Enucleation has been the standard therapeutic intervention for malignant melanoma of the uveal tract, but alternative approaches offer hope for tumor control and vision preservation.

**Introduction**

Malignant melanoma, the most common primary intraocular malignancy, is a neoplasm of the uveal tract. This is the pigmented layer of the eye that includes the iris, ciliary body, and choroid. The iris is the readily visible, most anterior portion. While the iris is perceived as giving the eye its color, such as blue, green, hazel, or brown, the melanocyte is the only pigment-synthesizing cell of the uveal tract. The amount of melanin varies according to racial and familial characteristics, and light diffraction explains the other aspects of iris color. The iris functions as a diaphragm, constantly altering the size of the pupil according to the ambient light. The ciliary body is continuous with the iris, and it lies the sclera anteriorly. Its functions include secretion of aqueous fluid and alteration of the shape of the crystalline lens for the purpose of focusing. Posterior to it is the choroid, which lines the remainder of the sclera and functions as a source of oxygen and nutrients for the overlying retina.

**Epidemiology**

Uveal malignant melanoma is an uncommon tumor, occurring in six persons per million per year in the United States. It is more common in lightly pigmented persons and is infrequently seen in nonwhite races. It is estimated that the frequency of uveal malignant melanoma in American blacks is less than one eighth of the incidence in whites. In a series from a pathology referral center, eyes from black individuals represented a little more than 1% of the entire series, and mortality rates were similar for blacks and whites. The risk is also low in native Americans, African Americans, and Asians. Uveal melanoma is the most common noncutaneous melanoma, with a frequency of approximately 12% that of melanomas of the skin.

Approximately half of all persons diagnosed with a melanoma of the choroid or ciliary body will die of the disease within 15 years of enucleation. Interestingly, the rate of metastasis overall has not decreased during this century, despite advances in therapy. There is some indication that radiation therapy with tumor control may improve survival, but the numbers are small and duration of follow-up is relatively short. Survival with metastatic disease is poor. Iris melanomas, in contrast, are much more benign in their natural history, and local excision is usually curative when deemed necessary, probably because of the small size and readily visible location of iris melanomas.

The differences between cutaneous and uveal melanomas are intriguing. Melanomas of the skin have been increasing in frequency over the last several decades, while such a trend is less evident with ocular melanomas. Moreover, the rate of death from cutaneous melanomas has also been rising in recent decades, whereas the death rate from uveal melanoma has remained steady over the same period. In addition, the incidence of cutaneous melanomas appears to be dependent on latitude, presumably reflecting exposure to ultraviolet light. This trend has not been evident with uveal melanoma. A single case-control study did suggest a risk for uveal melanoma with ultraviolet exposure from both sunlight (as assessed by latitude) and sunlamps used for tanning melanoma, but the numbers are small and remain to be supported by larger studies.

Uveal melanoma shows a peak incidence at 55 years of age. Melanoma is slightly more common in men as shown in several series, but it is unclear whether this is a primary effect of gender or a secondary effect that is related to either an occupational or recreational exposure. Uveal melanoma is unusual in children. In one large clinical series, approximately 1% of all uveal melanomas occurred in patients 20 years of age or younger, and only one patient died. These results contrast a previous series in which the mortality rate for younger patients was similar to that for older patients.

Certain diseases and conditions may predispose to melanoma. Xeroderma pigmentosum, an inherited disorder of DNA repair, is characterized by innumerable skin cancers, including melanoma. Four patients have been reported to have uveal melanoma out of a total of approximately 830 patients in the literature. While this is far fewer than expected, it is a significant finding given the rarity of the disease and the potential for early detection in these patients.
Another predisposing condition is ocular or oculodermal melanocytosis. Ocular melanocytosis is a developmental condition in which the ocular surface (the episclera) and the uveal tract are hyperpigmented. When the surrounding skin is also involved, it is called oculodermal melanocytosis, or nevus of Ota. The orbit and meninges can also be involved. These two conditions are more prevalent in Asians, although uveal melanoma is rare in this group. However, when either of these types of melanocytosis occurs in whites, the incidence of uveal melanoma increases by approximately 30-fold, presumably due to the greater numbers of melanocytes in the uveal tract.

