Choroidal Melanoma: Innovations in Treatment

Expanded applications for radiation therapy have improved treatment.

BY PAUL T. FINGER, MD

Benjamin Franklin said, "An ounce of prevention is worth a pound of cure." In response, I say to my patients, "Think of sunglasses as sunblock for your eyes." Consider that the people of Queensland, Australia, living beneath the ozone hole, have the highest reported incidence of choroidal melanoma, at 10 per million per year[1]—twice as many choroidal melanoma patients per capita as in the United States and Europe. Additionally, the role of ultraviolet radiation in the development of choroidal melanoma is supported by its greater incidence in patients with blue irides and outdoor occupations. Also consider that these tumors are more likely to be found in the posterior, more sun-exposed uvea, and that recent research has shown that iris melanomas are more commonly found on the lower, more sun-exposed iris.[2]

When a patient with choroidal melanoma presents in your office, however, prevention is no longer an option.

Treatment of choroidal melanoma has evolved from primary enucleation to local resection, laser photocoagulation, and, most commonly, eye- and vision-sparing radiation therapy.[3,4] More than 45 years ago, Stallard introduced the first radioactive eye plaques.[5] These original disc-shaped devices, containing rings of high-energy cobalt-60, were later replaced by lower-energy ruthenium-106, iodine-125, and palladium-103 sources.[6-8] Certain centers also employ external beam radiation therapy techniques such as proton beam, gamma-knife, and stereotactic radiotherapy.[9-12] Each of these radiation sources have been found capable of treating select uveal melanomas, but they differ greatly in their ocular radiation dose distribution and side effects.

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The evolution of treatment for choroidal melanoma was profoundly affected by the multicenter Collaborative Ocular Melanoma Study (COMS).[13,14] This 16-year long clinical trial, funded by the National Institutes of Health, included 2 prospective randomized clinical studies. In sum, the medium-sized choroidal melanoma trial found no survival benefit from enucleation vs. episcleral iodine-125 plaque irradiation. As a result, at The New York Eye

Cancer Center when new patients are made aware of this finding, they almost always choose an eye- and vision-sparing alternative to enucleation. The other randomized arm of COMS, the large melanoma (COMS-large) study, examined pre-enucleation, photon-based (4 Gy x five daily fractions), external beam orbital irradiation. The COMS-large study found that irradiation of eyes with large choroidal melanomas before enucleation did not improve survival.[13] Therefore, at most centers, no patients with choroidal melanoma undergo preenucleation external beam irradiation. However, in part due to the results of the medium-sized tumor COMS trial, most patients with COMS-large tumors no longer have their eyes removed and are treated with eye-preserving radiation therapy techniques (eg, plaque and proton).

INNOVATIONS IN TREATMENT OF CHOROIDAL MELANOMA

Worldwide, methods of treatment of choroidal melanoma are based on ocular, patient, and socioeconomic factors. Characteristics of each individual choroidal melanoma include its size, associated exudative retinal detachment, and possible hemorrhage or secondary glaucoma, as well as the patient's visual acuity. Further, the decision is affected by the patient's motivation to keep his or her eye and the treatment modalities available. In general, choroidal melanoma treatment is performed to prevent metastatic disease, to maximize visual acuity, and to preserve the eye.

SURGERY

Enucleation. Enucleation surgery is typically performed when the melanoma is considered too large for eye-sparing techniques, there is no vision, there is extensive extrascleral tumor extension, and in painful, glaucomatous eyes.[3,4] Additionally, in developing countries it may be performed when eye- and vision-sparing radiation techniques are not available.

At The New York Eye Cancer Center, almost all enucleated patients can be fitted with an ocular prosthesis that requires minimal maintenance and offers excellent cosmesis.[15] We typically place a temporary prosthetic eye on the fifth postoperative day, at the time of bandage removal. Prosthetic motility is typically less than that of the natural eye, and mucus discharge is both common and treatable with olopatadine ophthalmic solution (Patanol, Alcon). Patients are counseled to wear unbreakable polycarbonate glasses to protect the remaining eye.

Innovations in enucleation include the use of porous orbital implants (Figure 1).[4] The rough outer surface and vascular ingrowth limits migration seen with solid, smooth spheres.[16] On the other hand, exposures and infections are much more common with porous spheres. In that migration is an impediment for prosthetic fitting and in an effort to improve cosmesis, I typically employ integrated orbital implants during enucleation surgery for choroidal melanoma.

Figure 1. A porous orbital implant used for volume replacement at enucleation.

