ELSEVIER

Brachytherapy 13 (2014) 1–14

BRACHYTHERAPY

The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma

The American Brachytherapy Society - Ophthalmic Oncology Task Force

ABSTRACT

PURPOSE: To present the American Brachytherapy Society (ABS) guidelines for plaque brachytherapy of choroidal melanoma and retinoblastoma.

METHODS AND MATERIALS: An international multicenter Ophthalmic Oncology Task Force (OOTF) was assembled to include 47 radiation oncologists, medical physicists, and ophthalmic oncologists from 10 countries. The ABS-OOTF produced collaborative guidelines, based on their eye cancer–specific clinical experience and knowledge of the literature. This work was reviewed and approved by the ABS Board of Directors as well as within the journal's peer-reivew process.

RESULTS: The ABS-OOTF reached consensus that ophthalmic plaque radiation therapy is best performed in subspecialty brachytherapy centers. Quality assurance, methods of plaque construction, and dosimetry should be consistent with the 2012 joint guidelines of the American Association of Physicists in Medicine and ABS. Implantation of plaque sources should be performed by subspecialty-trained surgeons. Although there exist select restrictions related to tumor size and location, the ABS-OOTF agreed that most melanomas of the iris, ciliary body, and choroid could be treated with plaque brachytherapy. The ABS-OOTF reached consensus that tumors with gross orbital extension and blind painful eyes and those with no light perception vision are unsuitable for brachytherapy. In contrast, only select retinoblastomas are eligible for plaque brachytherapy. Prescription doses, dose rates, treatment durations, and clinical methods are described.

CONCLUSIONS: Plaque brachytherapy is an effective eye and vision-sparing method to treat patients with intraocular tumors. Practitioners are encouraged to use ABS-OOTF guidelines to enhance their practice.

Keywords: Plaque; Brachytherapy; Radiation; Guidelines; Methods; ABS; Consensus; Melanoma; Retinoblastoma

Introduction

Brachytherapy has been used to treat intraocular tumors since 1930 (1). Subsequent reports described ^{60}Co, ^{106}Ru, ^{125}I, ^{103}Pd, ^{90}Sr, and ^{131}Cs plaque sources (2–12). Modern plaques currently include assemblies of gold shells with low-energy photon seeds (^{125}I, ^{103}Pd, and ^{131}Cs) or solid beta (^{106}Ru and ^{90}Sr) plaques (13). Despite the international use of ophthalmic brachytherapy for both uveal melanoma and retinoblastoma (Rb), there exist no prospective randomized or case-matched clinical trials comparing the clinical effectiveness or side effects related to these radionuclides. The sole standardized clinical trial for choroidal melanoma, The Collaborative Ocular Melanoma Study (COMS), was restricted to the use of ^{125}I plaques (14, 15).

In 1985, the COMS provided the first standardized methods for multicenter tumor diagnosis, plaque construction, and ^{125}I plaque dosimetry (14). Then, the COMS conducted a 12-year study that demonstrated the relative equivalence of ^{125}I plaque compared with enucleation (removal of the eye) for the prevention of metastatic melanoma for a specific cohort of select medium-sized coroidal melanoma (15). An unintended consequence was that the method of using ^{125}I seeds in COMS-shaped gold carrier plaques was established as the most common plaque method in North America (16–18). Similarly, Lommatzsch *et al.* have established a long tradition of using ^{106}Ru plaque therapy in Europe (19–25).

The guidelines defined herein will exclude general aspects recently published by the American Association of Physicists in Medicine (AAPM) and the American Brachytherapy Society (ABS) (13, 26). The AAPM Task Group 129 (TG-129) has recently provided medical

Received 9 September 2013; received in revised form 5 November 2013; accepted 21 November 2013.

Corresponding author. Paul T. Finger, MD, The New York Eye Cancer Center, Suite 5B, 115 East 61st Street, New York City, NY 10065. Tel.: +1-212-832-8170; fax: +1-212-888-4030.

E-mail address: paulfinger@eyecancer.com

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2013.11.008

physics guidelines in two publications. The first compared the currently available methods of plaque treatment planning and contrasted the patterns of intraocular dose deposition of ^{103}Pd and ^{125}I plaques for an average-sized hypothetical intraocular tumor located at a variety of positions within the eye (26). Therein, comparative dosimetry revealed that the lower energy photons from ^{103}Pd irradiation were more rapidly absorbed within the target volume (hypothetical tumor and 2-mm margin) with less irradiation to most normal ocular structures (26). The second AAPM TG-129 report was published with the ABS and offers preferred methods for dose calculation, plaque handling, and quality assurance (13). This same AAPM report also includes an appendix describing current clinical controversies and applications.

Herein, we supplement the aforementioned work with an ABS-sanctioned study of clinical eye plaque brachytherapy. A panel of eye cancer specialists was assembled to broadly reflect current multicenter international practice patterns. Thus, the ABS Ophthalmic Oncology Task Force (ABS-OOTF) includes a total of 47 ophthalmic oncologists, medical physicists, and radiation oncologists from Canada, Finland, France, Germany, India, Japan, United Kingdom, the United States, Russia, and Sweden. Charged with developing modern guidelines for the use of plaque brachytherapy for uveal melanoma and Rb, consensus methods and indications for treatment are presented.

Methods and materials

Formation of the committee

This study involved a review of the literature. This included but was not limited to searching PubMed for the following terms: brachytherapy, choroid, iris, ciliary body, orbit, melanoma, retinoblastoma, ^{125}I, ^{103}Pd, ^{106}Ru, ^{90}Sr, ^{60}Co, ^{131}Cs, radionuclide, plaque, slotted, notched, proton beam, helium ion, cyberknife, gamma knife, stereotactic radiosurgery, intensity-modulated radiation therapy, extrascleral extension, COMS, dose, dose rate, and side effects. This review was supplemented by the participating authors' general working knowledge of the literature.

In addition, internet-based surveys (SurveyMonkey, Palo Alto, CA, USA) of the subjects explored herein were sent to the participating eye cancer specialists. The results of the literature review and survey were adapted to the *Brachytherapy* journal's instructions for authors by the corresponding author (PTF). Then, every ABS-OOTF member was allowed at least one opportunity to review and comment. Based on this feedback, the report was edited and returned to at least one representative from each center for a second review. As possible, all comments and suggestions were included in this report. In addition, the report was submitted to the ABS for additional review and approval before submission to the journal, *Brachytherapy*.

Table 1
American Brachytherapy Society Ophthalmic Oncology Task Force levels of consensus

Level 1: Uniform panel consensus, evidence primarily from the published literature.
Level 2: Uniform panel consensus, based on clinical experience.
Level 3: No uniform panel consensus or specific recommendation.

Many important recommendations of the ABS-OOTF were graded using levels of consensus modified from the 2003 ABS levels of Nag *et al.* (27) (Table 1).

ABS-OOTF's recommended methods

The ABS-OOTF recommends that plaque procedures should be performed in specialized medical centers with expertise in ophthalmic brachytherapy (Level 1 Consensus). Such centers should include a team composed of a subspecialty-trained plaque surgeon, a radiation oncologist, and a medical physicist experienced in plaque brachytherapy. Furthermore, it was agreed that these centers read and become familiar with the 2011 and 2012 published eye plaque dosimetry, construction, and quality assurance guidelines published by the TG-129 and ABS (13, 26). In addition, each program should have written quality assurance guidelines functionally in place at their institutions. The results of the ABS-OOTF review of the literature, our clinical experience, and collective judgment are as follows.

Case selection

The diagnosis of uveal melanoma and Rb is complex. However, modern methods have greatly improved the accuracy of clinical diagnosis. Although patient history and physical examination (slit lamp and ophthalmoscopy) are indispensible, state of the art ophthalmic oncology services also use high- and low-frequency ultrasound imaging, photography, intraocular angiography, fundus autofluorescence imaging, optical coherence tomography, CT, MRI, positron emission tomography/CT, and biopsy (28–36). In addition, wide-field fundus photography (RetCam; Clarity Medical Systems, Pleasanton, CS) has become indispensible for the diagnosis, staging, and monitoring the effects of Rb treatment. Although beyond the scope of this work, multimodality ophthalmic imaging plays an increasingly integral role in tumor diagnosis and follow-up. Although the initial diagnosis, follow-up for tumor control, and intraocular side effects are best revealed by the ophthalmic oncologist, these results should be periodically examined and reported by each brachytherapy center.