The relationship, if any, between the dysplastic nevus syndrome and uveal melanoma is controversial. Individual cases have been reported as having both dysplastic nevi and uveal melanoma, but no series shows a higher than chance association between the two.

It has been suggested that pregnancy may enhance growth and metastases in melanoma. However, large series fail to support this assertion. A search for estrogen and progesterone receptors in choroidal melanoma showed no evidence for such receptors.

Melanomas are rarely bilateral. However, the number of patients with bilateral involvement is greater than would be predicted by chance alone, thus implying a possible genetic predisposition. Singh and associates found eight patients with bilateral uveal melanoma in a large clinical series of 4,500 cases. No specific syndrome was identified other than ocular melanocytosis in two of the eight patients.

Melanomas generally occur as sporadic tumors. However, there are kindreds with melanoma, implying a possible familial trait. In one series of 4,500 patients with melanoma, 17 individuals had first-degree relatives with uveal melanoma. Statistically, only one such family would be expected, thereby implying a greater than random chance occurrence. The specific gene or trait, however, remains to be identified.

Melanomas of the ciliary body or choroid typically appear as discrete solid tumors. Melanomas of the choroid present as solid tumors beneath the retina (Fig 2). A secondary serous sensory retinal detachment adjacent to the tumor occurs frequently; this detachment can be responsible for visual loss, even if the tumor does not involve the submacular choroid directly. In addition, there can be retinal degeneration with pigmented changes overlying the apex of the tumor. The surface of some melanomas shows a patchy orange pigment, found ultrastructurally to be lipofuscin, in macrophages and retinal pigment epithelium.

Diagnosis and Evaluation

Patients with choroidal melanoma may present with complaints of visual loss, but many melanomas cause no symptoms and are discovered on routine ocular examination. In eyes with clear media, visual inspection by ophthalmoscopy remains the most reliable method for diagnosis.

Iris melanomas appear as single or multiple elevated lesions arising in the iris stroma. Pigmentation ranges from inapparent to dark brown. Occasionally there is diffuse iris involvement with minimal elevation, manifest as a monocular iris color change. Because the iris is visible, melanomas of the iris can be discovered by patients themselves (Fig 1). Assessing malignant potential can be difficult, even in those lesions with documented growth, since iris nevi may also grow. Iris melanomas can involve the angle and extend into the ciliary body or through the sclera. Alternatively, the first manifestation of a ciliary body melanoma may be the appearance of a peripheral iris lesion.

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membrane is impeded due to the constricting effect of Bruch’s membrane. Tumors with a collar-button configuration examined histologically show dilated vessels in the internal portion with inconspicuous vascularity in the external portion.

As noted above, the retina overlying the tumor may show degenerative changes, occasionally to the point of complete attenuation with tumor perforation into the vitreous cavity. Discohesive cells may proliferate within the vitreous cavity or along the retinal surface, causing a patchy pigmentation resembling retinitis pigmentosa.

Serial observation of growth rates of melanomas may give some clues to prognosis. In one retrospective study, the growth rate and the estimation of doubling time were assessed for 145 patients. Estimates of doubling time ranged from less than six months to more than four years, with a median of 1.4 years. More rapid growth and doubling times predicted metastatic disease and radiation treatment failure.

While the discrete, solitary tumor is the most frequent configuration, uveal melanomas can take on a diffuse pattern in which much of the uveal tract is uniformly thickened. This configuration is rare, occurring in approximately 5% of cases. Patients typically have poorly differentiated tumors and early metastases. Rarely, melanomas can be multicentric in one or both eyes.

A rare syndrome has been described by Barr et al in which patients have bilateral diffuse uveal melanocytic tumors associated with a systemic malignancy. These patients died of their primary malignancy, but they did not develop metastatic melanoma. Much of the ocular melanocytic proliferation was benign, although there were areas of malignant transformation. The authors speculated that humoral factors may play a role, but the precise relationship between the melanocytic proliferations and the systemic malignancy remains unclear.

