Radiation Therapy for the Retina Specialist

Innovations and pearls for the management of ocular tumors.

BY PAUL T. FINGER, MD

Radiation plays a key role in the treatment of ocular tumors. In many cases it offers an eye- and vision-sparing alternative to enucleation. The most commonly used forms of radiation therapy are external beam radiotherapy (EBRT) and ophthalmic plaque brachytherapy. This article reviews some pearls and innovations in the use of radiation therapy, accumulated during 23 years of subspecialization and innovation in the field of ocular oncology.

EXTERNAL BEAM RADIOTHERAPY

In ophthalmology, EBRT is primarily used to treat choroidal metastasis, primary intraocular lymphoma, and less frequently retinoblastoma. There are numerous forms of EBRT, including electron beam, photon beam, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), particle therapy (proton and neutron), the gamma knife, stereotactic radiosurgery, and the newest form, volumetric-modulated arc therapy, also known as RapidArc (Varian Medical Systems, Palo Alto, CA).[1]

The distribution of ocular radiation in tissue—how much goes to the targeted zone and how little goes to surrounding normal structures—affects the effectiveness of the treatment as well as the type and incidence of complications.[1] Because each form of EBRT uses different energies, each has unique characteristics that can be exploited to ensure that most of the radiation is delivered to the tumor and a safety zone around the tumor (margin), while the least goes to the healthy surrounding structures, including the brain and the sinuses. For EBRT, the radiation oncologist will choose the technology that offers the best distribution of radiation dose.

For most cases of juxtafoveal choroidal metastasis, which have for the most part metastasized from breast or lung, prompt EBRT offers the best chance for preservation of vision. If treatment is delayed for the institution of chemotherapy, often the tumor has time to grow through the fovea. Once beneath the fovea, even if the tumor is controlled and regresses, it will leave a vision-limiting foveal scar. Surgeons seeing juxtafoveal metastases should immediately consult with the radiation and medical oncologists to establish the source and institute prompt radiation therapy to preserve vision. One should keep in mind

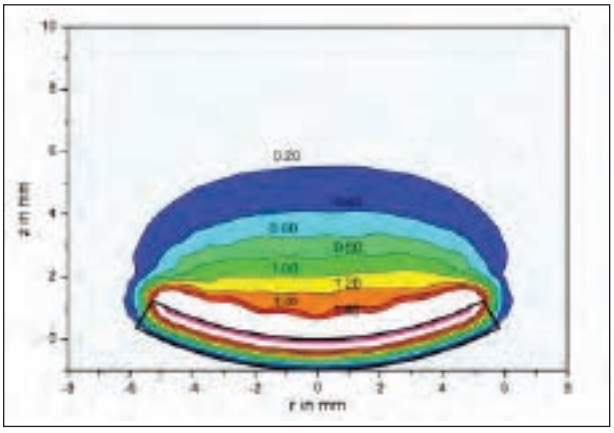

Figure 1. Ru-106 plaques have a small penumbra, minimal side-scatter, and a rapid drop-off in radiation intensity (Courtesy Bebig CoRP).

(Courtesy Bebig Corp.)

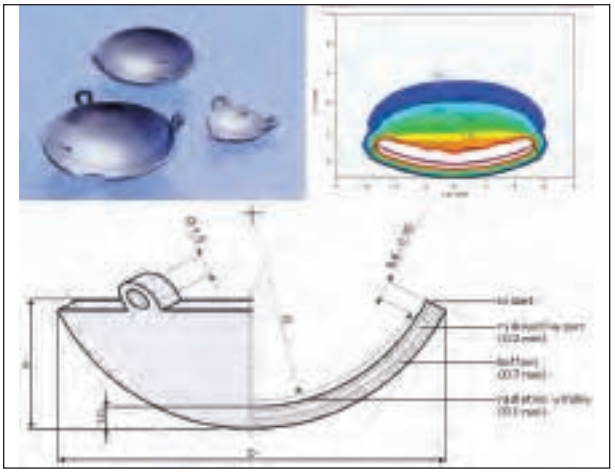

Figure 2. Schematic of Ru-106 plaque shows that the silver radiation window, under which the radioactive part sits, is only 0.1 mm thick (Courtesy Bebig Corp, Berlin, Germany.).

that most patients with choroidal metastasis have a poor prognosis. Therefore, prompt EBRT offers the best chance to keep them seeing and improve their quality of life.