Uveal melanoma

Indications for the use of plaque therapy have expanded since 2003 ABS guidance (Table 2) (27). Reports now include brachytherapy for most uveal melanomas. This includes iris, ciliary body, choroidal, subfoveal, juxtapapillary,

Table 2
Changes in general guidelines for the treatment of uveal melanoma

2003 ABS recommendations	Current ABS recommendations
Clinical diagnosis of uveal melanoma is adequate for treatment. Histopathologic verification is not required. Small melanomas may be treated if there is evidence of growth.	Clinical diagnosis of uveal melanoma is adequate for treatment. Histopathologic verification is not required. Small melanomas can be treated at the eye cancer specialist's discretion.
COMS medium and large uveal melanomas can be treated, after counseling about likely vision outcomes.	AJCC T1, T2, T3, and T4a–d uveal melanoma patients can be treated, after counseling about likely vision, eye retention, and local control outcomes.
Patients with peripapillary melanomas have poorer vision and local control outcomes and should be accordingly counseled.	Patients with peripapillary and subfoveal and those with exudative retinal detachments typically have poorer resultant vision and local control outcomes. They should be accordingly counseled.
Patients with gross extrascleral extension, ring melanoma, and tumor involvement of half of the ciliary body are not suitable for plaque therapy.	Tumors with T4e extraocular extension,[a] basal diameters that exceed the limits of brachytherapy, blind painful eyes, and those with no light perception vision are not suitable for plaque therapy.

ABS = American Brachytherapy Society; COMS = Collaborative Ocular Melanoma Study; AJCC = American Joint Commission on Cancer.
[a] ^{106}Ru and ^{90}Sr plaques are less accommodating for nodular extrascleral extension.

and circumpapillary melanomas (37–46). The reported literature also includes treatment of small and large tumors as well as those with limited extrascleral extension (47–53).

The ABS-OOTF agreed to adopt the, 7th edition, American Joint Committee on Cancer (AJCC) eye cancer staging system for uveal melanoma for many reasons. Some examples include the COMS small, medium, and large categories only applied to choriodal melanomas without extrascleral extension; the AJCC uveal melanoma T-staging system has been shown to predict metastasis in more than 7000 cases; and the use of tumor, node, and metastasis staging brings ophthalmic oncology into the mainstream of general oncology (54–56). Clearly, universal staging promotes multicenter cooperation and data analysis.

Therefore, rather than describing a specific range of uveal melanoma sizes or locations, the ABS-OOTF recommends (Level 2 Consensus) that brachytherapy exclusion criteria include tumors with gross (T4e or >5 mm) extraocular extension and blind painful eyes and those with no light perception vision. The ABS-OOTF recognizes that there will be instances in which alternative treatments are unacceptable, and patient preference for brachytherapy must be considered.

Special circumstances: uveal melanoma

1. There exists a controversy (Level 3 Consensus) about treatment of certain uveal melanomas. For example, in the diagnosis of ''small'' AJCC T1 uveal melanomas, the ABS-OOTF recommends (Level 2 Consensus) that in the absence of thickness ≥2 mm, subretinal exudative fluid, and superficial orange pigment lipofuscin tumors, patients could be offered the alternative of ''observation'' for evidence of change (within 6 months), typically for documented growth before intervention (52, 57–59). This is particularly applicable for tumors near the fovea and optic nerve, or monocular patients in which treatment is likely to cause radiation-related vision morbidity (60–62). Patients should also be counseled concerning the as yet unquantified, albeit small risk of metastasis related to ''observation as treatment.''
2. Ocular melanosis, the Nevus of Ota, and even natural pigmentation can darken the uvea and can prevent successful intraoperative tumor transillumination. This (in turn) makes definition of the target volume and plaque placement particularly difficult (63). These cases typically require experience and skills in scleral depression, focal transscleral transillumination (fiber optic or HeNe), and intraoperative ultrasound imaging to confirm proper plaque placement.
3. Select centers routinely biopsy uveal melanomas for pathologic, genetic, and molecular biologic analyses (64, 65). However, patients must be counseled that studies of the ocular and metastatic risks of biopsy have been small, limited in follow-up, single center, and thus did not reach Level 2 Consensus (66).
4. Brachytherapy for tumors near, touching, or surrounding the optic disc is also controversial (37). As seen within the eye, the optic disc diameter is typically 1.8 mm. However, as the optic nerve exits the eye into the orbit, it is surrounded by additional components such as the optic nerve sheath and widens to 5–6 mm (67). Thus, if a round plaque is perfectly placed against the retrobulbar optic nerve sheath, its posterior extent will be offset at least 1.5 mm from the edge of the optic disc. Therefore, the orbital optic nerve size prevents standard plaque positioning as to cover the tumor and safety margin. In the past, 4-mm notches were placed in plaques to compensate. However, 4-mm notches cannot overcome the 5- to 6-mm optic nerve sheath obstruction to allow proper plaque positioning. In that brachytherapy for juxtapapillary tumors has been associated with higher rates of failure of local control, some centers have used laser to extend the treatment zone, whereas others have used external beam radiation therapy (EBRT) (e.g., protons) (68, 69).

In 2005, slotted plaques were devised with 8-mm openings (37, 70). In contrast to a notch, a slot allows the optic nerve sheath to enter the plaque carrier, thus more posteriorly locate the seed sources and move the target volume into a normalized position (surrounding the choroidal melanoma). It is important to note that plaque slots make dosimetry more complex. In these cases, medical physicists must locate seed sources to both "fill-in" the gap created by the slot and cover the target volume (71). Slotted plaques can be made by cutting standard size plaque shells or by special request from a local source (e.g., Trachsel Dental Studio, Rochester, MN, USA).

However, the ABS-OOTF also recognizes that the penumbra at the edge of beta (^{106}Ru and ^{90}Sr) plaques is relatively sharp compared with the low-energy gamma of ^{125}I and ^{103}Pd plaques (13, 26, 72, 73). Thus, tumor tissue within the slot is likely to receive less radiation with slotted ^{106}Ru and ^{90}Sr plaques compared with ^{125}I and ^{103}Pd slotted plaques in treatment of juxtapapillary and circumpapillary tumors.

Uveal melanoma metastasis

The ABS-OOTF recommends (Level 2 Consensus) that all patients with uveal melanoma should be evaluated for metastatic disease before treatment (74). However, staging methods vary throughout the world. They range from relatively nonspecific hematologic surveys, chest X-rays, and ultrasonographic or radiographic imaging of the abdomen (MRI or CT) to total body positron emission tomography/CT (33, 74, 75). The ABS-OOTF notes a trend toward greater use of abdominal ultrasound screening in Europe and Russia. However, all regimens focus on the liver as primary or sentinel organ at risk. We agree with the COMS that early detection of metastatic melanoma allows for adjunctive systemic therapy (76). A statistically significant comparison of the efficacy of each form of metastatic survey has not been performed.

The ABS-OOTF recommends (Level 2 Consensus) that the presence of metastatic disease from uveal melanoma is not an absolute contraindication for brachytherapy. For example, there exist ocular situations in which brachytherapy may limit or prevent vision loss from tumor-associated retinal detachment or when tumor growth will soon cause secondary angle closure glaucoma. In addition, brachytherapy of the primary tumor may allow the patient to enter systemic treatment trial in which a small proportion will survive. The ABS-OOTF does not recommend brachytherapy for patients whose death is imminent or those who cannot tolerate surgery.

Retinoblastoma

Brachytherapy is less commonly used as a primary treatment for Rb (23, 77, 78). More frequently, radioactive plaques are used secondarily, after local treatment failure (after cryotherapy, chemotherapy [systemic or ophthalmic artery perfusion], focal therapy [e.g., laser or cryotherapy], EBRT, or a combination thereof (79)). For example, a specific indication for plaque treatment may be found when there is residual macular Rb that failed control with chemoreduction with subsequent focal therapy. Also in cases when focal therapy would surely affect the patients potential for vision.

The ABS-OOTF recommends (Level 2 Consensus) that ideal tumors for primary brachytherapy are located anterior to the equator and in unilaterally affected children. For secondary treatment, residual or recurrent tumors are treated irrespective of location. Exceptions include anterior segment involvement (typically an indication for enucleation) and juxtapapillary location (there exists no reports of slotted plaque therapy for Rb). There exists a worldwide consensus to avoid EBRT when possible. For example, nonplaque brachytherapy implants have been used for orbital recurrence of Rb (80, 81).