Local resection. Opening the eye. Prior to the advent of radiation therapy, selected anterior uveal melanomas were removed by local resection. Since that time, several newer methods of tumor resection have been proposed.[17-19] However, it is important to note that in treatment of uveal melanoma, internal resection techniques have not been prospectively compared to the more widely used techniques (enucleation or radiation) for local control, morbidity and risk for metastasis.

External resection. Case selection includes large anterior melanomas that would otherwise be treated by enucleation. Typically requiring hypotensive anesthesia, transscleral resections for choroidal melanoma can be either lamellar or full thickness. Of these, partial thickness techniques have been more commonly employed. Partial thickness resection requires dissection of a lamellar scleral flap, ocular decompression by limited pars plana vitrectomy, removal of the tumor with its deep scleral lamella, and closure of the eye by suturing of the lamellar scleral flap. After resection, intraocular pressure is modulated with saline. As with internal resection, these tumors are treated with pre- or postoperative radiation therapy to prevent recurrence. Poor local control rates, coupled with a high incidence of

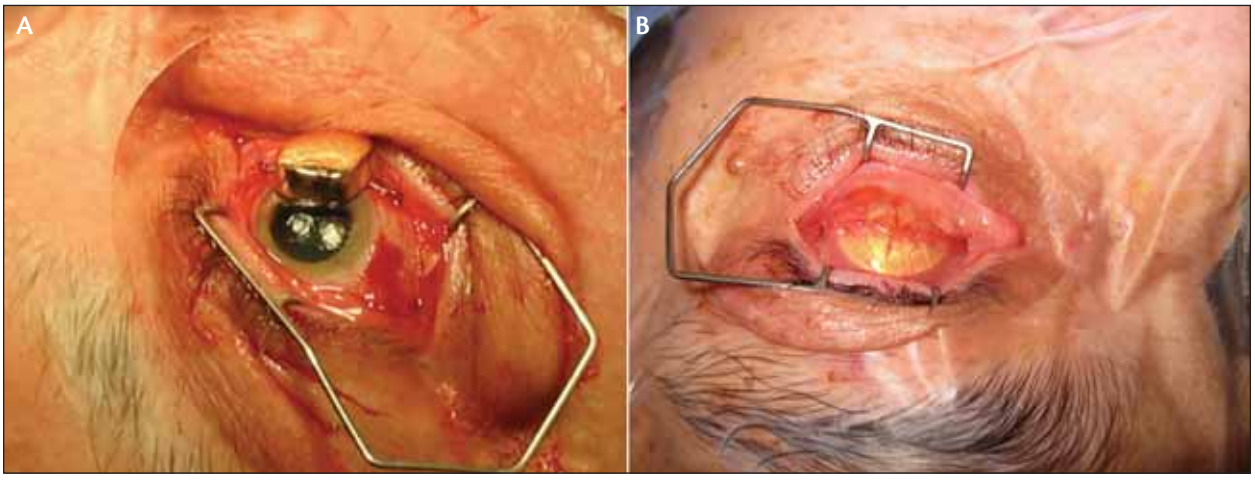

Figure 2. A custom-designed gold plaque for treatment of iridociliary melanomas, seen before closure with a Gunderson flap (A). A total anterior segment plaque for a case of diffuse iris melanoma (after conjunctival flap closure; B).

postoperative complications (secondary rhegmatogenous retinal detachment, intraocular hemorrhage, ocular hypotony) and concerns about tumor dissemination, has limited the widespread use of external resection.[19]

Internal resection. The typical indication for internal resection (endoresection) is when a choroidal melanoma is considered too large for radiation alone and the alternative is removal of the eye.[17,18] This approach is primarily used to prevent or treat "toxic tumor syndrome," also known as secondary intraocular inflammation, after irradiation of large choroidal melanomas. Limitations of this surgery include that the tumor must be located in the posterior choroid and that there should be no extrascleral tumor extension.

To perform internal resection, the choroidal melanoma would be pretreated with plaque or proton irradiation. Then, utilizing pars plana vitrectomy, the tumor is approached through a retinotomy or beneath a retinal flap. The bulk of the melanoma is removed with the aspiration cutter. An air-fluid exchange drains residual subretinal fluid, and then endolaser photocoagulation is used to destroy residual visible tumor and to achieve retinopexy. Silicone oil is typically required. Although endoresection aims to reduce tumor-related ocular morbidity, it adds known risks of vitreoretinal complications.[17,18]

EXTERNAL TECHNIQUES: RADIATION

Laser photocoagulation. Light has been used to focally destroy choroidal melanomas. At first, Meyer-Schwickerath employed a xenon arc laser.[20] Since that time, lasers have been used, including argon, krypton, and infrared (for transpupillary thermotherapy or TTT).[21,22] It is important to note that, to date, no laser method has produced acceptable local control rates in treatment of choroidal melanomas. However, laser has added risks including intraocular hemorrhage and retinal changes (detachment, edema, and traction). Both acute laser-induced optic neuropathy and scleromalacia with extraocular extension have been reported.

