

CLINICAL INVESTIGATION

Eye

## THE AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS FOR BRACHYTHERAPY OF UVEAL MELANOMAS

SUBIR NAG, M.D.,\* JEANNE M. QUIVEY, M.D.,<sup>†</sup> JOHN D. EARLE, M.D.,<sup>‡</sup> DAVID FOLLOWILL, PH.D.,<sup>§</sup> JAMES FONTANESI, M.D.,<sup>¶</sup> AND PAUL T. FINGER, M.D., F.A.C.S.,<sup>||</sup> FOR THE AMERICAN BRACHYTHERAPY SOCIETY

\*Department of Radiation Oncology, Ohio State University, Columbus, OH; <sup>†</sup>Department of Radiation Oncology, University of California, San Francisco, CA; <sup>‡</sup>Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL; <sup>§</sup>Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; <sup>¶</sup>Department of Radiation Oncology, Wayne State University, Detroit, MI; <sup>||</sup>Department of Ophthalmology, New York Eye Cancer Center, New York, NY

**Purpose:** This article presents the American Brachytherapy Society (ABS) guidelines for the use of brachytherapy for patients with choroidal melanomas.

**Methods:** Members of the ABS with expertise in choroidal melanoma formulated brachytherapy guidelines based upon their clinical experience and a review of the literature. The Board of Directors of the ABS approved the final report.

**Results:** Episcleral plaque brachytherapy is a complex procedure and should only be undertaken in specialized medical centers with expertise in this sophisticated treatment program. Recommendations were made for patient selection, techniques, dose rates, and dosages. Most patients with very small uveal melanomas (<2.5 mm height and <10 mm in largest basal dimension) should be observed for tumor growth before treatment. Patients with a clinical diagnosis of medium-sized choroidal melanoma (between 2.5 and 10 mm in height and <16 mm basal diameter) are candidates for episcleral plaques if the patient is otherwise healthy and without metastatic disease. A histopathologic verification is not required. Small melanomas may be candidates if there is documented growth; some patients with large melanomas (>10 mm height or >16 mm basal diameter) may also be candidates. Patients with large tumors or with tumors at peripapillary and macular locations have a poorer visual outcome and lower local control that must be taken into account in the patient decision-making process. Patients with gross extrascleral extension, ring melanoma, and tumor involvement of more than half of the ciliary body are not suitable for plaque therapy. For plaque fabrication, the ophthalmologist must provide the tumor size (including basal diameters and tumor height) and a detailed fundus diagram. The ABS recommends a minimum tumor <sup>125</sup>I dose of 85 Gy at a dose rate of 0.60–1.05 Gy/h using AAPM TG-43 formalism for the calculation of dose. NRC or state licensing guidelines regarding procedures for handling of radioisotopes must be followed.

**Conclusion:** Brachytherapy represents an effective means of treating patients with choroidal melanomas. Guidelines are established for the use of brachytherapy in the treatment of choroidal melanomas. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose reporting policies. These guidelines will be modified as further clinical results become available. © 2003 Elsevier Inc.

Uveal neoplasms, Choroid neoplasms, Melanoma, Brachytherapy, Iodine-125.

### INTRODUCTION

Enucleation had been considered the standard treatment for patients with posterior uveal melanoma. In an effort to preserve vision and the globe, episcleral plaque radiotherapy has become a commonly used alternative. Moore first used radon seed brachytherapy to preserve vision for a monocular patient with uveal melanoma (1). Stallard also

tried implanting seeds directly into the tumor, but went on to develop cobalt-60 (<sup>60</sup>Co) plaque radiotherapy (2). Since that time, a number of other radioisotopes (radionuclides), including gold-198, iodine-125, Ru-106/Rh-106, iridium-192, and palladium-103, have been used for episcleral radiotherapy with varying results from retrospective studies (3–24). In an effort to resolve some of the controversies, the Collaborative Ocular Melanoma Study (COMS) Group per-

Reprint requests to: Subir Nag, M.D., Chief of Brachytherapy, Arthur G. James Cancer Hospital, The Ohio State University, 300 W. 10th Avenue, Columbus, OH 43210. Tel: (614) 293-3246; Fax: (614) 293-4044; E-mail: nag.1@osu.edu

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Table 1. ABS levels of consensus opinion

Level 1:	There is uniform panel consensus, based on strong published literature, that the recommendation is appropriate.
Level 2:	Recommendation is based on suggestive evidence, including nonpublished clinical experience. There is no major disagreement among panel members.
Level 3:	There is paucity of data or major disagreement among panel members regarding the recommendation.

*Abbreviation:* ABS = American Brachytherapy Society.

formed a nationwide, multi-institutional, prospective randomized clinical trial to compare efficacy of enucleation vs. I-125 eye plaque radiotherapy for medium-sized choroidal melanomas and recently reported the preliminary results (25, 26). Other than the COMS guidelines, there are no standardized procedures for episcleral eye plaque use. The American Brachytherapy Society (ABS) therefore formed a panel to issue guidelines for the use of brachytherapy for choroidal melanomas.

