Proton Beam Irradiation of Uveal Melanomas: The First 30 Years
The Weisenfeld Lecture

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Melanoma of the uveal tract is a life-threatening tumor that also presents a major threat to the function of the eye. Although the disease accounts for few cancer deaths in the United States each year, approximately one quarter of affected patients eventually die from metastasis. This number is greater in patients with certain characteristics that are associated with poor prognosis. The annual incidence of eye melanoma in the United States is 6 cases per 1 million persons (approximately 1500 new diagnoses per year).1

NATURAL HISTORY

Most choroidal melanomas are thought to arise from preexisting choroidal nevi. It has been estimated that no more than 1 in 5000 choroidal nevi develop into a malignant tumor annually.2 Greater tumor thickness and visual symptoms3–5 have been associated with lesion growth in several studies of small, indeterminate lesions, and the probability of growth within 5 years is approximately 25% to 35%, depending on the presence of these factors. Available data suggest that observation in small, dormant lesions does not compromise melanoma-specific mortality.6

Data on the natural history of ocular melanoma are limited, since it would be unethical to conduct clinical trials that would require withholding treatment. However, under the auspices of the Collaborative Ocular Melanoma Study (COMS), in a small natural history study of 42 patients with medium-sized tumors who deferred or declined treatment, the 5-year mortality rate was 30% in the natural history group compared with 18% in patients with similar sized tumors who received immediate treatment in the COMS, suggesting that undergoing treatment is the prudent course of action.7

Angiogenic mechanisms are suspected to play a role in the natural history of many solid tumors,8 and recent preclinical studies have begun to elucidate the role of these mechanisms in ocular melanoma. Apte et al.9 have demonstrated that uveal melanoma cells produce angiostatin, a plasminogen fragment that has antiangiogenic properties and inhibits micrometastasis, suggesting control of metastatic foci growth by the primary tumor. A more recent experimental study of exposure to exogenous angiostatin in a murine ocular melanoma model10 yielded similar results.

MANAGEMENT OF UVEAL MELANOMA

The earliest treatment for uveal melanoma was removal of the eye. Today, enucleation has been supplanted by radiotherapy as the standard of care for patients with uveal melanoma, offering patients preservation of an intact eye and, in many cases, preservation of visual function. Enucleation is usually indicated for tumors with large extrascleral extensions and extensive iris neovascularization or tumors involving more than 30% of the ocular volume. Other treatment modalities, such as local resection and transpupillary thermotherapy, are used in a few centers in selected cases.

Radiotherapy

The introduction of radiotherapy represented an important advance in the treatment of uveal melanoma, and today radiotherapeutic plaques11–14 and external beam irradiation15–19 are the most commonly used therapeutic modalities. Ionizing radiation damages the DNA of the malignant cells, most commonly by causing double-strand breaks, which may be mispaired and disrupt the integrity of the chromosome. The effects of this damage become manifest during mitosis, at which point the cells cannot successfully replicate. Other consequences of irradiation include changes in growth factors and signal transduction pathways, apoptosis, and the regulation of the cell cycle.20 Damage to cells, particularly those that rarely divide and are highly differentiated, like those comprising the retina and the optic nerve, may also occur secondary to disruptions in their vascular supply.

The first isotope used for brachytherapy was cobalt-60, popularized by Stallard,21,22 but because it is associated with high rates of ocular morbidity,12,23 alternative isotopes that produce fewer side effects were sought. Today there are several of these, including ruthenium 106-rhodium 106 (106ru/106rh), which is used extensively in Europe for the treatment of small and medium sized tumors,13,24 and iodine 125, the most commonly used plaque in the United States,13 a gamma emitter that has greater tissue penetration,25 thus allowing larger tumors to be treated. Regardless of the type of plaque used, there are higher local recurrence rates compared with another radiotherapeutic approach, particle irradiation (5-year rates of approximately 8% to 12%26–29 versus 3%19 to 4%30–31 respectively).