Systemic evaluations for Rb vary widely but typically consist of orbital and intracranial MRI imaging. Due ionizing radiations oncogenic impact on children with RB1 mutations, CT imaging is used only when MRI is not available (82). In high-risk patients, imaging is coupled with lumbar puncture and bone marrow aspiration biopsy.

Determinations of metastatic risk are typically based on clinical and histopathologic staging of the enucleated eye (83, 84). However, fewer eyes are being enucleated because of chemoreduction with focal therapy consolidation and the recent use of ophthalmic arterial chemotherapy for intraocular disease. Both these techniques likely result in downstaging, in which histopathologic markers for metastasis may disappear, leaving only clinical staging (84–86).

Therefore, before plaque therapy, the ABS-OOTF recommends (Level 2 Consensus) that children with risk of extraocular Rb undergo systemic staging.

Plaque treatment planning

Communication between the radiation oncologist, ophthalmic oncologist, and medical physicist is critical for any successful brachytherapy program (Level 2 Consensus). To facilitate this communication, a treatment form and fundus diagram should be available to all participating specialists. It should be made part of the radiation oncology medical record and should be available to the surgeon in the operating room.

1. The treatment form contains demographic identifying information about the patient, laterality of the involved eye, the largest basal dimension of the tumor, when treatment is scheduled, and contact information for the treatment by eye cancer specialists. Each tumor should be staged according to the latest AJCC or equivalent Union for International Cancer Control (UICC) staging system (currently the 7th edition) (87, 88).
2. The fundus diagram should be created as to demonstrate the tumors clock hour orientation within the

eye, its longitudinal and transverse diameters, and its largest basal diameter. It should include measurements from the tumor to the fovea, optic nerve, lens, and opposite eye wall. This information is typically derived from judgments correlating the ophthalmic examination, ultrasound findings, and photographic images. The ABS-OOTF agreed (Level 2 Consensus) that neither CT nor MRI currently offers superior tumor measurements.

The medical physicist transfers this information to a computerized treatment planning system. Although described by the joint AAPM/ABS TG-129 report, this process also requires a determination of the radionuclide, prescription dose, and dose rate. For those centers using radioactive seeds, there must also be seed selection and orientation. The ABS-OOTF recommends that all centers perform preimplant treatment planning with documentation of doses to critical structures (26). The ABS-OOTF also recommends that each plaque dosimetry plan undergo independent verification by a qualified medical physicist. The methods of preplanning, dose calculation, plaque design, plaque handling, and quality assurance are recently described in the TG-129 reports (13, 26).

Radionuclide selection

The ABS-OOTF found that ^{125}I and ^{103}Pd plaques are used by three or more centers in North America, ^{125}I or ^{106}Ru in Europe, solely ^{106}Ru in Japan, and both ^{106}Ru or ^{90}Sr sources in Russia. Russian ^{90}Sr plaques are currently used for uveal melanoma up to 2.5 mm in height and Rb up to 3 mm (10).

In that normal ocular tissue, side effects are dose related (Level 1 Consensus); the ABS-OOTF suggests that each center should engage in an intraocular dose distribution comparison (tumor apex, tumor base, lens, fovea, optic nerve, and opposite eye wall) of locally available radionuclide sources before radiation source selection. We also agree (Level 1 Consensus) that each radionuclide offers different energies, intraocular dose distributions, and requirements for handling (Table 3). The ABS-OOTF recommends (Level 2 Consensus) the goal of treatment to be delivery of a curative dose to the tumor while offering the least possible radiation to normal ocular structures.

Dose prescription

In the survey of customs and practice of the ABS-OOTF centers, there exists significant variation in radionuclide characteristics, selection, and prescription dose. We recognize the significant differences in dose distribution patterns and a lack of internationally accepted dosimetry standards for each radionuclide. Furthermore, the ABS-OOTF could find no prospective randomized or case-matched studies comparing the efficacy or side effects of available plaque radionuclide techniques. Therefore, specific ABS-OOTF recommendations concerning the relative risks and benefits of each technique were considered beyond the scope of this report.

The ABS-OOTF guidelines offer an overview of the committee's current practices and published results (6, 20, 21–24, 49, 50, 52, 89). Dose prescriptions for uveal melanoma typically range from 70 to 100 Gy to the tumors apex. Two ABS-OOTF centers report using a minimum ^{106}Ru dose to the sclera and one center continues to use the COMS-mandated minimum 85 Gy of ^{125}I to 5 axial intraocular millimeters. Depending on the ABS-OOTF center, even higher tumor apex and minimum scleral "base" doses have been used for both ^{106}Ru and ^{90}Sr plaques.

The ABS-OOTF recommends (Level 1 Consensus) that the tumor apex or point of maximal thickness remains the prescription point. However, the prescription isodose line should encompass the entire tumor. In this, it may affect local control; dose rates should not be less than the COMS historical standard of 0.60 Gy/h for ^{125}I or that published for ^{103}Pd plaques (90). Dose modifications may be appropriate to account for different tumor sizes, implant durations, threshold doses to critical normal ocular structures, and the use of alternate radionuclide sources.

Plaque selection

ABS-OOTF centers using ^{106}Ru plaques (Bebig, Eckert and Ziegler Corp., Berlin, Germany) typically restrict tumor apical height less than a mean of 6 mm and rarely use commercially available ^{106}Ru plaques larger than 20 mm in diameter. In contrast, centers using ^{125}I or ^{103}Pd plaques do not as closely restrict their treatments based on tumor thickness. These patients with tumors greater than 12 mm in apical height or 20 mm in base are advised of their guarded prognosis for retaining useful vision and are counseled regarding alternative therapies. The largest commercially available gold COMS-type plaque (Trachsel Dental Studio) is 22 mm in diameter.

The ABS-OOTF recommends (Level 1 Consensus) that tumor diameters should not exceed the diameter of the planning target volume to prevent geographic miss. Thus, plaque apertures should exceed the largest tumor diameter as to create a tumor-free margin of safety to prevent geographic miss. That said, centers that use ^{106}Ru plaques must adjust for the 1-mm rim of silver designed to surround the periphery of the source aperture or "window." For small tumors, particularly those treated with ^{106}Ru plaques, durations may be as short as 3 days. However, in the survey of ABS-OOTF centers, brachytherapy for uveal melanoma treatment durations typically range from 5 to 7 days.

Rb brachytherapy practice patterns

Eligible Rbs are typically less than 15 mm in base and no more than 10 mm in thickness (23, 77–79, 91, 92). Some describe Group B (International Classification) as being the most commonly applicable stage. The ABS-OOTF

Table 3
Radiological characteristics of radionuclides used for episcleral brachytherapy

Emitters	Half-life[a]	Mean photon energy (keV)[a]	Water TVL (mm)[b]	Pb TVL (mm)[c]
Photon				
^{125}I	59.4 d	28.4	55	0.059
^{103}Pd	16.99 d	20.7	30	0.026
^{131}Cs	9.69 d	30.4	62	0.070
Emitters	**Half-life[a]**	**End point beta energy (MeV)[a]**	**CSDA range in water (mm)[d]**	
Beta				
^{106}Ru/^{106}Rh	371.8 d	3.541[e]	17	
^{90}Sr	28.8 y	0.546[f]	1.9	

Photon emissions less than 5 keV were removed from calculations of mean energy and tenth value layers (TVLs). Pb = lead; CSDA = continuous slow down approximation.

[a] http://www.nndc.bnl.gov/chart/.

[b] http://physics.nist.gov/PhysRefData/XrayMassCoef/ComTab/water.html.

[c] http://physics.nist.gov/PhysRefData/XrayMassCoef/ElemTab/z82.html.

[d] Handbook of Radioactivity Analysis, edited by M. F. L'Annunziata (2003): http://books.google.com/books?id=OfqdTC6deZkC&pg=PA19&lpg=PA19&dq=beta+particle+range+in+air&source=bl&ots=D7gm8TeI3a&sig=zmcdrOUS15NVqqfDl oPfOvhRCA&hl=en&ei=yN7MSfvZDprNlQfnqtXQCQ&sa=X&oi=book result&resnum=8&ct=result#v=onepage&q&f=false http://www.alpharubicon.com/basicnbc/article16radiological71.htm.

[e] http://www.nndc.bnl.gov/chart/decaysearchdirect.jsp/nuc=106Rh&unc=nds.