## METHODS AND MATERIALS

Selected members of the ABS with expertise in choroidal melanoma brachytherapy performed a literature review that, supplemented by their clinical experience, allowed formulation of specific recommendations and directions for future investigation in choroidal melanomas. These recommendations were made by consensus opinion and supported by published data whenever possible. In addition, an external multispecialty panel of recognized experts in the field reviewed the consensus recommendations and made revisions where indicated. The Board of Directors of the ABS approved the final report. The definition of the consensus levels used was similar to that used in previous ABS reports (27), as listed in Table 1.

## RESULTS

Episcleral plaque brachytherapy is a complex procedure, and the ABS recommends that these procedures should only be undertaken in specialized medical centers with expertise in this sophisticated treatment program. The results of the deliberation of the panel and the ABS recommendations are given in the following sections.

### *Initial workup*

The optimal treatment of uveal melanoma is dependent upon a number of tumor and patient characteristics. If the lens and vitreous are clear, an experienced ophthalmologist can usually make the diagnosis of uveal melanoma based on the characteristics observed by ophthalmoscopy, fundus photography, and ultrasound (28, 29). P-32 uptake scan is no longer necessary.

Before surgery, a metastatic workup including liver function studies (LFTs), a computed axial tomography (CT) of the abdomen and chest (if LFTs are elevated), a chest X-ray, and a physical examination including an assessment for hepatomegaly and subcutaneous nodules should be performed. In addition, an ophthalmic examination (including intraocular pressure, baseline, and best corrected visual acuity) is required.

The differential diagnosis includes certain benign vascular lesions and metastatic lesions (almost always adenocarcinomas of the breast, lung, bowel, kidney, or prostate) (28, 30–32). The diagnostic accuracy of the ophthalmologist has been verified by recently completed COMS studies of patients with carefully selected medium- and large-sized melanomas who underwent enucleation (33). However, diagnostic accuracy is less assured for patients with smaller lesions, which may be confused with benign nevi (34), and large tumors with substantial local hemorrhage or large secondary retinal detachments. Patients with a prior history of other nonocular malignancies are at higher risk for metastatic choroidal lesions.

### *Treatment of uveal melanomas*

In general, patients with small T1 uveal melanomas (<2.5 mm height and less than 10 mm in largest basal dimension) are typically observed for growth before treatment (34–36). Most patients with medium-sized T2 uveal melanomas of 2.5–10 mm in height and <16 mm basal diameter and large-sized (T3 and T4) melanomas >10 mm height or >16 mm basal diameter require treatment if the patient is otherwise healthy and without metastatic disease (N0, M0) (ABS Level 1 Consensus) (37, 38).

### *Surgical options*

Surgical options for the treatment of uveal melanomas include enucleation, orbital exenteration, and eye-wall resection (lamellar and full-thickness). Enucleation (removal of the eye) results in elimination of all visible tumor and a high probability of local control. If the tumor has extended through the wall of the eye into the orbit, a more extensive resection, orbital exenteration, and postoperative external beam radiation therapy are typically employed.

Enucleation is used for patients with a clinical diagnosis of uveal melanoma and a blind painful eye, those with tumor involving >40% of the intraocular volume, and for eyes with neovascular glaucoma. Enucleation is also appropriate for patients with medium to large uveal melanomas who have useful vision in their fellow eye and do not wish to pursue an organ-sparing approach (38, 39). Lamellar or full-thickness eye-wall resection is a technique with limited applicability (mostly anteriorly located lesions involving the iris or ciliary body with some posterior choroidal extension) and stringent requirements for surgical expertise. Nonetheless, one recent series of patients treated with eye-wall resection included 125 uveal melanomas patients followed for a mean of 6 years. In that series, 76% of eyes were successfully retained and 53% had a final visual acuity of at

least 20/40 (40). Unfortunately, many experience early vision loss resulting from complications of surgery (41). Robertson and others have expressed concern about residual intraocular melanoma after eye-wall resection. This may be why many of these patients require additional plaque or laser treatment for close or positive margins. A new form of laser photocoagulation (transpupillary thermotherapy) has also been used for small choroidal melanomas and marginal failures in previously irradiated patients with limited success (42).

### *Radiation therapy*

Radiation therapy of uveal melanoma allows for control of the tumor, sparing of vision, and preservation of the globe. The dose of radiation required to control uveal melanoma exceeds the tolerance of the retina, the optic nerve, the lens, the eyelids and lashes, and lacrimal apparatus. Thus the treatment plan and choice of radiation delivery system must optimize dose distribution to minimize treatment morbidity.

Radiation therapy may be delivered through the use of charged particle beams of protons (43–48) or helium ions (49–52), radiosurgery (53, 54), or episcleral radioactive plaques (2, 3, 5, 8, 9, 25, 55, 56). The selection among these treatment techniques is often dependent upon the expertise of the treating physician and accessibility of the patient to centers with specialized treatment facilities. Episcleral plaque brachytherapy is the most widely available treatment and survival results have been shown to be equivalent to charged-particle therapy (in a randomized study comparing He ion with I-125 brachytherapy) (49). Hence plaque brachytherapy represents a practical alternative for the treatment of uveal melanomas.

