. Furthermore, the relative cost effectiveness of those tests has never been addressed, given the paucity of therapeutic benefit in most patients with metastatic uveal melanomas. It appears that PET scanning is more sensitive than any of these options, but the data in support of that statement are tenuous [119].

Metastatic uveal melanoma has a different treatment response rate than cutaneous melanoma. The evaluation of such patients, especially staging for solitary versus diffuse metastases, is crucial. Treatment of metastatic melanoma is discussed in another article in this issue.

Cutaneous melanoma metastatic to the eye is uncommon [120,121]. We observe approximately an equal number of metastatic melanomas that have disseminated to the orbit as to the intraocular structures. Melanoma metastases to the choroid are extremely uncommon, although a few patients have had a unilateral choroidal melanoma with an initial normal opposite ocular examination, and then have developed a second melanoma in the other choroid, which presumably was metastatic. More commonly, metastatic melanoma involving the intraocular structures involves the anterior segment (Fig. 9), or diffusely involves the vitreous (Fig. 10). Rarely will it involve the posterior segment of the eye; most such cases I have

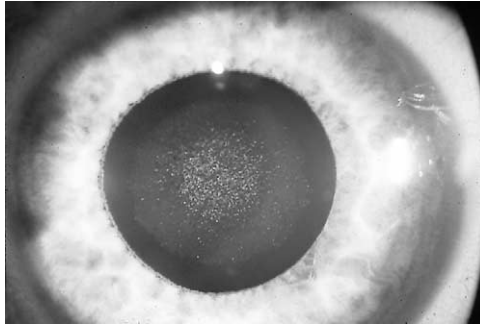


Fig. 9. Cutaneous melanoma metastatic to the anterior chamber. (See also Color Plate 2.)

examined have had retinal involvement, which is quite distinct from a choroidal melanoma.

Melanoma metastatic to the orbit will usually present with involvement of the extraocular muscles, (Fig. 11), although rarely it can appear as a solitary lesion that might be confused with primary, benign orbital tumor if the history of previous cutaneous melanoma were unknown. Virtually all of the patients I have managed with melanoma metastatic to the eye or ocular adnexa have succumbed to their systemic disease within six months. Local treatment has included surgical resection for focal lesions, chemotherapy, or radiation.

Paraneoplastic melanoma syndromes are extremely rare. Patients present with altered dark adaptation with marked field loss or diffuse pigmentation of the choroid [122,123]. The former syndrome is due to antibodies shared between melanoma and the normal retinal bipolar cells [122].

Our understanding of molecular biology of eye melanomas has increased exponentially. Genomic changes have a stronger association with prognosis than conventional clinical or histologic parameters. Clinical management of ocular melanomas has improved so that most eyes with uveal melanomas

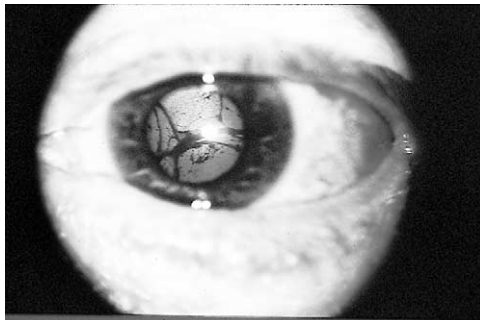


Fig. 10. Cutaneous melanoma metastatic to the vitreous; there is no solid tumor. (See also Color Plate 3.)

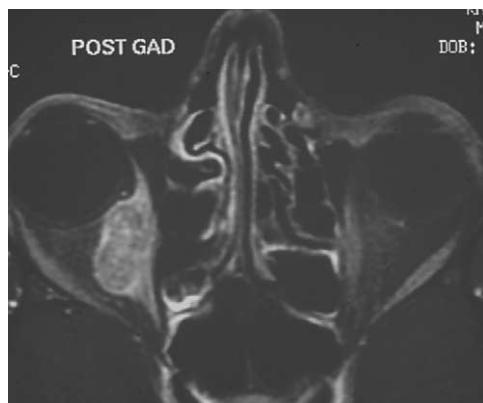


Fig. 11. Cutaneous melanoma metastatic to the orbit has the propensity to involve the extraocular muscles, as shown in this case.

can be salvaged, with about one third having excellent post-treatment vision. Unfortunately, a significant number of patients with large uveal melanomas develop metastatic disease, and our treatment of these patients has not been effective. In addition to developing less morbid techniques to salvage a greater number of eyes with melanomas, we hope to improve our ability to detect micrometastatic disease before it is symptomatic, and to treat widespread uveal melanoma more effectively.

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