[f] http://www.nndc.bnl.gov/chart/decaysearchdirect.jsp?nuc=l06Rh&unc-nds.

recommends (Level 2 Consensus) that vitreous seeding should be absent or within 2 mm of the tumor surface. Either low-energy ^{103}Pd, ^{125}I (for thicker tumors), or ^{106}Ru plaques (for thinner tumors) has been used. Using low-energy plaques, a solitary Rb is typically treated with a dose of 40–50 Gy to the tumor apex over 3–5 days. Depending on the ABS-OOTF center, typically higher tumor apex doses have been used for both ^{106}Ru and ^{90}Sr plaques.

Murphree (78) noted that a history of or synchronous treatment with chemotherapy potentiates radiation-related intraocular vasculopathy (retinopathy and optic neuropathy). In these cases, they advocated reduced apical ^{125}I prescription doses of 20–25 Gy or allowing several months between chemotherapy and brachytherapy (78).

Plaque surgery

Survey of ABS-OOTF centers suggests that brachytherapy using both low-energy photon-emitting sources (^{103}Pd and ^{125}I) and beta-emitting ^{103}Ru have been performed as outpatient procedures. However, centers must comply with local government regulations. The surgeries should be performed under either general or regional anesthesia, by a subspecialty-trained surgeon, thus experienced in plaque insertion. Ocular muscles should be relocated if they interfere with plaque position. This includes both rectus and oblique muscles.

Typically localized by transpupillary or transocular illumination of the globe, the tumor base shadows its subjacent sclera. The edges of the shadow are marked on the sclera with tissue dye. An additional 2–3 mm "free margin" is typically measured and marked around the tumor base. Some centers directly sew the plaque over the marked target, whereas others preplace sutures using "dummy" plaques. The ABS-OOTF defines "normal plaque position" (Level 1 Consensus) that the target volume includes the tumors base and safety margin. The ABS-OOTF survey found that compared with ^{103}Pd and ^{125}I plaques, larger physical safety margins are typically used with ^{106}Ru.

Extra care must be taken in transilluminating thicker (e.g., >5-mm thick) uveal melanomas. Here, the tumor can cast eccentric shadows, thus yielding false tumor base diameters. Small posterior and amelanotic tumors can also be a challenge to mark. Here, two techniques are helpful including: posterior point source illumination (e.g., fiber optic or HeNe light sources or scleral depression combined with indirect ophthalmoscopy) and/or intraoperative ophthalmic ultrasound verification (93, 94). When this is not possible (e.g., iris and iridociliary melanoma), high-frequency ultrasound imaging and direct transcorneal visualization play a more important role during intraoperative tumor localization (28).

In all cases, the plaque is sutured as to cover the scleral-marked target volume. Then, the extraocular muscles and conjunctiva are reattached as not to disturb brachytherapy. When using plaque with low-energy seeds, the eye is typically covered with a lead patch shield. Typically, after 5–7 days, the patient is returned to the operating room, where the plaque is removed under regional or general anesthesia. The ABS-OOTF agreed (Level 2 Consensus) that displaced muscles should be reattached into their insertions after plaque removal. However, one ABS-OOTF center did not find it necessary to reattach the inferior oblique muscle. If an amniotic membrane is used to buffer the cornea during brachytherapy, it should be removed before conjunctival closure (95, 96).

Follow-up after brachytherapy

After brachytherapy, patients are followed for local control, complications, and systemic disease. Most ABS-OOTF

centers examine treated eyes every 3–6 months. This time interval can be modulated based on the likelihood of secondary complications. For example, intervals are shorter for patients with posteriorly located tumors at higher risk of radiation maculopathy and radiation optic neuropathy. These complications typically occur within the first 3 years of follow-up (see radiation complications in the following sections) (8, 51, 60–62). Similarly, most local tumor recurrence occurs during the first 5 years. Therefore, larger and juxtapapillary tumors (at higher risk for regrowth) may require closer follow-up. In addition, patients should be periodically reexamined for evidence of metastatic disease and second nonocular primary cancers (74, 75, 97, 98). The ABS-OOTF agrees (Level 1 Consensus) that periodic radiographic abdominal imaging of the liver can be used to detect hepatic melanoma metastasis. We also concur that early detection yields patients with smaller tumor burdens who would more likely benefit from systemic treatment and clinical trials.

Alternative surgical techniques

Uveal melanomas are alternatively be treated by enucleation or exenteration. The former is used when the tumor is confined to the eye and the latter considered in the presence of gross orbital tumor extension. Photon-based EBRT is rarely used prior to enucleation because the COMS large tumor trial found no statistically significant survival advantage (75, 99). In contrast, most centers continue to apply after exenteration or after enucleation radiation therapy in cases when there is residual orbital melanoma and Rb (80, 81, 100, 101).

Local resection (internal evacuation or external lamellar sclerouvectomy) is used to remove select (typically select medium sized or large) uveal melanoma but not Rb. Some centers irradiate (e.g., proton beam) the uveal melanoma before endoresection or place a radioactive plaque over the tumors base after transscleral resection (102, 103). Such adjunctive radiotherapy targets presumed residual melanoma that may seed the orbit or locally recur. Other centers consider vitreous melanoma seeds to be an indication for enucleation.

The ABS-OOTF recognizes (Level 3 Consensus) that adjuvant radiation therapy may be used to reduce the risk of local tumor recurrence in cases of presumed residual subclinical disease. However, we also recognize that there exist no prospective comparative or case-matched studies examining the relative risks and benefits of resection techniques compared with primary brachytherapy or enucleation (103).

Retinoblastomas of stage AJCC T4 or International Classification D and E are not candidates for brachytherapy and are typically treated by enucleation (92). The ABS-OOTF achieved Level 1 Consensus that primary enucleation before extraocular extension, optic nerve invasion, and/or massive choroidal infiltration offers greater than 95% primary tumor-free survival (83, 84, 92). Although Rbs with extrascleral tumor extension are treated with combinations of systemic chemotherapy, surgical excision (enucleation or exenteration), and external beam irradiation as well as systemic surveillance. There exists Level 1 Consensus that if possible, EBRT should be avoided due to secondary carcinogenesis and orbital bone dysplasia (82, 104). Preferred practice patterns for treatment of Rb are even more complex and beyond the scope of this review (105).

Alternative radiation therapy techniques

Proton therapy was pioneered at the Harvard Cyclotron Laboratory and by the researchers at the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital (106). Since that time, at least 12 additional institutions around the world have embraced this technique with numerous additional centers under construction (107–109). These centers typically use a proton radiobiologic effectiveness value of 1.1 compared with ^{60}Co. For uveal melanoma, doses of approximately 60 Gy are delivered in four (15 Gy) daily fractions. Although there exists no significant comparison between high-dose-rate proton beam vs. low-dose-rate plaque brachytherapy, the ABS-OOTF recognizes (Level 1 Consensus) that both the dose rates and the dose volumes differ. Furthermore, we agree (Level 1 Consensus) that all external beam radiation techniques (proton, helium ion, gamma knife, and stereotactic radiosurgery) require an anterior ocular and/or adnexal entry dose with resultant dose-related collateral damage to those exposed normal tissues (even when treating posterior tumors). However, we also recognize (Level 1 Consensus) that there is relative dose sparing of tissues posterior and lateral to the proton beam.

In contrast, plaque brachytherapy places the source on the sclera beneath (adjacent to) the tumor. Thus, in the treatment of posterior choroidal melanomas, radiation must travel through the sclera before entering the tumor and through the eye before exiting through normal anterior ocular tissues (26). Primarily because of dose gradient and side-scatter effects, plaque brachytherapy delivers comparatively more radiation to subjacent sclera and adjacent ocular structures (13).

The ABS-OOTF recognizes (Level 1 Consensus) that in the treatment of posterior uveal melanomas, there is less resultant radiobiologic effect on normal anterior ocular structures using low-energy (^{103}Pd, ^{125}I) plaque brachytherapy compared with proton beam. This relative dose sparing may explain why clinical studies have revealed more anterior segment complications and secondary enucleations after charged particle therapy (107, 108, 110–114).

External beam radiation techniques (proton, helium ion, gamma knife, and stereotactic radiosurgery) are also complicated by mobile target volume (eye movement). Since eye plaques are sewn to the eye wall beneath their target volume,

when the eye moves so does the plaque. In contrast, when a target volume is externally created to extend within the eye (all EBRT techniques), mobility of the eye makes intraocular dose deposition less predictable. This is why during proton therapy, eye movements must be constantly monitored and the patient reminded (as needed) to fixate on a reference target. This is because eye movements cause misapplication of protons within the eye. In addition, should larger tumor-free safety margins become necessary, more normal tissues (anterior and posterior) fall within the cylindrical target volume. In addition, proton beam facilities are vastly more expensive (Table 4) (115, 116).