### *Patient selection for eye plaques*

1. Patients with a clinical diagnosis of malignant melanoma of the uvea are candidates for episcleral plaques. A histopathologic verification is not required (28, 33). Small melanomas may be candidates if there is documented growth.
2. Typically, small melanomas are observed for growth before treatment. Some patients with large melanomas may be candidates. However, visual outcomes may be compromised in these patients (57, 58). Patients should be informed of these factors when making treatment decisions.
3. Patients with peripapillary melanomas have a poorer visual outcome and lower local control, which must be taken into account in the patient decision-making process (57, 58).
4. Patients with gross extrascleral extension, ring melanoma, and tumor involvement of more than half of the ciliary body are not suitable for plaque therapy.

In general, visual outcomes after plaque brachytherapy

improve as the distance increases from the plaque or tumor to the macula and in treatment of smaller tumors (57).

### *Treatment planning*

For plaque fabrication the ophthalmologist must provide the following data (ABS Level 1 Consensus):

1. The tumor size, including basal diameters and tumor height, should be measured clinically by the ophthalmologist and confirmed with standard A and B scan ultrasonography.
2. A detailed fundus diagram with orientation of the tumor borders relative to surrounding structures including the optic nerve, foveola, equator, ora serrata, and center of the lens. The basal dimensions at the center of the tumor in the direction from the macula, the base dimension at the center of the tumor in the direction of the optic disc, and the minimum distance from the tumor edge to the macula and the optic disc are also recommended (59). An alternative method to the fundus diagram is a combination of CT or magnetic resonance imaging (MRI) combined with fundus photography from which an accurate three-dimensional (3D) reconstruction of the eye and tumor location can be generated for posterior hemisphere tumors (60, 61).

The treatment planning process for eye plaque radiotherapy requires several steps to generate an acceptable treatment plan. These steps include transferring tumor information from the fundus diagram, developing dose rate and dose prescription criteria, plaque and seed selection, preplan, final postplan dosimetry, and documentation of doses to critical structures.

### *Transferring tumor information from the fundus diagram*

A computerized treatment planning program is invaluable to assist in the calculation of the dose for the selected seed array, which is then mounted on the selected plaque (62). The planning system should be verified before using it for patient treatments. The best mechanism for the check is to compare the COMS single-seed calculation results using the planning computer with a simple TG-43 hand calculation (63). A more rigorous check would be to perform the same comparison with a fully loaded 12 mm plaque comparing doses along the central axis of the plaque. An independent audit of the system for more complicated seed arrangements and strengths can also be obtained from the Radiologic Physics Center, which served as the COMS physics center. There still remains some disagreement as to the new dosimetry data available for  $^{125}\text{I}$  dose calculations; therefore, the COMS calculations still remains the most commonly used planning system verification tool (64).

The location and dimensions of the tumor (base and apex) must be transferred to the treatment planning system to allow an accurate calculation of tumor and critical structure radiation doses. Of particular concern is the proximity of the plaque to the macula and optic disc structures in which an accurate estimation of the dose is crucial. One must realize

that there is an inherent uncertainty in the generation of the tumor size and location data from hand-drawn diagrams (59). This uncertainty can be reduced with the use of 3D reconstruction techniques. The dimensions of the tumor are important for the selection of the correct plaque size to be used in the treatment.

#### *Dose prescription*

The COMS dose prescription criteria for  $^{125}\text{I}$  have been widely used for the past 15 years and provide a useful standard for eye plaque treatment. In addition to COMS, other dose prescription methods exist. The prescription dose will depend on the prescription point, method of dose prescription, and dosimetry calculation assumptions. The prescription dose, following the COMS dosimetry calculation assumptions, was 85 Gy to the tumor apex for tumors, with a height of  $\geq 5$  mm from the tumor base center for tumors with a height of  $\leq 5$  mm (65). The COMS dosimetry calculation assumptions include point source approximation, no anisotropy corrections, no side attenuation or backscatter from the gold shield, and no attenuation by the Silastic insert. Calculation of the dose is per the TG-43 formalism (63). The dose will change significantly if line source approximation, anisotropy correction, attenuation of gold shield, and Silastic insert are taken into account. The COMS is investigating changes in dose calculations based on current estimates of these variables (66).

The ABS recommended  $^{125}\text{I}$  prescription dose is 85 Gy to the apex of the tumor using the COMS dosimetry assumptions and plaque construction techniques (ABS Level 1 Consensus). The 85 Gy isodose line should pass through the prescription point and encompass the entire tumor. The COMS allowed dose rate was between 0.43 and 1.05 Gy/h to the prescription point. Reports of dose rates of less than 0.60 Gy/h show lower control rates (58), thus the ABS suggests a  $^{125}\text{I}$  dose rate of 0.60–1.05 Gy/h delivering the total dose in 3 to 7 consecutive days (ABS Level 1 Consensus). Each institution should decide on the best dose rate at the prescription point such that the dose delivery is accomplished in a timely manner. The radiation oncologist should evaluate each case individually to verify that the prescription dose and dose rate are appropriate. The doses should be modified appropriately if line source approximation, anisotropy correction, attenuation of gold shield, and Silastic insert are taken into account (66). Dose modification may be appropriate to account for different tumor sizes, threshold doses to critical intraocular structures, and use of alternative radionuclides (2, 3, 8, 55, 56, 67, 68).