Melanomas can also diffusely involve the ciliary body in a pattern called ring melanoma. Such tumors can be difficult to diagnose since there is relatively little visible mass effect and since they occur in a diagnostically “silent” area of the eye. Clinically, the only sign of the melanoma may be focally increased pigmentation of the angle, anterior face of the ciliary body, or adjacent peripheral iris. Transilluminating the globe can occasionally help to show tumor size. This technique can be useful for delineating anteriorly located melanomas and is an excellent method to assess the basal size of the tumor. Ultrasound may also be useful to document these relatively silent tumors.

Other presentations of melanoma are less typical. Secondary glaucoma can occur through several mechanisms. Indeed, intraocular melanoma is part of the differential diagnosis in eyes with unilateral glaucoma. If the tumor extends through the retina or arises in the ciliary body or the iris, discohesive cells can collect in the trabecular meshwork and impede aqueous outflow. This form of secondary glaucoma is called melanomatalytic glaucoma. Necrotic melanomas can release viable and necrotic cells along with free pigment and pigment laden macrophages, thereby causing a similar condition. Tumors of the ciliary body and the iris, especially if extensive, can also involve the trabecular meshwork directly. Another mechanism occurs when large choroidal and ciliary body tumors shift the lens-iris diaphragm forward, causing secondary pupil block glaucoma.

Ultrasound is the most useful ancillary technique, although the findings are characteristic rather than specific for melanoma. Both A-scan and B-scan ultrasound shows choroidal melanomas to have low to moderate internal reflectivity, sometimes called acoustic hollowing because part of the tumor typically appears dark on B scan. The A scan is accurate in helping to estimate the height of the tumor, which aids in distinguishing thin melanomas from nevi and in assessing growth over time. The choroid just beneath the melanoma often shows artifactual excavation, an ultrasonically lucent area just beneath the choroid. B scans typically show orbital shadowing, an ultrasonically dark area posterior to the sclera behind the tumor. Ultrasound will also disclose the collar-button shape of the tumor if it has broken through Bruch’s membrane and any extraocular extension of the tumor.

Ultrasound is particularly useful in the diagnosis of melanoma in eyes in which the posterior pole cannot be visualized directly. Melanomas in such eyes are often unsuspected. One series estimated that up to 20% of all eyes with opaque media harbor a melanoma. Probably more recent figures would be lower, but such cases continue to occur. Melanomas themselves can cause a dense vitreous hemorrhage that obscures them from view. Because of the possibility of unsuspected melanoma, ultrasound should be done routinely in all eyes with opaque media. Eyes with a unilateral dense cataract may also contain an unsuspected melanoma that may have caused the cataract by direct pressure on the lens; diagnostic ultrasound should be obtained to rule out this possibility.

Fluorescein angiography is another technique that can supply supporting evidence for the diagnosis of melanoma. Approximately two thirds of cases in one series showed a “double circulation” pattern, which is characteristic of melanomas that have broken through Bruch’s membrane. This “double-circulation” pattern refers to the filling of the retinal vessels overlying the tumor, superimposed on dilated vessels within the tumor itself. This pattern can sometimes be seen in melanomas that have not extended through Bruch’s membrane. The retinal pigment epithelium is frequently altered overlying choroidal melanomas, and focal defects are seen as “hot spots” as they leak fluorescein.

Melanomas that have invaded the retina may show vascular anastomoses between the tumor and the retina, as well as leaking microaneurysms in the retinal vessels overlying the tumor. Other typical fluorescein patterns include areas of retinal capillary nonperfusion and blockage of larger retinal vessels. None of these findings, however, is diagnostic for melanoma, and not all melanomas demonstrate these patterns.