The ABS-OOTF survey indicates that proton beam has been used as an alternative to enucleation for tumors considered unsuitable for brachytherapy. This includes tumors that touch or surround the optic disc, for very large tumors and where ^{125}I and ^{103}Pd plaques are not available. In addition, a novel strategy tries to prevent secondary inflammation; "vitritis" or "toxic tumor syndrome" has been described after brachytherapy for large choroidal melanoma. Here, large uveal melanomas are first treated with proton beam and then removed by internal resection (102). There are only a few centers using this technique (ABS-OOTF Level 3 Consensus).

Clinical results

Reporting the results of treatment is particularly challenging. Consider that when multiple centers use the same radionuclides source, they often differ in plaque construction, dosimetry, doses, and dose rate. Furthermore, until acceptance of the AJCC staging system, there existed no universal method to report the size of uveal melanomas. Furthermore, there is no uniform method of reporting with respect to follow-up duration, visual acuity, local control, or metastasis. Herein, we have assembled a noninclusive table of representative case series with >100 treated patients (Table 5).

Select observations derived from Table 5 include that the radionuclides ^{125}I and ^{106}Ru are best represented, and on average, the data are more than 10 years old. Note that a mean of 341 patients was reported per center, average follow-up was 4.5 years and tumor size reporting lacks AJCC or UICC standardization. With respect to treatment, the mean and median prescription dose were 83 and 80 Gy, respectively (range, 70–100 Gy). Similarly, reported and 5-year local control rates averaged 89.5% (range, 69.9–97.9%). However, there exist no data to allow a meta-analysis comparing relative tumor size and location. In general, there exists no information concerning cases lost to follow-up. Note that the median rates of metastasis are quite similar except for series reporting on larger tumors (48). Finally, visual acuity results vary widely.

Visual acuity outcomes are difficult to compare, in that they depend on many factors including but not limited to preexisting exudative retinal detachments, subfoveal tumor position, radiation dose to critical structures, cataract onset, cataract repair, secondary vitreous hemorrhage, radiation maculopathy, optic neuropathy, and the availability of anti-vascular endothelial growth factor (anti-VEGF) treatment. Clearly, this outcome analysis supports the need for more uniform data collection and reporting among eye cancer specialists.

Table 4
Comparison of plaque and proton therapy

Plaque	Proton
Surgical insertion and removal	Surgical clip implantation
Continuous low-dose-rate treatment 5–7 d (^{125}I and ^{103}Pd) 3–7 d (^{106}Ru)	4 Daily high-dose-rate fractions
Mobile radiation field	Static radiation field
Fewer anterior segment complications	More anterior segment complications
Posterior segment complications	Posterior segment complications
Less expensive	More expensive

Radiation complications overview

Ophthalmic brachytherapy complications have been related to both radiation and patient-specific factors. These include total dose, dose rate, dose volume, dose to critical structures, tumor size, location, and the biologically variable responses to irradiation.

Radiation cataract

The ABS-OOTF survey indicates (Level 1 Consensus) that there exists no increased risk associated with radiation cataract removal (62, 117). However, almost all centers recommended waiting until 6–12 months after brachytherapy.

Intraocular radiation vasculopathy

Radiation induces a progressive vasculopathy caused by loss of pericytes and endothelial cells (118). Clinical findings include transudation of intravascular components (blood, serum, and lipids) and small vessel closure (cotton wool spots). First retinal findings include hemorrhages, edema, and cotton wool infarcts. However, it is the earlier onset radiation macular edema causes reversible vision loss. Later, small vessel closure leads to ischemia, neovascularization, and irreversible atrophy. Variations of this process are also seen in the optic disc and iris.

The ABS-OOTF concur (Level 2 Consensus) that untreated radiation maculopathy and optic neuropathy typically result in poor visual acuity. The prognosis for vision diminishes with vasculopathy of the macula, optic nerve, vitreous hemorrhage, and neovascular glaucoma. In that radiation maculopathy is the most common cause of radiation-associated vision loss, we present a classification for radiation retinopathy based on prognosis for vision (Table 6).

Table 5
Review of uveal melanoma clinical case series

Author	Year	Patients No.	Radionuclide	Follow-up Mean or median, mo	Thickness Mean or median (range)	Basal diameter Mean or median (range)	Radiation dose Apex, mean	Local control Overall, %	Local control 5 y	Metastasis Overall	Metastasis 5 y	Visual acuity Final %, >20/200
Lommatzsch (3)	1987	309	^{106}Ru	80	3.7 (1.2–11.8)	9.7 (4.5–21.5)	100	69.9	84	12.9	NA	NA
Quivey *et al.* (90)	1996	239	^{125}I	36	5.5 (1.9–11.0)	10.9 (4–18)	70	91.7	82	7.5	12	NA
Fontenesi *et al.* (17)	1993	144	^{125}I	46	Small, n = 15; medium, n = 84; large, n = 45	NA	75	97.7	94.4	2.7	2	71.3
Seregard *et al.* (24)	1997	266	^{106}Ru	43	4.4 (1.0–13.1)	10.0 (3–23)	100	83	82	11	14	NA
COMS (16)	2006	657	^{125}I	96	4.8 (2.5–10.0)	11.4 (up to 16)	85	NA	NA	9	9	63
Bechrakis *et al.* (128)	2002	152	^{125}I	30.1	9.0 ± 1.1	14.6 ± 2.4	98 ± 18	88.8	NA	11.1	NA	5.6
Shields *et al.* (48)	2002	354	^{125}I	60	9.0 (9.8–16)	14.0 (5–21)	80	91	91	24	24	43
Puusaari *et al.* (49)	2003	97	^{125}I	43.2	10.7 (4.5–16.8)	16.1 (7.3–25)	87	94.8	94	28.9	35	42 at 1 year
Damato *et al.* (89)	2005	458	^{106}Ru	47	3.2 (0.7–7.0)	10.6 (5–16.6)	80	97	97.9	8.1	NA	57
Finger *et al.* (6)	2009	400	^{103}Pd	51	3.8 (1.5–12.3)	10.5 (5–19.9)	73	97	NA	6	7.3	79
Mean	2000	308		53.2			84.8	90.1	89.3	12.2	14.8	53.2
Median	2002	354		46.5			82.5	91.7	91	10	12	57

NA = not available; COMS = Collaborative Ocular Melanoma Study.
Tumor measurements are expressed in millimeters, follow-up in months, patients' number in number of patients, % <20/200 in those with better than 20/200 vision.

The ABS-OOTF agreed (Level 2 Consensus) that intravitreal anti-VEGF therapy is useful to suppress radiation-induced neovascular glaucoma, radiation maculopathy, and optic neuropathy. Therapy is used to suppress transudation, thus ameliorate edema and counter neovascularization (119–123). However, although these techniques are widely used, the ABS-OOTF recognizes that no published prospective randomized or large-scale studies examined the effects relative to initial radiation dose, dose rate, or source.

The literature also contains two alternative approaches to the treatment of radiation retinopathy. Laser photocoagulation in the form of posterior tumor demarcation resulted in sector devascularization best seen on fluorescein angiography. This technique along with sector pan retinal photocoagulation has been reported to slow or prevent radiation retinopathy by two independent centers (124, 125). Treatment converted slow ischemia within and anterior to the target to scar. In theory, laser devitalization of the ischemic tumor and treated retina may decrease intraocular production of VEGF.

However, brachytherapy also affects the eyelids, eyelashes, conjunctiva, tear production, corneal surface integrity, sclera, and ocular muscles (8, 100, 126, 127). Within the eye, radiation can cause iritis, uveitis, synechiae, neovascular glaucoma, cataract, posterior neovascularization, hemorrhage, retinal detachment, retinopathy, and optic neuropathy. The most common late sight limiting posterior segment complication is radiation maculopathy. Unusual complications include persistent strabismus and scleral thinning. All the aforementioned side effects can result in loss of vision and quality of life.