#### *Plaque design*

This section deals primarily with I-125 eye plaque commonly used in the United States. Both rimmed and unrimmed plaques have been used. The COMS used a rimmed plaque to allow for insertion of Silastic seed carrier (69). The standard COMS plaques are circular with diameters of 12, 14, 16, 18, and 20 mm (65). The standard COMS plaque was appropriate for standardization needed in a multi-institutional study.

Standard circular plaque may not be the best choice for tumors located close to the optic disc or cornea or for elongated tumors. Notched plaques can be used for peripapillary tumors that will allow for better coverage of the tumor by placing the optic disc within the cut out notch of the plaque (70). Plaques with individually collimated sources to reduce laterally directed radiation, well-suited for tumors close to the macula or optic disc, have also been described (61).

Unrimmed custom-made plaques have been used at some centers to optimize coverage of irregularly shaped tumors or for tumors located close to the optic disc or ciliary body. They can be circular, notched, oval, or kidney shaped. The inner surface of the plaque is concave and raised from the surface of the sclera to reduce the dose to the sclera and increase the depth dose. These plaques are less bulky and can often slide under the extraocular muscles more easily than the rimmed plaques. The COMS plaques can be ordered from Trachsel Dental Studio, Rochester, MN, whereas custom-made plaques are usually manufactured at local dental studios. When the plaques or Silastic inserts are received for a treatment, the physicist should verify the seed slot location in each seed carrier and the curvature of the gold shields and Silastic inserts. The seed slot locations and the manufacturing of the standard COMS plaques is well-established, and a cursory check is probably sufficient. More rigorous checks should be made if plaques are custom-made (70).

The optimal margin required around the tumor base is not known, and the margin also depends on the plaque type. The COMS plaque encompassed the tumor with a 2–3 mm margin on all sides to allow for errors in plaque placement, plaque movement and uncertainties in the location of the tumor edge (69). Unrimmed custom-made plaques extend the dose distribution beyond the physical edge of the plaque and hence can have a smaller margin.

#### *Isotope selection*

The most common isotope (radionuclide) used in ocular brachytherapy in the United States is  $^{125}\text{I}$ ; this isotope was the only radioisotope allowed for use in the COMS trial (63). Other radioisotopes such as  $^{60}\text{Co}$ ,  $^{222}\text{Rn}$ ,  $^{106}\text{Ru}$ ,  $^{192}\text{Ir}$ , and  $^{103}\text{Pd}$  have been used (2, 3, 8, 55, 56). The characteristics of the commonly used radioisotopes used in ocular brachytherapy are listed in Table 2.  $^{60}\text{Co}$  and  $^{192}\text{Ir}$  have high-energy gamma emission, deliver large radiation doses to unaffected ocular structures, and also present radiation exposure hazards to caregivers. The low gamma emission of  $^{125}\text{I}$  and  $^{103}\text{Pd}$  presents less radiation exposure hazards to personnel and is easily absorbed by the overlying gold plaque, thus reducing the dose to the surrounding normal extraocular structures (60, 61). Compared with  $^{125}\text{I}$ ,  $^{103}\text{Pd}$  has a lower energy and hence a more rapid dose fall-off (16). This dose gradient has been proposed to decrease the incidence of radiation complications.  $^{106}\text{Ru}$  is a beta emitter and has an even more rapid dose fall-off. Although the large dose gradient for  $^{106}\text{Ru}$  may allow dose concentration to the

Table 2. Characteristics of radioisotopes used for episcleral brachytherapy

Symbol	Half-life	Average energy (MeV)	HVL in lead (cm)	HVL in water (mm)	Cost per use
Co-60	5.26 y	1.25	1.2	108	Low
I-125	59.6 days	0.028	0.002	20	Medium
Ir-192	74.2 days	0.38	.3	63	Low
Ru/Rh-106	367 days	3.5 (beta)	Range max E = 1800 mg/cm <sup>2</sup>	24	High
Pd-103	17 days	0.021	0.0004	15	Medium

Abbreviation: HVL = half-value layer.

tumor base while minimizing dose to contralateral ocular structures, it may result in a high scleral dose and potentially low dose to the apex for tumors of apical height >3 mm (71, 72). The dose gradient to the tumor and the underlying sclera is essentially the same for all commonly used gamma sources (other than Pd-103). The above dosimetric differences should be taken into account when selecting the isotope.