Indocyanine green angiography is an alternative technique for imaging choroidal vasculature. The excitation and emission wavelengths are in the near-infrared range, a
region in the spectrum where melanin is relatively transparent. Thus, indocyanine green angiography shows details of choroidal circulation more effectively than does fluorescein. This technique can be combined with scanning laser confocal microscopy to study the vasculature at a particular level. In two patients, the clinical findings could be correlated with the histologic configurations of the tumor vessels, allowing a possible estimate of prognosis. The relationship of the tumor vascular patterns seen histologically and the prognosis are discussed more fully below.

Magnetic resonance imaging (MRI) has been proposed as a helpful diagnostic technique because melanin is paramagnetic and has specific characteristics (enhanced proton relaxation with shortened T1 and T2 relaxation times) on imaging. However, melanomas vary in degree of pigmentation as well as other intrinsic features so that the so-called "characteristic" pattern is seen in only approximately 20% of cases. Since MRI is expensive and currently is not as sensitive as other methods, its routine use is not indicated.

Fine-needle aspiration biopsy is a technique that may be useful in the differential diagnosis in selected cases. A needle is inserted directly into the tumor from the vitreous side, and the tumor is sampled for cytologic analysis. In this way, benign simulating lesions can be diagnosed, thus avoiding a mistaken enucleation or radiation treatment.

As with any sampling technique, both false-negative and false-positive results may be obtained, but in experienced hands and with a cytopathologist experienced in evaluating ocular specimens, this technique is both sensitive and specific. In one study of 53 patients with a variety of histologically determined diagnoses, only one false positive and two false negatives occurred. Fine-needle aspiration also can be useful as a predictor of subsequent metastasis in patients undergoing radiation therapy. In a study of 116 patients about to undergo either plaque or external irradiation, fine-needle aspiration was performed just before treatment. The percentage of epithelioid cells correlated strongly with survival and with tumor recurrence. However, as is always the caveat with fine-needle aspiration, the sampled area may not be representative of the entire tumor.

A general physical examination and additional tests are done to diagnose metastatic disease. The most frequent site of metastasis is the liver, so the workup should include liver enzyme levels, and, if indicated, liver ultrasound or scan. Early liver metastases can be difficult to diagnose, which is unfortunate since prompt palliative treatment may enhance survival somewhat. In one series, patients whose metastases were symptomatic and who received no treatment survived a median of one year, while those whose metastases were found on screening examination and who were treated survived for a mean of somewhat more than three years. Whether prophylactic treatment for possible metastasis before it is clinically evident would enhance survival is not known. Other frequent sites of metastatic disease are the lung and the central nervous system. The skin and subcutaneous tissue and the skeleton are other reported sites.

Overall, however, once metastasis has occurred, survival is poor, and no treatment has been found to be effective.

A number of lesions can simulate melanoma, especially those that appear dark clinically. Over time, the numbers of eyes removed for the mistaken diagnosis of melanoma has diminished considerably, due to both more accurate preoperative diagnosis and a greater awareness of simulating lesions. The rate of false-positive diagnoses has dropped from 12.5% in 1970 to 1.4% in 1980. In the first report from the Collaborative Ocular Melanoma Study, only two of 413 enucleated eyes were diagnosed incorrectly, for a rate of 0.48%. More recent figures from this same study gave a rate of 0.33% (five of 1,527 eyes). These results, however, may not be generalizable to all clinical practices, although large clinical centers with considerable experience are likely to have similar results.

Melanocytic nevi can simulate small melanomas, and the clinical differentiation between the two can be difficult. Moreover, some previously diagnosed small melanomas have, upon further review of the histology, been reclassified as nevi since they were only minimally elevated and had benign cytology. A particular type of nevus, the magnocellular nevus or melanocytoma, can grow to be very large. Melanocytomas can arise anywhere in the uveal tract, although the most common location is adjacent to the optic nerve head. Melanocytomas are black, in contrast to the beige, tan, or brown color of melanomas. Growth of melanocytomas does not necessarily indicate malignant transformation.

Metastatic tumors can simulate amelanotic melanomas. However, they tend to be bilateral and multifocal. The patient usually has a known primary, although lung carcinomas are notorious for presenting as metastatic eye disease.