An alternative approach, external beam irradiation (EBRT), utilizes heavy charged particles, such as protons32–34 or helium ions.35 Stereotactic radiosurgery with the gamma knife36,37 is another modality, but the dose distributions are not as precise as in proton radiotherapy, and additional data on outcomes must be ascertained before comparisons to proven radiotherapies can be made. Although good outcomes have been achieved with helium ion radiation,38 it has now been abandoned due to its excessive cost. At the present time, heavy charged-particle irradiation with protons is the most widely...
used modality of EBRT for the treatment of intraocular tumors because of its attractive dose distributions. However, choice of treatment many times depends on the availability of treatment facilities, and proton facilities have been lacking. Currently, there are more than 20 proton centers worldwide, including facilities in Canada, Europe, Japan, South Africa, and the United States. In the United States, the first facility to treat uveal melanomas was the Harvard Cyclotron (HCL) in Cambridge, Massachusetts. In April 2002, the Northeast Proton Therapy Center (NPTC) at Massachusetts General Hospital in Boston became fully operational, and treatments were transferred from the HCL to the NPTC. At this new facility, more than 1000 patients can be treated per year, and one of three treatment rooms is dedicated to the treatment of eye tumors. The Crocker Nuclear Laboratory at the University of California, Davis, and the Loma Linda University Medical Center also offer proton therapy. In 2004, the Midwest Proton Radiotherapy Institute began operations, and by the end of 2006 two additional proton centers should be available (at Shands Medical Center, Jacksonville, Florida, and M. D. Anderson Cancer Center, Houston, Texas) to treat patients with eye tumors and other malignancies. With greater access to proton facilities, patients with uveal melanoma will have greater opportunity to undergo proton therapy for their tumors.

THE MASSACHUSETTS EYE AND EAR INFIRmary ocular oncology service

The Massachusetts Ear and Eye Infirmary (MEEI) in Boston is a national and international referral center for the diagnosis and treatment of eye neoplasms. The inaugural treatment of proton irradiation for choroidal melanoma was completed at the MEEI in 1975. During the past 30 years, more than 3000 patients with eye melanoma have been treated according to established standardized protocols for evaluation, treatment, and follow-up.

Founding of the Ocular Melanoma Registry

In the early 1980s we established the Uveal Melanoma Registry, a population-based registry for ocular melanomas. To date, detailed demographic and clinical data have been collected on most patients treated by proton irradiation. A series of detailed reports have been published on local tumor control, melanoma-related mortality, melanoma and visual loss. Overall, these analyses have demonstrated that currently used doses of proton radiation are highly effective in achieving local control in eye melanoma, with no deleterious effect on survival.49,50 These analyses have demonstrated that presently used doses of proton radiation are highly effective in achieving local control in eye tumors. The Crocker Nuclear Laboratory at the University of California, Davis, and the Loma Linda University Medical Center also offer proton therapy. In 2004, the Midwest Proton Radiotherapy Institute began operations, and by the end of 2006 two additional proton centers should be available (at Shands Medical Center, Jacksonville, Florida, and M. D. Anderson Cancer Center, Houston, Texas) to treat patients with eye tumors and other malignancies. With greater access to proton facilities, patients with uveal melanoma will have greater opportunity to undergo proton therapy for their tumors.

Charged-Particle Irradiation with Protons

In 1946, Wilson suggested proton beam irradiation as a potential treatment for tumors within the human body. It was used as early as the 1950s to treat pituitary tumors and we treated the first patient with an eye melanoma in 1975.59 High-energy protons, bearing a single positive charge are generated at a cyclotron by removing the orbital electron from hydrogen atoms in a vacuum with a high-voltage field. After acceleration, a particle beam with a flux of 2 billion protons/second is directed from the emission port. The energy of this beam can be modulated to cover target tissue of any shape and at any depth with a near uniform dose because of the physical characteristics of the particles (i.e., minimal scatter and delivery of maximum dose at the end of the beam path; Bragg peak effect).35,36 This near-uniform dose delivered to the tumor combined with the sharp reduction of dose outside the treated area should increase the therapeutic ratio of tumor control to normal tissue complications when compared with other radiation modalities. These advantages of proton irradiation are supported by histopathological findings that reveal thickening or thrombosis of the tumor vasculature but intact choroidal vasculature and RPE adjacent to the tumor and beyond tumor margins and are especially critical for the treatment of intraocular melanomas, which tend to occur in the posterior pole of the eye adjacent to the optic nerve and fovea. Eyes with tumors close to these critical structures can maintain visual potential after treatment because of the favorable radiation gradient of the beam. Larger tumors can be treated because the overall irradiated volume is reduced, thereby increasing the tolerance of the eye to irradiation.