#### Preplanning the eye plaque treatment

After an isotope has been selected, a preplan helps to determine the seed strength, tumor coverage with the appropriate isodose line, and the implant duration. The total implant duration can be manipulated to suit the availability of the operating room, patient, and physician. The preplan is run with varying seed activities in an interactive process to generate a plan that can be delivered in the desired time. During the preplanning process, the coverage of the tumor is also assessed. Either a uniform or nonuniform loading of the plaque may be used to achieve the appropriate tumor coverage and minimize the dose to the critical structures such as the macula and optic nerve (60, 61). A plaque loaded symmetrically and uniformly with seeds of the same activity (within  $\pm 10\%$ ) has the advantage of simplicity and is appropriate for multi-institutional studies. Custom-made plaques loaded centrally with a few high-activity seeds will produce a different 3D dose distribution compared with plaques evenly loaded with many low-activity seeds. Non-uniform loading can be accomplished, if required, by loading different activity seeds or by loading seeds of same activity in a nonuniform distribution. If different seed activities are used in a plaque, one must be cautious not to mix the seeds and incorrectly load the plaque. If the seeds are not arranged symmetrically, special care should be taken to ensure correct orientation of the plaque during placement. Factors affected by seed positioning (e.g., anisotropy) can be used to shape the intraocular dose distribution but require more precise plaque orientation during insertion. The plaque design and seed arrangement depend on individual institutional and physician preference. However, the dosimetric differences between the different loading patterns should be kept in mind when selecting a particular treatment plan.

After the required seed strength and date of surgery are known, the seeds are ordered from the manufacturer. After

the seeds arrive, a final preplan is run again with the exact seed strengths to determine the total prescription implant time. Special attention to the time difference between the seed activity assay date and the surgical date must be made to account for seed strength decay. The ABS recommends that each institution should verify the seed activity used in the dose calculation (ABS Level 1 Consensus).

Each institution should have a dosimetry system that can be reliably used to verify the manufacturer's stated activity of a sample of the sources. A well-type ionization chamber is appropriate for this procedure. There are three levels of verification as follows.

1. Records can be maintained relating ionization readings to the manufacturers' stated strength of a specially calibrated seed purchased with each new batch of seeds. This will identify batch-to-batch gross inconsistencies in stated or measured strengths.
2. The institution should have a long-lived check source (e.g., <sup>241</sup>Am, <sup>137</sup>Cs) that can be used on the same electrometer scale as the isotope used for the plaque. This would verify the constancy of the dosimetry system factor.
3. It is recommended that the institution obtain a National Institute of Standards and Technology-traceable calibrated source from one of the Accredited Dosimetry Calibration Laboratories. This source will be used to assign a calibration factor to the institution's dosimetry system and should be the same model as used for clinical treatments. The constancy of this factor is checked with the long-lived check source mentioned in (4) above. This enables the institution to calibrate each seed and verify the manufacturers stated activity.

A physicist should verify and check all dose calculations for accuracy before the eye plaque treatment. It should be recognized that manufacturers may require up to 10 working days to provide seeds of a specific activity. Further time is required for plaque fabrication and sterilization. This has to be taken into account when scheduling the plaque insertion date.

#### Dose calculations

The original COMS radiation dose calculations and other reported series assumed a point source, with no effect from the gold shield, Silastic insert, or anisotropy (65, 73, 74). At

the beginning of the COMS trial, these dosimetry assumptions were valid because there was no consensus on which published dosimetry data to use to calculate a more accurate dose. As a result, the dose prescription was based on these calculations in order that the institutions entering patients onto this trial could report the radiation doses in a uniform and consistent manner.

Since the beginning of the COMS trial, new dosimetry data, including TG-43, have been published. The effects of the Silastic insert, gold shield, line source approximation, and anisotropy are currently better understood and can be used to calculate the radiation doses more accurately (74–95). The inclusion of these data makes the dose calculations more complicated, but there are planning systems such as Plaque Simulator (227 BEBIG GmbH, Berlin, Germany) that incorporate the new data and the COMS assumptions in its calculations (60, 61, 84, 96).

Dosimetry calculations with the newer data result in a significant change to the dose calculations. As new data have become available and accepted, recalculations suggest that the original calculations based on the original assumptions for the COMS trial overestimated the true doses by as much as 30% depending on the plaque size and location of the critical structure relative to the tumor center (66, 77, 80, 81, 97). The primary reason for the dose reduction is the attenuation in the Silastic insert and the reduction in the scatter contribution resulting from the gold shield (64). Although the ABS does not recommend one method of dose calculation, it does recommend that the parameters used in the dose calculation should be specified when recording doses. The physicist and radiation oncologist should understand the differences in the dose calculation methods when comparing doses reported from different centers.

#### *Fabrication of eye plaques*

Some seed arrays prefigured by Silastic carriers are designed to attach to a rimmed plaque or by “slots” in the gold plaque surface. Alternatively, the seeds may be directly glued upon the plaque. Both methods are acceptable depending on institutional preference. The orientation of the plaque and the location and orientation of seeds within the plaque are critical if an asymmetric application is planned. It is important to not load the plaque until the final treatment plan has been approved. There is always the possibility that, because of the seed strength assay, the seeds may have to be placed in the plaque in a special loading position.

In the COMS method, the seeds are individually placed in the Silastic insert wells with a pair of tweezers or a vacuum pickup device one at a time. After the Silastic insert is loaded according to the treatment plan, the Silastic insert is covered by the gold shield that has had its inner rim coated with a thin layer of bonding agent to ensure that the Silastic insert does not fall out. The plaque should then be inspected to ensure the Silastic insert is in good contact with the gold shield and that the Silastic is even with respect to the gold shield lip. The completed plaque should then be placed in the appropriate sterilization container.