While metastatic tumors can have a variety of presentations, they typically are thinner than melanomas and amelanotic and often are a creamy yellow, with overlying retinal pigment epithelial mottling. Choroidal lesions can also mimic scleritis, uveitis, and vireitis.

Metastatic lesions of the iris may resemble the Koeppe and Busacca nodules of sarcoid.

Subretinal blood, particularly blood beneath the retinal pigment epithelium, can appear as a dark, rounded lesion simulating a melanoma. With time, this blood will disappear or be replaced by a fibrous scar. Diseases such as age-related macular degeneration can present with subretinal pigment epithelial blood beneath the macular or extramacular disciform scar, simulating melanoma. The disciform scar itself can be elevated enough, with variegated pigmentation, to simulate a melanoma.

Retinal pigment epithelial proliferation occurs in response to many stimuli, including ocular trauma, intraocular infection and inflammation, and retinal detachment. Sometimes the resulting masses become quite large and nodular, posing a diagnostic problem. Diagnostic fine-needle aspiration has been helpful in some cases.

Choroidal hemangioma can simulate melanoma. These lesions may be solitary and unassociated with systemic disease, or they may be part of the Sturge-Wever syndrome. Hemangiomata are orange-red in appearance, nearly the same color as the fundus, and usually do not change size appreciably. Ultrasound shows more internal reflectivity than is typical for melanoma.

There has been a single case report of a choroidal hemangioma assuming a mushroom-shaped configuration.

Choroidal osteoma, an idiopathic or postinflammatory discrete bony lesion, can resemble an amelanotic melanoma by ophthalmoscopy, but it can be diagnosed by its characteristic ultrasound or computed tomographic (CT) scan appearance. Osteomas are typically juxtaocular and, for unexplained reasons, tend to be more frequent in girls. Osteomas are amelanotic lesions with minimal elevation. They typically appear as yellow-white and may show slow growth. Because of the bony nature of these lesions, the ultrasound shows high reflectivity, even with low intensity. Prior intraocular and periocular inflammation has been suggested as the cause of these lesions in some patients, but for most, the pathogenesis is obscure.

**Histology**

Because for years the standard therapy for melanomas was enucleation, the descriptive histology of these tumors has been thoroughly studied. Two different types of tumor cells have been described -- spindle and epithelioid. Spindle cells have elongated nuclei and relatively scant cytoplasm (Fig 4). By light microscopy, the cells may appear to form a syncytium but, as disclosed by electron microscopy, individual cells do have a plasma membrane. In Callender’s original scheme, spindle cells were of two types -- A and B. Spindle A cells, the most nearly benign type, had fine nuclear chromatin and a chromatin stripe along the nucleus. The slightly plumper B cells had a single, round nucleolus. Other cells, usually seen in larger tumors, are more discrete, larger, and more pleomorphic. They have a round or oval nucleus and relatively abundant cytoplasm, and they are associated with a worse prognosis. Because they resemble epithelial cells, they are called epithelioid cells (Fig 5).
Callender undertook the first classification of uveal melanomas by histologic criteria and categorized them into six groups.\(^{57}\) This classification system has subsequently been modified to correlate with prognosis more precisely.\(^{58}\) The modified Callender classification is still the most widely used scheme. However, it remains a subjective analysis, not easily reproducible or consistently applied between different pathologists.\(^{59}\) This is at least partly due to the fact that the division between spindle and epithelioid cells is an artificial one; tumor cell morphology represents a continuum.\(^{58}\) An objective histologic classification would be valuable, particularly for comparison of results from different institutions. Several potential methods have been devised to assess prognosis more objectively.