RADIOACTIVE PLAQUES

Radioactive plaque therapy is the most common and widely used treatment for choroidal melanoma.[2] This is because it is the most conformal; it concentrates the radiation within the targeted zone (the tumor) and reduces the amount of energy delivered to normal structures (compared with EBRT).[1,2]

Every retinal surgeon knows that no two liquid vitreous replacements are the same; silicone oil, SF_6, and C_3F_8 all have different characteristics. Retinal surgeons choose the vitreous replacement that fits their particular clinical challenges. Like vitreous replacements, not all radioactive plaques are created equal. Unfortunately, in ophthalmic oncology, most centers use only one type of plaque.

The three radioactive isotopes currently most widely used in ocular oncology are iodine-125 (I-125), palladium-103 (Pd-103), and ruthenium-106 (Ru-106).[2] Ideally, ophthalmic and radiation oncologists should choose from these radiation sources based on each isotope's ability to deliver radiation to each tumor in question with relative sparing of surrounding normal tissues. At The New York Eye Cancer Center, we routinely perform preoperative comparative dosimetry using different forms of radiation.[3] Our choice of plaque type is based on the comparative radiation dose to the sclera, tumor, fovea, optic nerve, and opposite eye wall. Like vitreous replacements, there are general differences among these three radioactive isotopes.

Ru-106 plaques emit beta particles that travel a relatively short distance in tissue. Therefore, Ru-106 plaques have both minimal side-scatter and a rapid axial drop-off in radiation intensity. As shown in Figure 1, at a distance of only 4.5 mm from the surface of the plaque, the radiation level has dropped to 20% of its full strength. This means that Ru-106 plaques cannot completely irradiate tumors more than 5 mm tall. Thus, the reported failure rate for these plaques in treating tumors of that size and greater is high. In addition, due to the limited side-scatter, Ru-106 plaques can more easily be placed in the wrong spot. This is why many surgeons use larger Ru-106 plaques to allow

Figure 3. Standard COMS-type gold plaque with three I-125 seeds. Typically all the slots are filled with seeds.

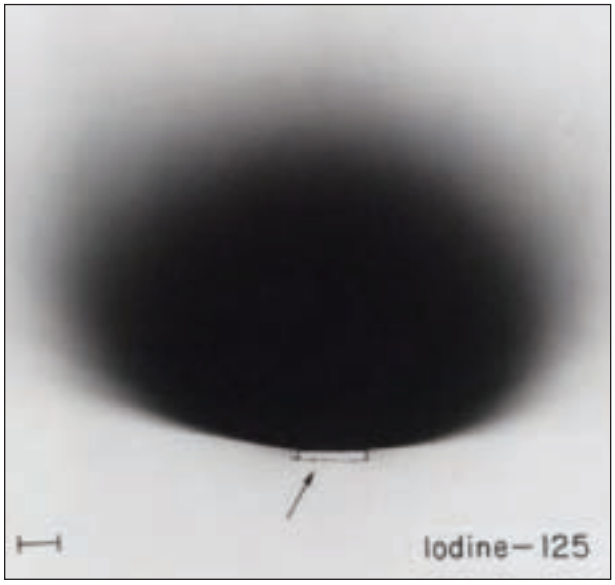

Figure 4. X-ray film showing the radiation field created by an I-125 plaque.

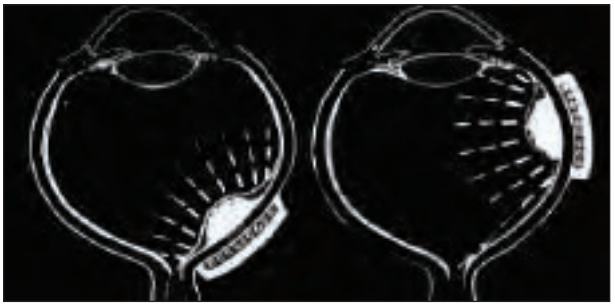

Figure 5. Plaque treatment of an anterior tumor will tend to cause more cataract, while treatment of a posterior tumor will tend to cause more radiation maculopathy and radiation optic neuropathy. (Reprinted courtesy *Br J Ophthalmol.* 2000;84(9):1068-1070.)