If custom-made plaques are used, the sources are glued onto the concave surface of the gold plaque using a cyanoacrylate adhesive in the pattern determined from the preplan. Some institutions then cover the seeds with a thin layer of dental acrylic fixative. Last, a spacer (such as a rigid contact lens) is commonly placed over the sources. This technique will create a concave plaque surface to be placed onto the convex sclera. This spacer (and the COMS insert) also separates the  $^{125}\text{I}$  sources from the sclera, improving the ratio of dose at apex of tumor to the dose at the sclera. Some centers use collimated sources in a thinner plaque (61).

There are three commonly used ways to sterilize the plaque. The first is gas sterilization, which requires additional lead time of ~24 h. The advantage of this process is that the plaque will be ready and in the operating room when the procedure begins. The container with the plaque must have holes in it to allow the sterilization gas to enter. The second technique is steam sterilization. This process requires less lead time (3–10 min flash) and can be quickly carried to the operating room and allowed to cool for at least 0.5–1 h before the plaque procedure. Plaques with Silastic inserts should not be steam sterilized, because it will deform the insert and alter seed position.

Note that Cidex sterilization is not recommended for use with the COMS-type inserts because of the possibility of a patient reaction to the Cidex trapped between the Silastic and gold (70). Institutions that affix the seeds within the plaque with adhesives wait for them to cure and then place the plaque in Cidex for a minimum of 15 min, followed by copious irrigation.

#### *Plaque placement*

Low-energy plaque ( $^{125}\text{I}$  or  $^{103}\text{Pd}$ ) radiotherapy can be performed as an inpatient or outpatient procedure. The plaque is placed by the ophthalmologist under local or general anesthesia. Anterior tumors and those with visible anterior margins can be localized by transillumination of the globe. With the eye illuminated, the tumor creates a transillumination shadow on the eye-wall, which is marked with tissue dye. An additional 2–3 mm free margin is also marked on the sclera or cornea around the tumor base. More posterior tumors are localized by point source illumination, scleral indentation ophthalmoscopy (around the plaque), and ultrasonography (98–101). If an extraocular muscle is overlying the tumor, the muscle should be detached for proper positioning of the plaque. A dummy plaque can be used to position the sutures on the sclera and to verify the position before the placement of the radioactive plaque (57). The radiation oncologist should verify the position and orientation of the plaque in relation to the tumor. The time of insertion should be written on the chart for final dose calculations. A lead eye patch may be placed over the eye, if appropriate. Some institutions confirm the plaque location using ultrasonography or MRI (102). Some institutions keep the patients hospitalized for the duration of the irradiation, whereas others discharge the patients home, bringing them

Table 3. Episcleral plaque therapy and outcome

Author/Institution	Year	No. of pts.	Isotope	Mean follow-up (months)	Mean tumor size (mm)	Dose (Gy)	Local control (%)	5-y local control (%)	Distant met. (%)	5-y distant met. (%)
Quivey/UCSF (57)	1993	239	125-I	36	10.9 × 9.2 × 5.5	70	91.7	82	7.5	12
Jones/Med. College Wisconsin	2002	63	125-I	36	4.5 (ht)	85–100	84	NA	4.8	NA
Quivey/Wills Eye Hospital (58)	1996	150	125-I	68	9.7 × 8.5 × 3.7	95	78	81	17.3	17.3
Fontanessi/Univ. Tennessee (5)	1993	144	125-I	NA	975 mm <sup>3</sup>	75	94.4	NA	4	NA
Packer/North Shore Univ. (111)	1992	64	125-I	65	NA	91	87.5	92.2	17.2	17
Lommatzsch/Leipzig (8)	1987	309	Ru-106	80	Most small	100	69.9	84	12.9	NA
COMS (25)	2001	650	125-I	96+	11.4 × 4.8	85	NA	NA	9	9
Seregard/Sweden (119)	1997	266	Ru-106	43	10 × 4.4	100	90	NA	11	14
Kleineidam/Hamburg (105)	1993	184	Ru-106	NA	8 × 3.3	250	82	82	13.6	13.6
Karlsson/Hahnemann Univ. (120)	1989	277	60-Co	NA	11.3 × 9.9 × 6.3	81	85.9	86	NA	21.6
Beitler/NY Hosp-Cornell (112)	1990	116	60-Co	46	648 mm <sup>3</sup>	100	82.7	NA	12	NA
Lean/LJSC (110)	1989	56	125-I/192Ir	39	13.2 × 12.3 × 6.8	94.5	91	NA	9	NA
Finger/NYU (16)	2002	100	103-Pd	55	2.5–8 (ht)	80.5	96	NA	6	NA

*Abbreviations:* met. = metastases; UCSF = University of California, San Francisco; USC = University of Southern California; COMS = Collaborative Ocular Melanoma Study; NYU = New York University/New York Eye Cancer Center; NA = not available; ht = height.

back a few hours before the planned removal. Typically, all patients are surveyed before discharge after plaque insertion and removal. NRC or state licensing guidelines regarding procedures for handling of radioisotopes and care of radioactive patients must be followed.