One technique measures the mean of the nucleolar area using a computerized system to sample routinely stained slides in a random fashion. The standard deviation of the mean of the nucleolar area (thus a measure of both size and variation in size) derived from 50 random, computer-selected high-power fields has been shown to be an excellent predictor of prognosis by some investigators. Tumors with larger nucleoli and with more variation in size have a worse prognosis. The nucleolar size and variation correlate closely with the modified Callender classification; thus, this method simply provides an objective method for classification.\(^{58}\) In another series, nucleolar size also was useful in helping to differentiate iris melanomas from nevi.\(^{60}\) Others, however, have not been able to confirm these results.\(^{61}\)

An alternative method of evaluation looks at vascular supply to the tumor.\(^{62}\) Nine different vascular patterns have been described and categorized by staining routinely processed slides with periodic acid-Schiff to enhance the vascular characteristics of the tumor. Of these nine, only one (the closed loop configuration) was a significant predictor of death from melanoma.\(^{38}\) The investigators were able to amplify their prognostic data by scanning the images into a computer to enhance and to quantify the relative area taken up by the vascular patterns. They found that cross-sectional tumor area combined with presence and amount of particular vascular patterns resulted in a high prediction of death from metastases.\(^{62}\) Other investigators have not found the presence of vascular loops to be as strong a predictor as was the measurement of the mean diameter of the largest nucleoli or the cell type.\(^{63}\)

Quantification of nucleolar organizer regions has also been correlated with prognosis. Nucleolar organizer regions are those areas of the nucleolar DNA that direct ribosomal RNA transcription and production of ribosomal proteins. Silver stains can be modified to highlight these areas. By this technique, benign nevi were found to have a mean of fewer than two such regions per cell, whereas melanomas had more than four. These measurements also correlated with tumor size and mitotic index.\(^{54}\) These results need to be duplicated with a larger series since this study had relatively few cases. More study, possibly with pooling of cases from several laboratories, is needed to refine and compare all of these techniques.

**Therapy**

Twenty years ago, eyes with suspected ciliary body and choroidal melanoma were enucleated routinely. In 1978, Zimmerman and colleagues\(^{65}\) challenged this traditional approach to therapy by suggesting that enucleation might actually hasten death from metastatic disease. They observed a postenucleation rise in mortality that peaked at approximately two years after surgery. Presumably, compression on the globe during the enucleation procedure caused tumor cells to exit via the vortex veins, thus causing metastasis. Not all agreed with these conclusions.\(^{66}\) One difficulty was the lack of data on the natural history of the tumor. Relatively few patients had refused enucleation, and they did not constitute a random sample of all patients with melanoma. Moreover, relatively little work had been done on alternative methods of therapy. A salutary effect of the observations of Zimmerman et al, however, was that clinicians took a more cautious approach. No longer were patients rushed to enucleation; rather, time was taken to be more certain of the diagnosis and to document tumor growth more carefully.

One difficulty with this tumor is the wide variety of behaviors it exhibits. In one patient, a melanoma remained stable, apparently dormant, for many years, then suddenly grew, metastasized, and killed the patient. In another case, a choroidal melanoma that was manifest as a rapidly enlarging lesion in an area of the fundus documented photographically as tumor free 16 months earlier. These are two extremes, but they illustrate how varied the biologic activity of this tumor can be.\(^{41}\)

Much work has been done in the past 20 years to develop alternative methods of therapy, particularly for those eyes with good vision. The most frequently used alternative method is radiation therapy. Radiation kills a tumor either by producing free radicals that destroy cellular DNA immediately or by induction of mutations that go on to kill tumor cells over a protracted period of time. Radiation also induces vascular fibrosis and secondary hypoxia, which again may take time to cause tumor cell death. Thus, radiation provides both short- and long-term effects.\(^{67}\)

Radiation can be given as an alternative to enucleation or as a preliminary treatment before enucleation in order to decrease the likelihood of metastasis. No large-
The most frequently used system for delivering radiation is plaque radiotherapy (brachytherapy). A metal shield containing small radioactive seeds is sutured to the outside of the sclera overlying the tumor. The radiation dose is principally delivered to the base of the tumor, with a gradual lessening toward the apex. The plaque size is designed to include a margin of 2 mm around the tumor. It is left in place until the calculated dose of radiation has been delivered, approximately five to seven days, then it is removed. Several different isotopes have been used including cobalt 60, ruthenium 106, iodine 125, and palladium 103. Cobalt-60 was one of the first isotopes used for plaque therapy for choroidal melanoma. It is a high-energy gamma emitter, and thus there is a risk of damage to normal ocular structures several millimeters away from the source. Iodine 125, probably the most frequently used isotope at present, is also a gamma emitter but at a much lower energy. Thus, designing protective shields is easier and normal ocular structures are at less risk.