Originally described by Oosterhuis, TTT was suggested for the treatment of small tumors near the optic disk or fovea.[21] Employed in an effort to spare these structures from damage, TTT required a modified delivery system with beam widths of 1 to 3 mm and exposure times of up to one minute.[22] Due to failures of local control, TTT has largely been abandoned as a primary treatment for choroidal melanoma. More recent reports suggest that patient selection should include very thin tumors, treatment of circumpapillary tumors that cannot be reached by plaque, and a sandwich technique in which TTT is used in combination with a radiation plaque.[22] At The New York Eye Cancer Center, TTT is used only for choroidal melanomas with marginal tumor recurrences, in selected tumor-related vasculopathies, and for patients who cannot tolerate plaque surgery.

Radiation therapy. Like vitreous substitutes, not all radiation sources are the same.[3] Although each form of radiation can destroy a choroidal melanoma, there are unique differences in side effects based on each form's characteristic radiation dose distribution in and around the eye. Over the years I have published a number of scientific articles that demonstrate that radiation side effects are dose dependent.[23-26] Therefore, we should judge our radiation sources not only by their capacity to deliver radiation to the tumor but also by their ability to spare normal ocular structures. If we keep this in mind, we will accomplish our primary goal of destroying

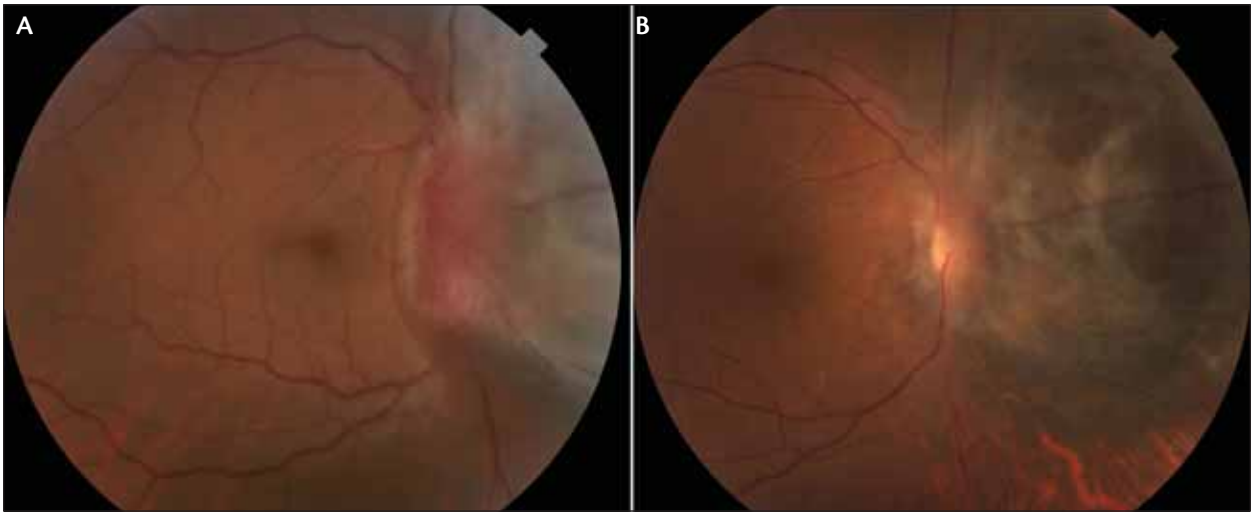

Figure 3. Before (A) and 18 months after (B) slotted plaque brachytherapy. An 8-mm wide slot was cut into the posterior aspect of the plaque to accommodate the optic nerve and its sheath within the plaque during treatment.

the tumor (to prevent metastasis) and also maximize our chances for retention of vision and of the eye.

External beam radiation therapy. Choroidal melanomas can be treated with cylindrical or shaped beams of machine-generated radiation. Examples include proton therapy and more recently cyberknife and stereotactic radiosurgery. Localization can be challenging for external beam techniques. For example, proton therapy typically requires surgical clips to be sewn to the episclera for localization, while forms of external beam radiation therapy depend on radiographic imaging and eye stabilization.