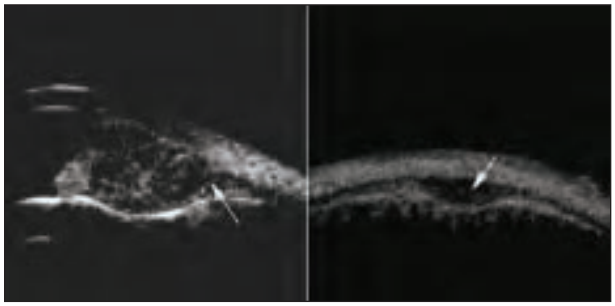

Figure 6. High-frequency ultrasound longitudinal (left) and transverse (right) images. (Courtesy *Arch Ophthalmol.* 2007;125(8):1051-1058.)

more room for error. Furthermore, there are safety concerns with Ru-106. Figure 2 shows that the silver radiation window of the plaque, under which the radioactive material sits, is only 0.1 mm thick. Therefore it is imperative to take precautions not to scratch that delicate inner surface.

Gold plaque seed carriers (Figure 3), as used in the Collaborative Ocular Melanoma Study (COMS), have become a standard for radiation therapy.[4] In 1985 when COMS was begun, I-125 seeds were the only commonly and widely used radioactive seed. At that time available only from 3M Corp. (St. Paul, MN), they are now available from numerous suppliers. Figure 4 shows an I-125 plaque and its penumbra. Its hemispheric distribution is clearly different from that of the Ru-106 plaque in Figure 1 in terms of side-scatter and depth. Depending on the power of the seeds used (I-125 or Pd-103), radiation can be cast 10, 12, even 14 mm into the eye, so taller tumors can be treated. We have extra-wide 22- and 24-mm plaques for use with tumors up to 20 mm in diameter. However, particularly with tall tumors, both the tumor and normal ocular structures are more heavily irradiated, with attendant risk of complications. At first I was reluctant to treat these large tumors. However, it has been my experience that these tumors have excellent local control and the patients are grateful to keep their eye and some vision.

Radiation side effects are dose-dependent. Just as all plaques are not the same, all plaque locations are not the same. For example, plaque treatment of an anterior tumor will tend to cause more cataract because the plaque is close to the lens, while treatment of a posterior tumor will tend to cause more radiation maculopathy and radiation optic neuropathy (Figure 5).[5]

It is important to note that less radiation to the macular retina will result in preservation of central vision. This is why I consider comparative preoperative dosimetry vital. Two major review articles suggest that the severity, location, and incidence of radiation-induced complications, including vision loss, are related to the type of radiation used, its method of delivery, the amount of radiation delivered to normal ocular structures, the size and location of the tumor, and the tumor's response to irradiation.[1,2] As a general rule, less radiation to normal structures means fewer and less severe side effects.[2,5]

This is why I became interested in Pd-103 (Pd-103 Theraseed; Theragenics, Buford, GA), the other seed source that can be incorporated into COMS gold seed plaques. In 1991, I substituted Pd-103 seeds in ophthalmic plaques because they emitted lower energy radiation compared to I-125, resulting in more rapid absorption once the radiation had traveled through and killed the tumor.[3] Faster absorption also meant less radiation reaching normal ocular structures beyond the tumor. Our results with Pd-103 for 400 consecutive patients[3] compared to results from published series using other radiation sources[4] were superior in almost every category including recurrence, secondary enucleation, metastasis, development of neovascular glaucoma, and visual acuity outcome.

TAKE HOME POINTS

- For most cases of juxtafoveal choroidal metastasis (for the most part breast or lung), prompt EBRT offers the best chance for preservation of vision.
- Like vitreous replacements, all plaques are not created equal. Centers should choose their plaques based on preoperative comparative dosimetry.
- The side effects of radiation are dose-dependent. Treatment of anterior tumors risks cataract and posterior tumors radiation maculopathy.
- Less radiation to the macular retina will result in better preservation of central vision.