Early Proton Therapy Research.

Preclinical studies of proton therapy for the treatment of intraocular tumors were begun in the early 1970s. The selectivity of proton irradiation was illustrated by using small-diameter collimated beams, positioned on the fundus by stereotactic radiography, to induce lesions in monkey eyes that were confined to the intended radiation field. Further, normal retinal architecture as close as 1 mm from the edge of such lesions was observed over 3 years after proton irradiation. Once the concept of the utility of proton beam irradiation for ocular melanoma had been established, further research was performed to improve the accuracy with which this therapy could be delivered. This concept was substantiated by the results we observed after treatment in our earliest patients. Subsequent research was directed toward evaluating clinical outcomes, with particular emphasis given to comparisons of survival in patients who received proton irradiation to those who had undergone enucleation.

Proton Therapy Preparation and Techniques.

Details of the proton treatment protocol for intraocular melanomas have been described previously and I will present a brief
summary herein. To align the tumor with the proton beam during treatment, the tumor is first localized by transillumination and/or indirect ophthalmoscopy during surgery and four tantalum rings are sutured to the sclera at the edges of the tumor. The dimensions of the lesion are measured on the sclera, and drawings are made to document the shape of the tumor and the location of the tantalum rings. These data are subsequently input into a treatment-planning computer program. (For tumors involving the ciliary body and peripheral choroid, transillumination is used to define tumor margins in relation to anatomic landmarks of the iris and cornea without the need for surgical intervention.)

This interactive, three-dimensional treatment-planning program is used to determine all treatment parameters, including the fixation angle, the proton range modulation, the shape of the field-defining aperture, and the relative positions of the tumor-defining rings and beam aperture. These parameters are synthesized during a simulation to create a patient-specific treatment plan. During the simulation, roentgenograms are taken to determine the location of the tantalum rings in the treatment position. This information, along with the data from the drawings generated at the time of the surgery, and ultrasonographic findings (axial eye length and tumor height) determined at the diagnostic examination, are used to create a three-dimensional model of the tumor that is superimposed on a model of a normal eye, scaled to the patient’s eye. These parameters are defined to develop a treatment plan that will optimize the radiation dose to the tumor while minimizing irradiation of critical structures.

A high-magnification closed-circuit television system is used to view the eye throughout the procedure. Before irradiation, the patient’s head is immobilized, and the orientation of the eye is established. A fluoroscopic system is used to position the tumor relative to the proton beam axis and to monitor immobilization of the eye during treatment. The treatment field is checked with a beam-simulation field light, and treatment begins after confirming that the position and fixation are adequate. A 1.5-mm margin is included in the treatment field to allow for setup error, possible microscopic extension, and motion during treatment.

Each patient receives a standard radiation dose of 70 cobalt Gy equivalents (CGE), delivered in five equal fractions over 7 to 10 days (63.6 proton Gy times 1.1 relative biological effectiveness equals 70 CGE—that is, the dose that would be biologically equivalent to the numerically same dose if delivered by a cobalt 60 photon beam).

Outcomes after Proton Therapy. Using the extensive data stored in our Uveal Melanoma Registry, we evaluated clinical outcomes in more than 2000 patients treated since 1975. Most patients were symptomatic at baseline examination, had blue-gray irises, and had pigmented tumors. Nonrhegmatogenous retinal detachment was diagnosed in 57% of patients, tumors with extrascleral extension were uncommon (<4%), and 68% were located within 3 mm of the optic nerve or macula. Approximately 17% of patients had tumors greater than 16 mm in diameter and 5 mm in height. These tumor characteristics suggest that patients with larger tumors and tumors near the optic disc and fovea are preferentially referred to centers that offer proton therapy.