#### Plaque removal

The plaque is typically removed in the operating room under local anesthesia. The removal time should be recorded on the chart for final dose calculations. The seeds in the Silastic insert should be counted in the operating room. The patient and the room should be surveyed to verify that all of the seeds have indeed been removed. Final doses to the tumor and critical normal structures should be calculated and recorded. These doses may vary from the planned doses due to scheduling problems in surgery or other unforeseen events. The plaque is then transported to the radioactive source handling area with the appropriate shielding. Silastic inserts can be removed under water to minimize the possibility of seed scattering. Seeds attached by cyanoacrylate are removed by soaking the plaque in acetone. In either case, the seeds are removed and counted before placing them in the original shipping container.

#### Ruthenium eye plaques

<sup>106</sup>Ru has been used in the treatment of ocular melanomas for several decades and long-term follow-up regarding its efficacy, side effects, and long-term visual acuity outcomes are available (8, 20). <sup>106</sup>Ru is a beta emitter and has a very rapid dose fall-off allowing dose concentration to the tumor base while minimizing dose to contralateral ocular structures (71, 103). <sup>106</sup>Ru may therefore be preferable for treatment of small melanomas. It has been suggested that a dose of 120–160 Gy be used to maximize the curative potential of this isotope. However, this extreme dose gradient results

in a high scleral dose and potentially low dose to the apex for tumors of apical height >3 mm. The experience with Ru-106 for the treatment of ocular melanomas show increased complications with increasing scleral dose (71), increasing risk of local failure with increasing tumor size (72) and increased risk of disseminated disease with large tumor size although this is not universally accepted (104, 105). There are also reports that confirm that useful vision can be maintained; however, again, the issues relating to tumor size (>5 mm height) and location (foveal and macular) become important (106).

#### Palladium-103

<sup>103</sup>Pd plaque brachytherapy can be used to treat intraocular tumors (3, 16, 22, 23, 24, 107). <sup>103</sup>Pd seeds are equivalent in size to <sup>125</sup>I and can be used in standard eye plaques. Methods of dosimetry are also similar. Compared with <sup>125</sup>I, the use of <sup>103</sup>Pd has a lower energy and hence a more rapid dose fall-off (16). This dose gradient has been proposed to decrease the incidence of radiation complications. Preservation of vision and a low incidence of radiation retinopathy have been noted after treatment of anterior uveal melanomas (107, 108). Though clinical experience with this isotope (radionuclide) is limited, we believe prospective randomized studies comparing the different radionuclides would be valuable.

#### Results of episcleral plaque therapy

The COMS Group performed a nationwide, multi-institutional, prospective randomized clinical trial to compare efficacy of conventional enucleation with I-125 eye plaque radiotherapy for medium-sized ocular melanomas. The COMS Medium Tumor Trial closed to accrual in July 1998, and the Data Safety and Monitoring Committee (DSMC) allowed visual acuity data to be reported in 2001 (26).

Table 4. Episcleral plaque therapy and visual outcome

Author/institution (ref.)	Vision >20/200	VA lost <2 lines	Enucleation	Cataracts	Vitreous hemorrhage	Neovascular glaucoma	Radiation maculopathy	Optic nerve atrophy	Radiation retinopathy
Quivey/UCSF (57)	58%	NA	NA	14%	20.8%	6.8%	18.2%	NA	NA
Jones/Wisconsin (108)	NA	58%	11%	NA	NA	NA	NA	NA	62.8%
Fontanesi/Univ. Tennessee (5)	40.9%	NA	10%	30%	NA	5.5%	NA	8%	21.5%
Packer/North Shore Univ. (111)	43.3% (20/100)	26.5% @ 5 yrs	17.2%	45.3%	14 pts	10.9%	NA	NA	23.4%
Lommatzsch/Leipzig (8)	22.7% (1.5-5)	NA	20.7%	2%	3%	3 pts	26.8%	7.4%	NA
Beitler/NY Hosp.-Cornell (112)	NA	NA	7 patients	28%	16 patients	9 patients	NA	NA	NA
Lean/USC (110)	59% (5/200)	NA	20%	36%	12%	11%	NA	20%	29%
COMS (25,26)	37%	2 lines/yr	12%	NA	NA	NA	NA	NA	NA
Shields/Wills Eye/Hahnmann (14)	67%	NA	NA	NA	NA	NA	NA	NA	NA
Finger/NYU (16)	73%	40%	6%	8%	2%	3%	18%	1%	NA

Abbreviations: UCSF = University of California, San Francisco; USC = University of Southern California; COMS = Collaborative Ocular Melanoma Study; NYU = New York University/New York Eye Cancer Center; NA = not available; VA = visual acuity.

Detailed data are presented displaying the progressive loss of vision sustained by the patients over the 3 years reported. Other than radiation dose, factors found to have prognostic significance were pretreatment vision, diabetes, and tumor height, shape, and retinal detachment. Visual acuity declined at a rate of about two lines per year on average. Nearly half the patients had the visual deterioration selected above by 3 years. The large subgroup without the high-risk characteristics (i.e., without diabetes, with dome-shaped tumors less than 5 mm, more than 2 mm from the foveal avascular zone and without retinal detachment) maintained an average 20/40 or better acuity through the 3-year follow-up period. In eyes without these additional risk factors, the probability of losing six or more lines in 3 years was 12%, and the probability of 20/200 or worse acuity was 9%. A total of 6.2% had had the plaqued eye enucleated by the third year of follow-up.