Think of external beam therapies as directed columns or 3-D volumes of radiation that course through the eye to the tumor and encompass it. In order for the tumor to stay in the beam, the eye must stay still. During proton therapy eye movements are monitored on a video screen, and the beam is turned off if the eye wanders during the typical 5 minutes of treatment. In radiation therapy language this is called a mobile target volume. There are 2 ways to compensate for eye movement: One can either increase the size of the beam (the margin around the tumor) and therefore the dose delivered to normal ocular structures, or immobilize the eye during treatment.

Further, external beams must typically traverse the anterior segment to reach a posterior choroidal melanoma. It is no wonder that a 1997 survey of radiation for choroidal melanoma found more anterior segment complications (eg, eyelash loss, dry eye, neovascularization of the iris, neovascular glaucoma, and cataract) associated with proton irradiation compared with plaque techniques.[3] Further, as the maximum external beam dose volume is shifted anteriorly to treat ciliary body melanomas, these complications become greater. Conversely, radiation retinopathy and optic neuropathy were more commonly reported in the treatment of posterior and juxtapapillary choroidal melanomas.[27]

Plaque brachytherapy. In the treatment of choroidal melanoma, plaque radiation therapy is the most widely employed eye- and vision-sparing radiation technique in the developed world. It involves sewing a disc-shaped plaque device onto the sclera so as to cover the base of the intraocular tumor plus a free margin. (Both areas together equal the targeted zone.) Radiation travels from the plaque through the sclera and into the choroidal melanoma.

Mobile target volume has little impact for eye plaques because they are fixed in position on the sclera and move with the eye. Unlike in external beam therapy, no anterior segment entry dose is required in order to reach a posterior choroidal melanoma. Lasting innovations in plaque therapy have included a transition from high-energy cobalt-60 to lower energy ruthenium-106 and iodine-125, as well as standardization of plaque construction and dosimetry by the COMS.

In 1990, I realized that palladium-103 seeds offered even lower energy photons than iodine-125.[28] Therefore, for an equivalent tumor apex dose, most normal ocular structures would receive less radiation with palladium-103 compared with iodine-125. This finding has since been recognized by the American Brachytherapy Society and most recently demonstrated via computer modeling by representatives of the American Association for Physicists in Medicine (TG-129).[29,30]

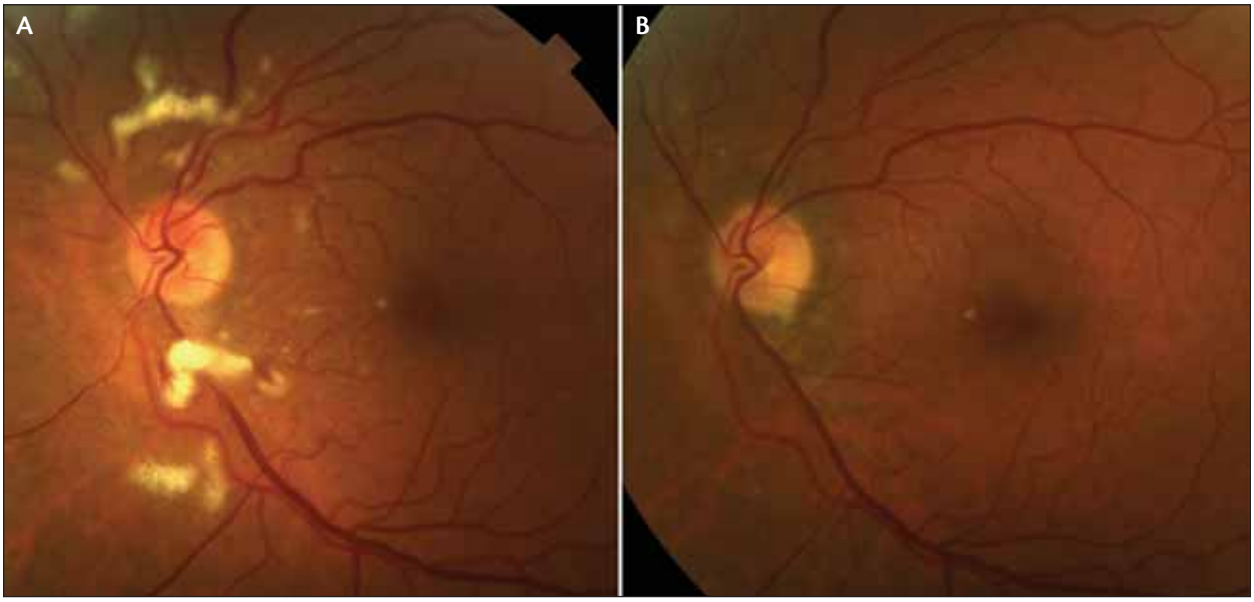

Figure 4. Radiation retinopathy after ophthalmic plaque radiation therapy of a nasal tumor (A). After multiple periodic intravitreal anti-VEGF treatments there is resolution of cotton-wool spots, hemorrhages and retinal edema (B).