Staging of radiation side effects

The ABS-OOTF recognize that there exists no comprehensive staging system for the ophthalmic side effects of radiation therapy. Although many of these findings are fundamentally, albeit less specifically, classified by the United States National Cancer Institute (Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, National Cancer Institute, National Institute of Health, Department of Health and Human Services (http://ctep.cancer.gov)), the ABS-OOTF recommends that a radiation-specific ophthalmic side effect staging system should be developed to improve communication for patient care, research, and publication.

Discussion

This presentation of ABS-OOTF guidelines for ophthalmic plaque brachytherapy offers both consensus and controversy. We recommend that brachytherapy should be performed by a team composed of a skilled subspecialty-trained plaque surgeon, radiation oncologists, and medical physicists in experienced subspecialty centers. We agreed that the recent joint AAPM/ABS TG-129 published guidelines for plaque

Table 6
Classification for radiation retinopathy

Stage	Sign	Symptom	Location	Best viewed by	Risk of vision loss
1	Cotton wool spots	None	Extramacular	Ophthalmoscopy	Mild
	Retinal hemorrhages	None	Extramacular	Ophthalmoscopy	Mild
	Retinal microaneurysms	None	Extramacular	Ophthalmoscopy/FA	Mild
	Exudate	None	Extramacular	Ophthalmoscopy	Mild
	Uveal effusion	None	Extramacular	Ophthalmoscopy/OCT	Mild
	Chorioretinal atrophy	None	Extramacular	Ophthalmoscopy	Mild
	Choroidopathy	None	Extramacular	ICG	Mild
	Retinal ischemia (<5 DA)	None	Extramacular	FA	Mild
2	Above findings	None	Macular	All	Moderate
3	Any combination of the above plus				
	Retinal neovascularization	Vision loss	Extramacular	FA	Severe
	Macular edema—new onset	Vision loss	Macular	FA/OCT	Severe
4	Any combination of the above plus				
	Vitreous hemorrhage	Vision loss	Vitreous	Ophthalmoscopy	Severe
	Retinal ischemia (≥5 DA)	Vision loss	Both	FA	Severe

FA = fluorescein angiography; OCT = optical coherence tomography; ICG = indocyanine green angiography; DA = disc areas.
Vision loss must be related to associated sign(s). This table is modified and updated from an original classification (124).

construction, dosimetry, and quality assurance should be read and widely used at active centers (13, 26). We also concurred that many radionuclide sources can be used, but only ^{125}I, ^{103}Pd, and ^{106}Ru are used in three or more ABS-OOTF centers. Although there exist tumor thickness restrictions for ^{106}Ru and ^{90}Sr, taller tumors can be treated with ^{125}I or ^{103}Pd techniques (7, 11, 13, 72).

Overall, the ABS-OOTF expanded general indications for uveal melanoma patient selection (Table 2). Fianlly, we found that plaque brachytherapy is not commonly used for Rb. However, indications include: small anterior tumors in unilateral cases, for salvage after chemoreduction with subsequent alternative therapies and in select cases in which macular laser will likely cause loss of vision.

The ABS-OOTF recommends that the eye cancer community use universal AJCC–UICC staging to define tumor size, location, and associated variables (87, 88). This would enable multicenter communication, comparative analysis, and patient education. This in turn, would allow for collection of numbers large enough to reach statistical significance. The ABS-OOTF recommends the development of a site-specific staging system for complications after ophthalmic radiation therapy. This would facilitate scientific comparisons between treatments, help predict ophthalmic side effects, and improve informed consent.

Unanswered questions

However, the ABS-OOTF acknowledges the myriad unanswered questions that challenge ophthalmic plaque brachytherapy researchers. Select questions offered by the ABS-OOTF include: What are the radiobiological differences between continuous low-dose-rate plaque brachytherapy in comparison with fractionated high-dose-rate proton beam irradiation? What is the ''correct'' apical prescription dose and dose rate required for treatment of uveal melanoma, and how do we accommodate for the steep dose gradient within the tumor? For example, should there be a dose deescalation study or a thickness-based sliding scale in treatment of uveal melanoma? Can there be international standards for dosimetry to determine the relative efficacy of photons, electrons, and protons? Is there a role for radiation sensitizers during plaque therapy? Should the presence of intravitreal melanoma seeds affect case selection? What is the role and best timing for the use of anti-VEGF agents in treatment of radiation maculopathy and optic neuropathy? Are there differences in the efficacy of anti-VEGF agents related to radionuclide, radiation dose, and dose rate? Do notched and slotted plaques address geographic miss in the treatment of juxtapapillary and circumpapillary tumors? With regard to Rb, are there oncogenic risks of plaque brachytherapy? What are the optimal parameters for tumor size selection and radiation dose (if used before or after chemotherapy)? The ABS-OOTF hopes future research will answer some of these questions.

Summary

Currently, plaque brachytherapy offers an eye and vision sparing alternative to enucleation annually for thousands of patients' worldwide. Herein, we present the current ABS guidelines for patient selection, informed consent, and methods of treatment. We encourage all centers to use these guidelines to formulate their treatment patterns and reporting policies. However, we realize that such guidelines are dynamic and will need to be modified as to conform to ever evolving clinical evidence.

Conclusions

The ABS-OOTF, comprised 47 eye cancer specialists from 10 countries, present our current guidelines and methods of plaque brachytherapy for uveal melanoma and

Rb. We point out what is currently accepted as known, unknown, and a need for standardization, staging as well as future research.

Acknowledgments

The research was supported (in part) by The Eye Cancer Foundation, Inc. (http://eyecancerfoundation.net) and The American Brachytherapy Society.

The ABS – OOTF Committee

Canada - Princess Margaret Hospital
Sick Kids Hospital – Toronto, Ontario
E. Rand Simpson–Ophthalmic Oncology
Brenda Gallie–Ophthalmic Oncology
Normand Laperrierre–Radiation Oncology
Akbar Beiki-Ardakani–Medical Physics

Finland - Helsinki University Central Hospital
University of Helsinki, Helsinki
Tero Kivelä–Ophthalmic Oncology
Virpi Raivio–Ophthalmic Oncology
Jorma Heikkonen–Medical Physics

France - The Curie Institute, Paris
Laurence Desjardins–Ophthalmic Oncology
Remi Dendale–Radiation Oncology
Alexandro Mazal–Medical Physics

Germany - University of Duisburg-Essen, Essen
Norbert Bornfeld–Ophthalmic Oncology
Wolfgang Sauerwein–Radiation Oncology
Dirk Flüehs–Medical Physics
Lorenzo Brualla–Medical Physics

India – Centre for Sight Superspecialty Eye Hospital, Hyderabad
Santosh G. Honavar–Ophthalmic Oncology
Vijay Anand P. Reddy–Radiation Oncology

Japan – National Cancer Center Hospital, Tokyo
Shigenobu Suzuki–Ophthalmic Oncology
Naoya Murakami–Radiation Oncology

Russia - Helmholtz Research Institute of Eye Diseases, Moscow
Svetlana Saakyan–Ophthalmic Oncology, Radiology
Vladimir Valskiy–Ophthalmic Oncology, Radiology
Anush Amiryan–Ophthalmic Oncology, Radiology

Sweden - St. Erik's Eye Hospital, Stockholm
Stefan Seregard–Ophthalmic Oncology
Charlotta All-Eriksson–Ophthalmic Oncology
Lars Hjelmqvist–Ophthalmic Oncology
Göran Lundell–Radiation Oncology
Georges Sinclair–Radiation Oncology
Marie Lundell–Medical Physics

United Kingdom - Liverpool University Medical Center, Liverpool
Bertil Damato–Ophthalmic Oncology
R Doug Errington–Radiation Oncology
Philip Mayles–Medical Physics
Helen Mayles–Medical Physics

United States - Emory Eye Cancer
Emory University Medical Center Atlanta, Georgia
Chris Bergstrom–Ophthalmic Oncology
Hans Grossniklaus–Ophthalmic Oncology
Ian Crocker–Radiation Oncology
Elizabeth Butker–Medical Physics

United States - University of Tennessee – Memphis
Methodist University Hospital
St. Jude's Children's Research Hospital
Matthew Wilson–Ophthalmic Oncology
Barrett Haik–Ophthalmic Oncology
Holger Geischen–Radiation Oncology
Pradeep Patra–Medical Physics

United States - Tufts University Medical Center, Boston, Mass
Jay Duker–Ophthalmic Oncology
John Mignano–Radiation Oncology
Mark Rivard–Medical Physics