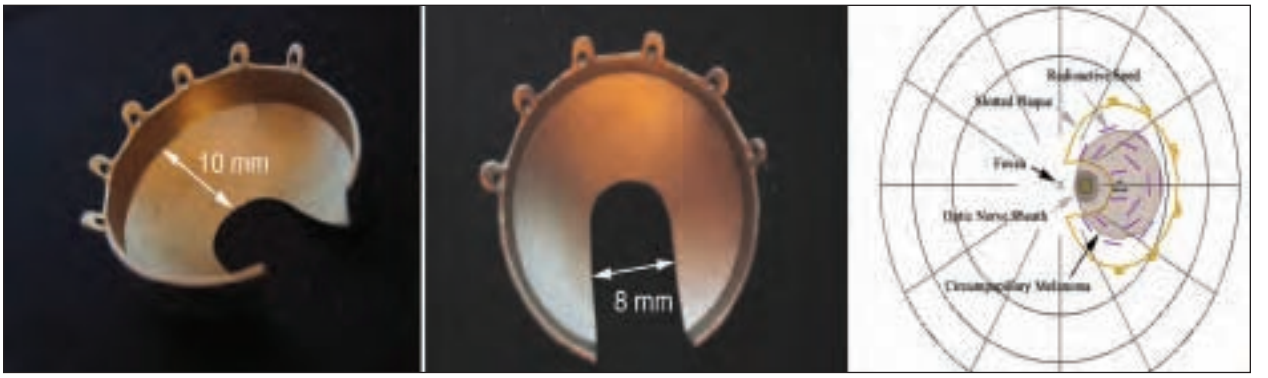

Figure 7. The Finger slotted plaque accommodates the retrobulbar optic nerve. (Courtesy *Br J Ophthalmol.* 2007;91(7):891-894.)

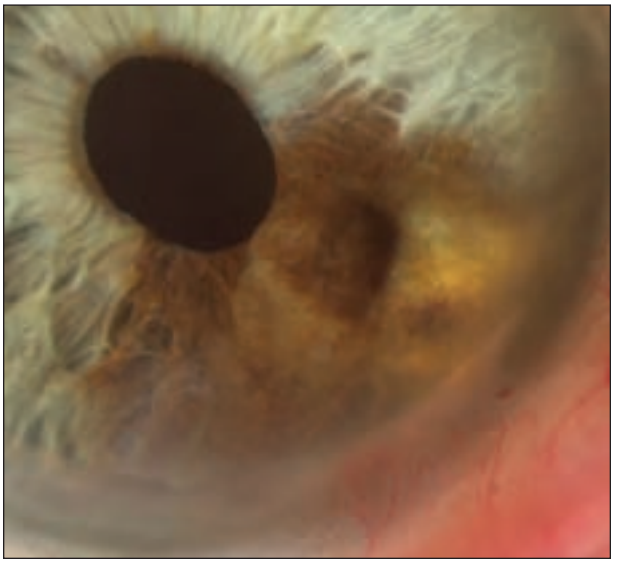

Figure 8. Ten years after Pd-103 plaque treatment of an iris tumor, the cornea is crystal clear.

It is my impression these improvements were due to numerous factors, including the low energy characteristics of Pd-103, an emphasis on delivering as little radiation as possible to the macula, the use of ultrasound to make sure that the plaque is placed correctly, and the plaqueing experience amassed by a single surgeon working in ocular radiation oncology since 1986. As a result of these factors, our local control rate is high—97% in the published series.[3] Better local control means fewer cases of metastasic uveal melanoma and less ocular morbidity (such as secondary enucleations).

IMAGING INNOVATIONS

Improved local control is also the result of improvements in imaging techniques, both for diagnosis and for plaque localization.[6]

In 1998, we first described the use of three-dimensional (3-D) ultrasound for plaque localization during and after surgery.[6] Currently, 3-D ultrasound is used in our center routinely for all applicable patients.[6] In 3-D ultrasound, a series of consecutive two-dimensional images is reconstructed to create a 3-D volume. Interactive sectioning of this "virtual eye" allows viewing in two meridians simultaneously. For example, the inserted plaque can be sectioned (quartered) so as to simultaneously view both the longitudinal and transverse meridians to ensure perfect plaque placement.