Tumor Control. Most treated tumors show regression after the first 6 months of treatment (range, 1–24 months), and they continue to regress for years after therapy (Fig.1). The delayed regression observed in the irradiated tumors is probably due to the prolonged intermitotic phases of melanoma cells, and is unlikely to represent viable tumor cells; histopathologically, we have found that mitotic figures become less common with longer intervals between irradiation and enucleation, with no mitotic figures found more than 30 months after irradiation. Further, irradiated tumors are more likely to show signs of necrosis and fewer mitotic figures than tumors in enucleated eyes, suggesting that the tumor’s capacity for cellular reproduction is compromised.

The direct visualization of intraocular melanoma margins permits more precise treatment planning, and, as a result, recurrences after proton irradiation are rare.7,20,37,41,71 with the highest annual rate (1%) observed 1 year after proton therapy. In our series, close to half of the regrowth occurred at the tumor margins, suggesting that, in a small number of patients, full coverage of the tumor at the time of irradiation was not achieved. When regrowth occurs, laser photocoagulation of flat marginal recurrences can be performed, and, in some cases, reirradiation of the tumor is performed.

Metastasis and Survival. Because of early concerns about the radioresistance of ocular melanomas, the survival experience of these patients has been carefully monitored over time. In our latest analysis of mortality,19,31,34,42 we analyzed 2069 consecutive patients with unilateral choroidal and/or ciliary body melanomas, who showed no evidence of systemic metastasis before treatment and were treated with proton radiation between 1975 and 1997. Five-, 10-, and 15-year tumor-specific survival rates were 86%, 77%, and 73% respectively. In general, similar 5-year rates have been reported by investigators who began treating ocular melanoma patients at newer proton facilities.17,30,51,74 These rates are also comparable to survival rates after treatment with iodine 125 plaques or enucleation.75 The highest annual death rate was observed 3 years after treatment (approximately 4%), and this rate did meaningfully decline until 7 years after treatment.

Common prognostic factors for melanoma-related mortality have been identified in patients who have undergone proton therapy or enucleation and include extrascleral extension,19,77,78 largest tumor diameter,19,34,77,78 patient age,19,34,77,78 tumor pigmentation,19,79 presence or absence of symptoms,19, iris color,31 and tumor origin (ciliary body versus choroid)34,44 or ciliary body involvement.77,78 In addition, failure to achieve local control negatively affects survival; the melanoma mortality rate in patients with tumor recurrences have been reported to be almost twice that of those without recurrence,31 and an elevated risk of metastatic death associated with tumor recurrence has also been reported.

Whereas these risk-factor data regarding prognosis are useful for evaluating the efficacy of proton therapy at the cohort level, it may not be helpful to a patient with newly diagnosed disease who wishes to understand his or her prognosis, given his or her particular disease profile. Using prognostic data derived from robust regression models, we are able to calculate risk scores and individual probabilities of outcomes, including melanoma-related mortality, that can be quickly and easily used by the provider to educate and counsel any patient who wishes to learn more about his or her prognosis. We have also used these probabilities to define low-, medium-, and high-risk...
groups with a range of risk scores serving to define each category. For example, the probability of metastatic death at 15 years after proton treatment is 27% for our entire cohort, but when we contrast the highest and lowest quartiles of mortality risk scores, it varies between 5% and 65%.

Despite the high local control rates realized with radiotherapy, death due to metastases may occur in over 50% of cases with certain characteristics. Hepatic metastases, notoriously refractory to treatment, are typical (~90% of patients), but other sites of metastasis are common, particularly lung (25%) and skin (11%), as the initial site. Few survive beyond 1 year of diagnosis of metastasis (median survival time, 2–8 months).