At The New York Eye Cancer Center and related hospitals, we routinely perform comparative dosimetry (iodine-125 vs palladium-103) to calculate doses to critical intraocular structures (fovea, optic nerve, lens, opposite eye wall). In each case we make sure each plaque delivers the best possible intraocular dose distribution.

INNOVATIONS FOR LARGE, IRIS AND JUXTAPAPILLARY MELANOMAS

Since the COMS, there has been a trend toward eye conservation for all uveal melanomas, less iridocyclectomy surgery, and more radiation therapy. Further, the orbital portion of the optic nerve proved to be a significant obstruction for plaque placement around juxtapapillary tumors.

Large choroidal melanomas. Many centers have found that most large melanomas can be treated with eye- and vision-sparing radiation therapy. For example, at The New York Eye Cancer Center, the largest uveal melanoma basal dimension treated with ophthalmic plaque is 22 mm, and the tallest has been 16 mm. Although postoperative management of these eyes is often complicated, patients are typically pleased to keep even poorly sighted eyes. After plaque radiation of large choroidal melanomas at The New York Eye Cancer Center, local control has been excellent, and in some cases vision results have been remarkable.

Iris and iridociliary melanomas. Iris melanomas, both local and diffuse, are also treated with radiation therapy.[31,32] Centers have reported treatments with both plaque (Figure 2) and proton beam. Using plaque therapy at up to 18 years follow-up, few and minor anterior segment complications have been noted.[31] In general, in contrast to resection, radiation typically allows preservation of the iris and its function. Almost all irradiated eyes develop cataract, and there is little risk of radiation maculopathy or optic neuropathy.

Juxtapapillary melanomas. Choroidal melanomas near, touching or encircling the optic nerve have been successfully treated with proton beam.[27] More recently Finger slotted plaques (Figure 3) were designed to incorporate the optic nerve into the plaque and thus extend the posterior plaque beyond the tumor's posterior margin, as is done in standard more anterior plaque placement.[33] A paper describing 5-year results with the slotted plaque technique is currently in press.[34]

ANTI-VEGF THERAPY

In a 1997 review, more than 50% of patients were noted to have less than 20/200 vision at or before 5 years after radiation therapy.[3] Although this was all-cause visual morbidity, the most common causes of severe irreversible loss of vision were radiation maculopathy and radiation optic neuropathy.

Beginning in 2007, Finger reported short-term findings of reductions in retinal and optic nerve edema, as well as decreased retinal hemorrhage, associated with periodic intravitreal injections of the vascular endothelial growth factor (VEGF)-inhibiting agents bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis,

Genentech).[35] Later reports,[36-38] and those of others, have supported these findings (Figure 4). Our recent observations suggest that the higher the radiation dose to fovea and optic nerve, the harder it is to overcome radiation vasculopathy with this method.

SUMMARY AND CONCLUSIONS

Three main goals in treatment of choroidal melanoma are: Destroy or remove the tumor to prevent metastasis, maintain vision, and preserve the eye. Although enucleation and surgical resection are available, most patients in the United States and Europe today are treated with plaque radiation therapy. The most widely used sources are iodine-125 and ruthenium-106. A few referral centers offer proton beam and palladium-103. Gamma-knife and stereotactic radiosurgery are the most exotic forms of external beam radiation therapy and should be considered investigational.

We know that all methods of radiation therapy can destroy a choroidal melanoma. However, evidence exists that radiation dose to fovea, lens, and optic nerve can be used to predict rates of complications and possibly response to anti-VEGF therapy. Therefore, it is important to compare the available radiation modalities. Radiation oncologists and medical physicists can perform computer-aided simulations to calculate doses to critical structures, and this information can be used to choose the "best" source of radiation prior to treating your patient.

Innovations and expanded applications for radiation therapy have improved treatment so that few patients have to lose an eye or lose vision due to choroidal melanoma. Our field has progressed from primary enucleation to modern and exotic methods of eye- and vision-sparing radiation therapy. ■

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