High-frequency ultrasound has improved our ability to pinpoint the location and distribution of anterior segment malignancies before surgery. In the past, estimation of size and location was based largely on transillumination of the eye to measure the base of the tumor. Ultrasound (Figure 6) allows one to clearly view and measure the length, width, and thickness of the tumor. High frequency ultrasonography provides two advantages: better establishment of tumor margins, which means greater success; and the use of smaller plaques, which translates to less radiation and less morbidity. In 2007, we described the first longitudinal study describing how high-frequency ultrasound can be used to determine the characteristics, location, and response to radiation treatment for iris and iridociliary melanomas.[7]

OTHER FRONTIERS AND INNOVATIONS

Finger's Slotted Plaques. Irradiation of tumors close to or encircling the optic nerve has been associated with local recurrence and poor vision outcomes. Some centers use transpupillary thermotherapy (TTT) to treat the "unreachable" circumpapillary tumor extent. Building on our work using 3-D ultrasound to measure optic nerve sheath diameters, I envisioned that a custom-designed slot could be made in a standard gold plaque shell to accommodate the orbital portion of the optic nerve. This required a preoperative slot-depth calculation by the ophthalmic surgeon so that the plaque could be fashioned to extend beyond the disc to cover the entire tumor plus a

2- to 3-mm margin. Clearly, this takes some measuring and custom plaque modification, but at The New York Eye Cancer Center, Finger's slotted plaques (Figure 7) are currently used for every eligible patient and contribute to our high local control rates by improving treatment of juxtapapillary and circumpapillary melanomas.[8]

Treatment of Iris and Iridociliary Melanoma. In 2001, I reported that both resectable iris and iridociliary tumors responded to plaque brachytherapy, that irradiated corneas stayed clear, and that this external approach avoided the risks associated with intraocular surgery (eg, hemorrhage, infection, retinal detachment, etc.).[9] I now rarely perform iridectomy or iridocyclectomy for iris or iridociliary tumors, respectively. In this series, plaque radiation therapy resulted in no visually significant corneal opacity or radiation retinopathy (Figure 8), although there was high incidence of secondary cataracts. Plaque radiation therapy offered the additional benefit of iris retention. One problem was that gold epicorneal plaques resting on the bare cornea were often painful during the 5 to 7 days of treatment. This is why I recently introduced the use of donor amniotic membranes to act as a buffer between the plaque and the cornea.[10] This innovation makes patients more comfortable and, because the membrane is human tissue and only 0.1 mm thick on average, does not affect radiation treatment.[10]

Antiangiogenic Therapy for Radiation Retinopathy and Optic Neuropathy. Another factor that has contributed to our superior visual acuity results is the use of intravitreal bevacizumab (Avastin, Genentech, Inc.) to treat radiation retinopathy and radiation optic neuropathy.[3] Since my initial investigation and subsequent patent of the use of vascular endothelial growth factor (VEGF)-inhibiting agents for radiation vasculopathy, the introduction of VEGF inhibitors has been a "game-changer" for these conditions.[11-14] For years retinal specialists watched patients go blind as a side effect of radiation treatment; with intravitreal bevacizumab, patients may still lose vision due to these side effects, but now at a snail's pace.[2,3,11-14] Most recently, we have found that more than 80% of patients with radiation retinopathy or radiation optic neuropathy respond to intravitreal anti-VEGF therapy. Poor responders or nonresponders are generally those with long-standing radiation retinopathy or tumors so large that the radiation dose is in excess of what can be treated this way. For the vast majority of patients, radiation retinopathy and radiation optic neuropathy are now treatable diseases.[11-14]

CONCLUSIONS

Radiation therapy offers patients potentially eye- and vision-sparing alternatives to enucleation. The most commonly used forms of radiotherapy are EBRT and ophthalmic plaque brachytherapy.

In 2008, due primarily to the advent of larger plaques, preoperative comparative dosimetry, and slotted plaques, fewer than 10% of eyes with choroidal melanoma were enucleated at The New York Eye Cancer Center. Unfortunately, even after radiotherapy treatment, some patients will subsequently require secondary enucleation because of tumor regrowth or uncontrollable neovascular glaucoma.[2,3] The severity, location, and incidence of radiation-induced complications are related to the type of radiation used, the method of delivery, the amount of radiation delivered to normal ocular structures, the size and location of the tumor, and its response to irradiation.[1,2,5]

The pearls offered in this article represent the observations and innovations of one who has spent 23 years in the field of ocular radiation oncology. It is to be hoped that future innovations will lead to treatments that reduce the amount of radiation delivered to normal ocular structures, improve our ability to preserve vision and life, and lead to a better quality of life for our patients with ocular tumors. ■

Paul T. Finger, MD, is Director of The New York Eye Cancer Center, Clinical Professor of Ophthalmology at New York University School of Medicine, and Director of Ocular Oncology at The New York Eye and Ear Infirmary. He may be reached via e-mail at pfinger@eyecancer.com.

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