Therapeutic interventions for hepatic metastases including intraarterial arterial perfusion, immunotherapy with compounds such as interleukin-2, chemoembolization, and surgical resection have been marginally successful, perhaps in part because they are often associated with dose-limiting toxicities.

Finding ways to prevent melanoma metastasis is of paramount importance, particularly in light of the current ineffectual means for treating metastasis. Primary therapy, whether irradiation or enucleation, has little effect on the development of distant metastasis and subsequent death. One hypothesis that would explain this phenomenon is that clinically undetectable micrometastases already exist at the time of initial diagnosis and treatment. Thus, we conducted a nonrandomized clinical trial to determine whether a 2-year course of adjuvant interferon-α-2a therapy (3 MIU by subcutaneous injection three times weekly), given after primary therapy of either proton irradiation or enucleation, improves disease-free survival in patients with characteristics that place them at high risk of melanoma metastasis. Historical control subjects, who had received proton therapy or enucleation only, matched on important prognostic factors to the interferon-treated patients, were used as a comparison group.

We found no benefit of adjunctive interferon (median dose received was 85% of theoretical total dose). Approximately 15% of patients in both the treated and control groups died of metastatic disease by 4 years after primary therapy. One possible explanation for this null finding is that the interferon dose we tested was too low to induce a biological effect. Nevertheless, adjuncts to radiation therapy, such as chemotherapeutics, immunomodulators, or a combination of these, remain a promising approach to prevention or treatment of melanoma metastasis.

Eye Loss. The probability of retaining the eye is approximately 90% at both 5 and 10 years after irradiation, with a slight decrease to 85% by 15 years after therapy. Removal of the eye may become necessary after treatment if there are serious complications or the tumor recurs. Neovascular glaucoma (NVG) is the most common complication leading to enucleation because it is the result of growth of new blood vessels on the ocular surface and the iris. NVG is responsible for just under one half of post-treatment enucleations at MEEI. Retinopathy that is associated with risk of enucleation include tumor height, proximity of the tumor to critical structures, tumor diameter, tumor pigment, and tumor shape. Five-year retention rates ranged from 73% to 98% in patients stratified according to risk scores defined by these characteristics.

Vision Loss. The strongest predictor of visual prognosis appears to be location of the tumor relative to the fovea and the optic nerve. Specifically, tumor location within 2 disc diameters (DD) of both the optic nerve and macula portends visual deterioration (worse than 20/200). Overall, the five year rate of vision loss in our cohort is 52%, but this rate is much greater (66%) when analysis is restricted to patients with tumors located within 4 DD of the optic nerve or macula. Other factors that elevate risk of poor vision include baseline visual acuity of 20/50 or worse, a history of diabetes, presence of retinal detachment involving one or more quadrants, increased tumor height, and increased tumor diameter. There is some evidence to suggest a threshold dose of 25 CGE to 35 CGE for induction of cytotoxic effects on optic disc or macula resulting in visual deterioration.

Complications. Rubecosis iridis and NVG are the most serious anterior segment complications, often leading to visual loss and enucleation. Tumor-induced angiogenic factors, inflammation secondary to necrosis of the melanoma, retinal detachment, and ischemic retina and iris from irradiation are possible stimuli. Rubecosis and NVG can be reduced when the anterior segment is spared. As many as 30% of eyes develop NVG when the anterior segment is directly traversed by the proton beam. More recently, we have found that larger tumor volume is the most significant factor associated with iris neovascularization; a similar finding was reported in patients treated by proton irradiation with tumors too large to be treated with plaque radiotherapy. NVG occurs in approximately 15% of all patients, generally within 3 years of treatment; annual rates drop to 1% or less by 5 years after treatment. Responsiveness of affected eyes to local steroids and cycloplegics as well as pan-retinal photocoagulation provides support to the role of inflammation and retinal ischemia in the pathogenesis of NVG in these patients.