One problem with all forms of radiation therapy is that numerous complications can ensue, primarily due to radiation vasculopathy. Newovascular glaucoma has been the most serious problem with external-beam radiation. The long-term results in terms of survival for external-beam radiation vs enucleation have been approximately equal. Small tumors and those away from the fovea have tended to do better in terms of vision retention.

Small tumors, especially those located relatively anteriorly, can occasionally be excised using an eye-sparing technique known as sclerouvectomy (eyewall resection). The entire tumor is removed en bloc, and a replacement piece of banked sclera is used to repair the surgical defect. A modification of en bloc resection is lamellar sclerouvectomy, which preserves the outer sclera and helps maintain the integrity of the eye. Some have claimed good results with this technique in selected patients, but others caution that melanoma cells commonly invade the adjacent sclera and that cells can be present at the margin of the resected tissue.

**Future Directions: The Collaborative Ocular Melanoma Study**

The Collaborative Ocular Melanoma Study (COMS), a multicenter national trial, was begun due to the controversy and uncertainty surrounding optimal treatment of uveal melanoma. This study is funded by the National Eye Institute of the National Institutes of Health. Enrollment of patients with ciliary body or choroidal melanoma began in 1987. Patients have been sorted into three groups: those with small, medium, and large tumors. Those with small tumors (up to 3 mm in elevation) are observed for tumor growth; if growth is sufficient to place the tumor in the medium group and if the patient remains eligible and willing, the eye is randomized for treatment. Patients with medium tumors (those between 3 mm and 8 mm in thickness and up to 16 mm in largest basal diameter) are randomized to either enucleation or plaque irradiation with iodine 125. Nearly 1,200 patients have been enrolled in this arm of the study. Large tumors (greater than 8 mm in elevation and 16 mm in basal diameter) are randomized to receive external irradiation or no irradiation before standard enucleation. The cutoff between medium and large tumors was changed from 8-mm elevation to 10-mm elevation partway through the recruitment period. Before enrollment closed in 1994, 1,003 patients were enrolled in this arm of the study.

Part of the purpose of the COMS is to assess the natural history of the tumor in order to design effective management and also to evaluate therapy in a nonbiased fashion. Also, the study includes assessment of quality of life as well as vision retention in patients whose tumors are irradiated. As with other multicenter trials, one objective is to standardize observation and treatment criteria so that patients from different institutions can be compared. Developing standardized criteria is the only way we will be able to obtain sufficient data on a large enough group of patients to draw valid conclusions about natural history and treatment. A weakness of the study is that external charged particle treatment was not included. Also, there is no plan to compare efficacy of different plaque isotopes.

More than a decade has passed since recruitment for the COMS began. Some preliminary results have been published recently, and one report confirms the very high accuracy rate of clinical diagnosis. Of a total of 1,532 eyes enucleated as part of the protocol, all but five were histologically confirmed as containing melanomas, for a rate of 99.7%. Four of the five erroneously diagnosed eyes contained metastatic adenocarcinoma, and one had a hemangioma.

Initial mortality figures from the trial of treatment options for large melanomas also were recently published. Approximately 80% (801 of 1,003) of the patients enrolled have been followed for five years or longer. Based on these patients, the estimated five-year survival rates were 57% for enucleation alone and 62% with preenucleation irradiation, a statistically insignificant difference. It is possible that longer duration may accentuate a small difference.

Results for the trial of enucleation vs brachytherapy for medium-sized tumors are not yet available. Previous experience would suggest that any difference in outcome between these two options also probably will be small, although it may still be clinically important. Any major advance in therapy for uveal melanoma will depend on gaining insights into the timing and mechanisms of metastasis.

References


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