The DSMC released mortality data in 2001 (109). At the time of that analysis, 1072 patients (81%) had been followed for mortality for 5 years and 416 (32%) for 10 years. Unadjusted 5-year survival rates were 81% and 82% for the enucleation and brachytherapy arms ( $p = 0.48$ ). Five-year rates for death with histopathologically confirmed melanoma metastasis were 11% and 9%, respectively. Survival curves demonstrate no difference in survival between the two groups. In addition to radiation dose, Cox multivariate models demonstrated independent and statistically significant effects on length of survival ( $p < 0.05$ ) for age, apical height, longest basal diameter, tumor shape, smoking status, and coexisting medical conditions. Adjustments for these yielded curves not statistically significantly different.

The outcomes of episcleral plaque studies are summarized in Table 3. It is difficult to compare these outcomes because the studies did not use uniform guidelines for dosimetry, tumor size, tumor location, or length of follow-up.

#### Radiation complications

Complications after eye plaque are caused by radiotherapy-specific factors (e.g., total dose, dose rate, and dose volume) and tumor-related factors (e.g., tumor size, location, and its biologically variable response to irradiation) (17, 108). Table 4 summarizes the visual outcome after episcleral plaque therapy (5, 8, 25, 26, 57, 110-114). These series are difficult to compare because the studies did not use uniform guidelines for dosimetry, tumor size, tumor location, or length of follow-up. Radiation effects are often delayed, and complications have been noted to increase over time (follow-up). Adnexal radiation complications (symptomatic dry eye or keratitis sicca) are rarely associated with  $^{125}\text{I}$  or  $^{103}\text{Pd}$  plaque radiotherapy (24). Late anterior segment complications have included dry eye, iris neovascularization, secondary glaucoma, and cataract. Acute posterior segment or intraocular radiation complications have included secondary retinal detachment and hemorrhage (vitreous, retinal, or choroidal). The most common late posterior segment complication is radiation retinopathy (108,

115). Less common complications include strabismus, scleral atrophy, cystoid macular edema, and optic neuropathy. All forms of radiation for choroidal melanoma can also induce exudative or hemorrhagic retinopathy. The potential of these complications should be explained to the patient for an informed decision regarding therapy. Treated patients are required to be closely followed for local treatment response and prompt intervention for late complications.

### Hyperthermia

Hyperthermia (a known radiation sensitizer) offers the potential to reduce the amount of ionizing radiation required to treat intraocular tumors (116–118). It is reasonable to hypothesize that dose reductions may decrease the incidence of ionizing radiation–associated complications for ophthalmic plaque radiotherapy. Intraocular hyperthermia has been generated by plaque-like antennas and ultrasound fields (116). Despite multiple phase I clinical trials, there have been no prospective comparative clinical trials to evaluate plaque radiation therapy vs. thermoradiotherapy for visual acuity or local control.

### Future directions

There remain many unanswered questions in the brachytherapy treatment of choroidal melanomas. In this article, the ABS has recommended a  $^{125}\text{I}$  dose of 85 Gy at the apex. However, it should be noted that some institutions routinely use lower doses (70–80 Gy) with good results (27, 28, 57, 67, 68). The lower dose is obviously preferable to reduce long-term morbidity if, in fact, these tumors can be controlled with lower doses. Also, unlike most implants, in which the tumor is irradiated from all sides, the radiation is given from only one side in plaque therapy. This leads to a steep dose gradient in which the dose to the sclera and the average dose to the tumor are dependent on the tumor height. Hence a tumor of 10 mm height will receive a much higher scleral dose and average tumor dose than a tumor of 3 mm height,

even if the same 85 Gy to the apex is prescribed to both. Plaques using individual source collimation have been reported to reduce this gradient (61). Another factor to note is that choroidal melanomas have the unique characteristic of having its blood supply from the choroid. Posttherapy fluorescein angiograms have shown that high scleral (and choroidal) doses result in a high incidence of vascular occlusion. Hence, it is possible that choroidal melanomas can be controlled by two mechanisms:

1. direct cell kill (in which case the minimum dose to the tumor and the average tumor dose would be important) and
2. loss of vascular supply (in which instance the choroidal dose would be important).

Reports of control of large melanomas after a low dose to the apex (but enough dose to the sclera/choroid to cause vascular sclerosis) are intriguing in this regard and point to the latter as a possible mechanism of tumor control for choroidal melanomas (68). If the scleral dose is the major factor for the larger (“taller”) tumors, one may need to prescribe the dose at a specified depth from the plaque, as in the report by Fontanesi and Meyer, in which the dose was prescribed to 3 mm from the plaque surface (68). Clearly, further research is required to establish the optimum dose and prescription method for the treatment of uveal melanomas. The ABS encourages prospective controlled clinical trials and correlation with quality of life outcomes to answer these questions.

## CONCLUSION

Brachytherapy represents an effective means of treating patients with choroidal melanomas. Guidelines are established for the use of brachytherapy in the treatment of choroidal melanomas. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose reporting policies. These guidelines will be modified as further clinical results become available.

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