Exposure of the lens to radiation leads to cataract development, typically in the posterior subs capsular (PSC) region. In our series, the occurrence of these lens changes was strongly radiation dose dependent and was also associated with tumor heigh. Overall, incidence of any PSC opacification was 40% 5 years after radiotherapy in one study. By 5 years after irradiation, PSC cataract is diagnosed in 19% of patients when less than 10% of the lens is included in the radiation field and in 54% when more than half the lens is irradiated. Extraction of the cataract may improve vision in some cases and poses no excess risk of tumor metastasis.

Radiation vasculopathy is characterized by capillary nonperfusion, telangiectasis, microaneurysm formation, hemorrhages, exudates, vascular sheathing, and neovascularization. Although radiation effects are usually confined to the treated area, radiation exposure of the optic disc or macula may be unavoidable in patients with tumors located in close proximity to these structures. In such cases, risk of radiation vasculopathy is inevitably high; the 10-year rate of maculopathy for tumors abutting the macula was 69% compared with 8% for tumors located at least 4 DD away (P for trend <0.001). Similarly, papillopathy developed in 65% of patients with tumors within 0.5 DD of the nerve and in approximately 1% of patients with tumors greater than 3 DD from the optic nerve. Not unexpectedly, visual prognosis was poor in patients with these radiation complications; visual acuities of 20/200 or better were observed in approximately one quarter of patients with a diagnosis of papillopathy and in 40% of patients with maculopathy.

Parapapillary and Paramacular Tumors: Special Considerations

As our data illustrate, radiation-induced complications such as maculopathy and papillopathy are major reasons for visual loss, particularly in patients with tumors involving the optic nerve and macula. Because this morbidity is found in the context of excellent control rates, it led us to reappraise the need for the high doses we currently use. To determine whether a lower radiation dose could safely reduce ocular morbidity, we con-
ducted a clinical trial comparing the standard dose of 70 CGE to an experimental dose of 50 CGE (28% reduction) in patients with small- to medium-sized paramacular or parapapillary choroidal melanomas (located within 4 DD of the macula, optic disc, or both structures). Patients were randomly assigned (1:1) a dose using a permuted block design, stratifying by tumor height and posterior tumor location, factors strongly associated with visual outcome.

We published our findings\(^\text{56}\) in 2000, concluding that lowering the total dose to 50 CGE did not yield benefits by 5 years after treatment in patients with smaller tumors near the optic disc or fovea. On the one hand, there were no differences in visual acuity or rates of maculopathy and papillopathy between the two dose groups; on the other hand, we also found no evidence of differences in tumor regrowth or metastasis.

We continued surveillance of these patients to identify any late-emerging effects of lowering the radiation dose and recently analyzed endpoint data at 10 years after treatment. Results were quite similar to those found 5 years after treatment; there continued to be no significant differences between the two dose groups with regard to ocular or systemic outcomes. Findings at the 5-year time point were suggestive of a beneficial effect of the lower dose for patients with tumors abutting the optic disc. However, we could not confirm a significant dose effect for this subgroup in our analysis of the longer-term data. A dose reduction greater than 28% may be necessary to improve functional outcomes in patients with parapapillary and paramacular tumors who receive high radiation exposure to critical structures. However, evaluation of a dose below 50 CGE may not be prudent, as it may pose an unacceptable risk of increased rates of recurrence.

Our most recent research endeavors have been designed to further our knowledge of patients with tumors near the optic disc and/or fovea. We felt that additional thorough analysis of treatment outcomes in this vulnerable population would be helpful to glean data that could be used to counsel patients, because this is a group for which proton irradiation may be the best or only conservative treatment option. Toward this end, we examined anatomic and functional effects of proton irradiation in two subgroups of patients: (1) those with small- to medium-sized tumors within 1 DD of the optic nerve and at least 2 DD from the fovea and (2) those with peripapillary and parapapillary tumors, defined as within 1 DD of the optic nerve, and therefore ineligible to enroll in the COMS. This subgroup included patients with tumors of any size that could involve the macula. The first subgroup was evaluated to learn more about the natural history of radiation papillopathy. The goal of the second subgroup analysis was to measure more precisely how tumor location in close proximity to critical structures may alter risk of functional and survival outcomes.

Tumor parameters for the natural history of radiation papillopathy study were chosen because these characteristics were likely to place patients at greater risk of vision loss due to papillopathy than radiation maculopathy. The optic disc received greater than 60 CGE in 90% of cases in which the tumor abutted the nerve (n = 50) and in 74% of cases in which the tumor was within 1 DD of the nerve (n = 43). Median baseline visual acuity was 20/25 in both groups.

During the period of observation (mean, \(\sim 5\) years), 63 patients (68%) developed papillopathy. Median time to papillopathy was approximately 2 years after proton therapy (range, 5 months–5 years). More patients with tumors touching the disc developed papillopathy within the first year of irradiation and by 5 years after radiation, 81% had developed complications, compared with 67% of cases with tumors that were not touching the disc but were within 1 DD of it. Despite these high rates of papillopathy, approximately half of the affected patients retained vision of finger counting or better as long as 4 years after diagnosis.

Although papillopathy may be inevitable in nearly all of these cases, severe debilitating vision loss does not always ensue. Few patients suffered total vision loss (n = 7), and 13 (21%) patients experienced improvement in visual acuity of three or more lines from visual acuity at the time of papillopathy diagnosis. This improvement was sustained for at least 2 years in 12 patients and for as long as 48 to 72 months in a few patients.

For the COMS-ineligible patient subgroup analyses, we identified 573 patients with parapapillary or peripapillary tumors from our Uveal Melanoma Registry who were followed up for approximately 8 years after proton irradiation. Of these, 240 patients had tumors extending into the macula, and 128 had tumors involving the macula and the optic nerve.

Cumulative rates of regrowth were quite low, with 6% recurring by 10 years after therapy. Approximately half of our patient series showed signs of radiation vasculopathy. Most complications occurred within the first 3 years after proton therapy, with just under one-half of patients experiencing papillopathy or maculopathy. Pretreatment visual acuity was at least 20/200 in 78% of patients but two thirds lost vision to worse than 20/200 after irradiation.

The experience of COMS-ineligible patients was similar to that of all patients with regard to mortality, recurrence, and enucleation outcomes, but they did less well in terms of vision loss and complications, given that exposure of critical structures to a high dose of radiation was unavoidable in these patients. Five-year rates of maculopathy and papillopathy were approximately one and one-half to two and one-half times greater in COMS-ineligible patients than in all patients. Similarly, whereas most (91%) COMS-ineligible patients suffered vision loss (worse than 20/200) by 10 years after proton therapy, vision deteriorated in two thirds of all patients. These findings suggest that proton therapy should be considered for patients with tumors encroaching or contiguous to the optic nerve because eye conservation is possible in most cases, with low rates of recurrence and metastasis.

**Future Directions**

Our experience with proton therapy, having treated more than 3000 patients during the past 30 years, provides convincing evidence of the advantages of this modality for patients with uveal melanoma, particularly those with tumors that are large and/or posteriorly located, for which other types of radiotherapy may be unsuitable or may produce more complications.

Improvements in proton treatment are needed, however. Strategies to reduce the cytotoxic effects of radiation on normal ocular tissues—for example, an increased fractionation scheme or treatment with a combination of radiation and antiangiogenic agents—could decrease functional loss and enucleation rates. Perhaps most important, because the high local control rates we achieve with protons and other types of radiotherapy have not translated to an effective “cure,” we must find successful ways to prevent and/or treat the development of metastasis. We have already discussed the importance of continued research into therapeutic interventions for metastasis. Another approach is a molecular one: as our knowledge of the human genome and proteome expands, we will have the opportunity to evaluate new cancer-susceptibility genes that may serve as targets for new interventions, as well as identify proteins that may be biomarkers of prognosis or treatment response. This multidisciplinary approach to research may one day translate into strategies for prevention,
early disease detection, and more effective therapies. Potential areas of inquiry may include the role of mutations in genes responsible for photodamage repair, immune response deficiencies, and environmental factors that may induce the dysfunction of these disease pathways.

References