United States - The New York Eye Cancer Center, New York City
Beth Israel Comprehensive Cancer Center
The New York Eye and Ear Infirmary
Paul T. Finger, ABS-OOTF Chair–Ophthalmic Oncology
Ekaterina Semenova–Ophthalmic Oncology
Walter Choi–Radiation Oncology
Nina I. Kalach–Medical Physics

References

[1] Moore R. Choroidal sarcoma treated by the intraocular insertion of radon seeds. *Br J Ophthalmol* 1930;14:145–156.
[2] Stallard HB. Radiotherapy for malignant melanoma of the choroid. *Br J Ophthalmol* 1966;50:147–155.
[3] Lommatzsch PK. Results after beta-irradiation (106Ru/106Rh) of choroidal melanomas. Twenty years' experience. *Am J Clin Oncol* 1987;10:146–151.
[4] Packer S, Rotman M. Radiotherapy of choroidal melanoma with iodine-125. *Ophthalmology* 1980;87:582–590.
[5] Sealy R, le Roux PL, Rapley F, *et al*. The treatment of ophthalmic tumours with low-energy sources. *Br J Radiol* 1976;49:551–554.
[6] Finger PT, Chin KJ, Duvall G, *et al*. Palladium-103 ophthalmic plaque radiation therapy for choroidal melanoma: 400 treated patients. *Ophthalmology* 2009;116:790–796.
[7] Rivard MJ, Melhus CS, Sioshansi S, *et al*. The impact of prescription depth, dose rate, plaque size, and source loading on the central axis using 103Pd, 125I, and 131Cs. *Brachytherapy* 2008;7:327–335.
[8] Finger PT. Radiation therapy for choroidal melanoma. *Surv Ophthalmol* 1997;42:215–232.
[9] Leonard KL, Gagne NL, Mignano JE, *et al*. A 17-year retrospective study of institutional results for eye plaque brachytherapy of uveal

melanoma using (125)I, (103)Pd, and (131)Cs and historical perspective. *Brachytherapy* 2011;10:331–339.
[10] Vakulenko MP, Dedenkov AN, Brovkina AF, *et al*. Results of beta-therapy of choroidal melanoma. *Med Radiol (Mosk)* 1980;25:73–74.
[11] Brovkina AF, Zarubei GD, Val'skii VV. Criteria for assessing the efficacy of brachytherapy of uveal melanomas, complications of therapy and there prevention. *Vestn Oftalmol* 1997;113:14–16.
[12] Murakami N, Suzuki S, Ito Y, *et al*. ^{106}Ruthenium plaque therapy (RPT) for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2012;84:59–65.
[13] Chiu-Tsao ST, Astrahan MA, Finger PT, *et al*. Dosimetry of ^{125}I and ^{103}Pd COMS eye plaques for intraocular tumors: Report of Task Group 129 by the AAPM and ABS. *Med Phys* 2012;39:6161–6184.
[14] Collaborative Ocular Melanoma Study Group. Ch 12: Radiation therapy. In: National Technical Information Service (NTIS), editor. *COMS manual of procedures*. Springfield, VA; 1995. PB95-179693.
[15] Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol* 2006;124:1684–1693.
[16] Earle J, Kline RW, Robertson DM. Selection of iodine 125 for the Collaborative Ocular Melanoma Study. *Arch Ophthalmol* 1987;105:763–764.
[17] Fontanesi J, Meyer D, Xu S, *et al*. Treatment of choroidal melanoma with I-125 plaque. *Int J Radiat Oncol Biol Phys* 1993;26:619–623.
[18] Packer S, Stoller S, Lesser ML, *et al*. Long-term results of iodine 125 irradiation of uveal melanoma. *Ophthalmology* 1992;99:767–773.
[19] Bergman L, Nilsson B, Lundell G, *et al*. Ruthenium brachytherapy for uveal melanoma, 1979-2003: Survival and functional outcomes in the Swedish population. *Ophthalmology* 2005;112:834–840.
[20] Summanen P, Immonen I, Kivelä T, *et al*. Visual outcome of eyes with malignant melanoma of the uvea after ruthenium plaque radiotherapy. *Ophthalmic Surg Lasers* 1995;26:449–460.
[21] Damato B, Patel I, Campbell IR, *et al*. Local tumor control after ^{106}Ru brachytherapy of choroidal melanoma. *Int J Radiat Oncol Biol Phys* 2005;63:385–391.
[22] Foerster MH, Bornfeld N, Wessing A, *et al*. Treatment of malignant melanomas of the uvea with 106-ruthenium applicators. Report on the first 100 Essen cases. *Klin Monbl Augenheilkd* 1984;185:490–494.
[23] Schueler AO, Flüehs D, Anastassiou G, *et al*. Beta-ray brachytherapy of retinoblastoma: Feasibility of a new small-sized ruthenium-106 plaque. *Ophthalmic Res* 2006;38:8–12.
[24] Seregard S, aft Trampe E, Lax I, *et al*. Results following episcleral ruthenium plaque radiotherapy for posterior uveal melanoma. The Swedish experience. *Acta Ophthalmol Scand* 1997;75:11–16.
[25] Lommatzsch PK, Werschnik C, Schuster E. Long-term follow-up of Ru-106/Rh-106 brachytherapy for posterior uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2000;238:129–137.
[26] Rivard MJ, Chiu-Tsao S-T, Finger PT, *et al*. Comparison of dose calculation methods for brachytherapy of intraocular tumors. *Med Phys* 2011;38:306–316.
[27] Nag S, Quivey JM, Earle JD, *et al*. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *Int J Radiat Oncol Biol Phys* 2003;56:544–555.
[28] Finger PT, Reddy S, Chin K. High-frequency ultrasound characteristics of 24 iris and iridociliary melanomas: Before and after plaque brachytherapy. *Arch Ophthalmol* 2007;125:1051–1058.
[29] Romani A, Baldeschi L, Genovesi-Ebert F, *et al*. Sensitivity and specificity of ultrasonography, fluorescein videoangiography, indocyanine green videoangiography, magnetic resonance and radioimmunoscintigraphy in the diagnosis of primary choroidal malignant melanoma. *Ophthalmologica* 1998;212:44–46.
[30] Finger PT, Garcia JP Jr, Pro MJ, *et al*. "C-scan" ultrasound imaging of optic nerve extension of retinoblastoma. *Br J Ophthalmol* 2005;89:1225–1226.
[31] Marigo FA, Finger PT, McCormick SA, *et al*. Iris and ciliary body melanomas: Ultrasound biomicroscopy with histopathologic correlation. *Arch Ophthalmol* 2000;118:1515–1521.
[32] Chin K, Finger PT. Autofluorescence characteristics of suspicious choroidal nevi. *Optometry* 2009;80:126–130.
[33] Freton A, Chin KJ, Raut R, *et al*. Initial PET/CT staging for choroidal melanoma: AJCC correlation and second nonocular primaries in 333 patients. *Eur J Ophthalmol* 2012;22:236–243.
[34] Shields CL, Kaliki S, Rojanaporn D, *et al*. Enhanced depth imaging optical coherence tomography of small choroidal melanoma: Comparison with choroidal nevus. *Arch Ophthalmol* 2012;130:850–856.
[35] Lommatzsch PK, Ballin RE, Helm W. Fluorescein angiography in the follow-up study of choroidal melanoma after 106Ru/106Rh plaque therapy. *Retina* 1987;7:148–155.
[36] Rootman DB, Gonzalez E, Mallipatna A, *et al*. Hand-held high-resolution spectral domain optical coherence tomography in retinoblastoma: Clinical and morphologic considerations. *Br J Ophthalmol* 2013;97:59–65.
[37] Finger PT, Chin KJ, Tena LB. A five-year study of slotted plaque radiation therapy for choroidal melanoma: Near, touching or surrounding the optic nerve. *Ophthalmology* 2012;119:415–422.
[38] Finger PT. Plaque radiation therapy for malignant melanoma of the iris and ciliary body. *Am J Ophthalmol* 2001;132:328–335.
[39] Yousef YA, Finger PT. Lack of radiation maculopathy after palladium-103 plaque radiotherapy for iris melanoma. *Int J Radiat Oncol Biol Phys* 2012;83:1107–1112.
[40] Shields C, Naseripour M, Shields J, *et al*. Custom-designed plaque radiotherapy for nonresectable iris melanoma in 38 patients: Tumor control and ocular complications. *Am J Ophthalmol* 2003;135:648–656.
[41] Petousis V, Finger PT, Milman T. Multifocal iris melanoma treated with total anterior segment palladium-103 plaque radiation therapy. *Graefes Arch Clin Exp Ophthalmol* 2011;249:937–940.
[42] Fernandes BF, Krema H, Fulda E, *et al*. Management of iris melanomas with ^{125}I plaque radiotherapy. *Am J Ophthalmol* 2010;149:70–76.
[43] Krema H, Simpson ER, Pavlin CJ, *et al*. Management of ciliary body melanoma with iodine-125 plaque brachytherapy. *Can J Ophthalmol* 2009;44:395–400.
[44] Lumbroso-Le Rouic L, Charif Chefchaouni M, Levy C, *et al*. ^{125}I plaque brachytherapy for anterior uveal melanomas. *Eye (Lond)* 2004;18:911–916.
[45] Brovkina AF, Zarubei GD, Fishkin IuG. Validation of the use of brachytherapy in uveal melanomas of juxtapapillary localization. *Vestn Oftalmol* 1991;107:41–44.
[46] Newman H, Chin KJ, Finger PT. Subfoveal choroidal melanoma: Pretreatment characteristics and response to plaque radiation therapy. *Arch Ophthalmol* 2011;129:892–898.
[47] Gray ME, Correa ZM, Augsburger JJ, *et al*. Ciliary body melanoma with limited nodular extrascleral extension and diffuse iris-angle infiltration treated by whole anterior segment plaque radiotherapy. *Int Ophthalmol* 2007;27:273–276.
[48] Shields CL, Naseripour M, Cater J, *et al*. Plaque radiotherapy for large posterior uveal melanomas (> or =8-mm thick) in 354 consecutive patients. *Ophthalmology* 2002;109:1838–1849.
[49] Puusaari I, Heikkonen J, Summanen P, *et al*. Iodine brachytherapy as an alternative to enucleation for large uveal melanomas. *Ophthalmology* 2003;110:2223–2234.
[50] Puusaari I, Heikkonen J, Kivelä T. Ocular complications after iodine brachytherapy for large uveal melanomas. *Ophthalmology* 2004;111:1768–1777.
[51] Puusaari I, Heikkonen J, Kivelä T. Effect of radiation dose on ocular complications after iodine brachytherapy for large uveal melanoma:

Empirical data and simulation of collimating plaques. *Invest Ophthalmol Vis Sci* 2004;45:3425–3434.
[52] Semenova E, Finger PT. Palladium-103 radiation therapy for small choroidal melanoma. *Ophthalmology* 2013;120:2353–2357.
[53] Semenova E, Finger P. Palladium-103 plaque radiation therapy for AJCC T3 and T4 sized choroidal melanoma. *JAMA Ophthalmol* 2013. Epubhead of print: November 28, 2013. http://dx.doi.org/10.1001/jamaophthalmol.2013.5677.
[54] Kujala E, Damato B, Coupland SE, *et al*. Staging of ciliary body and choroidal melanomas based on anatomic extent. *J Clin Oncol* 2013;31:2825–2831.
[55] Finger PT. Do you speak ocular tumor? *Ophthalmology* 2003;110:13–14.
[56] Kujala E, Tuomaala S, Eskelin S, *et al*. Mortality after uveal and conjunctival melanoma: Which tumour is more deadly? *Acta Ophthalmol* 2009;87:149–153.
[57] Augsburger JJ, Vrabec TR. Impact of delayed treatment in growing posterior uveal melanomas. *Arch Ophthalmol* 1993;111:1382–1386.
[58] Sobrin L, Schiffman JC, Markoe AM, *et al*. Outcomes of iodine 125 plaque radiotherapy after initial observation of suspected small choroidal melanomas: A pilot study. *Ophthalmology* 2005;112:1777–1783.
[59] Murray TG, Sobrin L. The case for observational management of suspected small choroidal melanoma. *Arch Ophthalmol* 2006;124:1342–1344.
[60] Finger PT. Tumour location affects the incidence of cataract and retinopathy after ophthalmic plaque radiation therapy. *Br J Ophthalmol* 2000;84:1068–1070.
[61] Finger PT, Chin KJ, Yu GP. Risk factors for radiation maculopathy after ophthalmic plaque radiation for choroidal melanoma. *Am J Ophthalmol* 2010;149:608–615.
[62] Finger PT, Chin KJ, Yu GP, *et al*. Risk factors for cataract after palladium-103 ophthalmic plaque radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;80:800–806.
[63] Mashayekhi A, Kaliki S, Walker B, *et al*. Metastasis from uveal melanoma associated with congenital ocular melanocytosis: A matched study. *Ophthalmology* 2013;120:1465–1468.
[64] Onken MD, Worley LA, Char DH, *et al*. Collaborative Ocular Oncology Group report number 1: Prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012;119:1596–1603.
[65] Harbour JW. The genetics of uveal melanoma: An emerging framework for targeted therapy. *Pigment Cell Melanoma Res* 2012;25:171–181.
[66] McCannel TA, Chang MY, Burgess BL. Multi-year follow-up of fine-needle aspiration biopsy in choroidal melanoma. *Ophthalmology* 2012;119:606–610.
[67] Garcia JP Jr, Garcia PT, Rosen RB, *et al*. A 3-dimensional ultrasound C-scan imaging technique for optic nerve measurements. *Ophthalmology* 2004;111:1238–1243.
[68] Sagoo MS, Shields CL, Mashayekhi A, *et al*. Plaque radiotherapy for juxtapapillary choroidal melanoma: Tumor control in 650 consecutive cases. *Ophthalmology* 2011;118:402–407.
[69] Houston SK 3rd, Markoe AM, Boldt HC, *et al*. Juxtapapillary uveal melanomas: Patient outcomes after treatment with proton irradiation for peripapillary and parapapillary melanomas. *Arch Ophthalmol* 2011;129:1218–1220.
[70] Garcia JP Jr, Garcia PM, Rosen RB, *et al*. Optic nerve measurements by 3D ultrasound-based coronal "C-scan" imaging. *Ophthalmic Surg Lasers Imaging* 2005;36:142–146.
[71] Finger PT. Finger's "slotted" eye plaque for radiation therapy: Treatment of juxtapapillary and circumpapillary intraocular tumours. *Br J Ophthalmol* 2007;91:891–894.
[72] Brualla L, Sempau J, Zaragoza FJ, *et al*. Accurate estimation of dose distributions inside an eye irradiated with 106Ru plaques. *Strahlenther Onkol* 2013;189:68–73.
[73] Lommatzsch PK, Lommatzsch R. Treatment of juxtapapillary melanomas. *Br J Ophthalmol* 1991;75:715–717.
[74] Freton A, Pavlick A, Finger PT. Systemic evaluation and management of patients with uveal melanoma. In: Schachat AP, Ryan SJ, editors. *Retina. Vol. III, Tumors of the retina, choroid and vitreous*. London, New York, Oxford, St. Louis, Sydney, Toronto: Elsevier; 2013. p. 2313–2315.
[75] Kivelä T, Eskelin S, Kujala E. Metastatic uveal melanoma. *Int Ophthalmol Clin* Winter 2006;46:133–149.
[76] Diener-West M, Reynolds SM, Agugliaro DJ, *et al*. Screening for metastasis from choroidal melanoma: The Collaborative Ocular Melanoma Study Group Report 23. *J Clin Oncol* 2004;22:2438–2444.
[77] Merchant TE, Gould CJ, Wilson MW, *et al*. Episcleral plaque brachytherapy for retinoblastoma. *Pediatr Blood Cancer* 2004;43:134–139.
[78] Finger P, Murphree A. Ophthalmic brachytherapy: Treatment of choroidal melanoma and retinoblastoma. In: Peyman G, Meffert S, Conway M, Chou F, editors. *Vitreoretinal surgical techniques*. London, UK: Martin Dunitz; 2006. p. 452–468.
[79] Shields JA, Shields CL, De Potter P, *et al*. Plaque radiotherapy for residual or recurrent retinoblastoma in 91 cases. *J Pediatr Ophthalmol Strabismus* 1994;31:242–245.
[80] Stannard C, Maree G, Munro R, *et al*. Iodine-125 orbital brachytherapy with a prosthetic implant in situ. *Strahlenther Onkol* 2011;187:322–327.
[81] Sealy R, Stannard C, Shackleton D. Improved cosmesis in retinoblastoma patients treated with iodine-125 orbital irradiation. *Ophthalmic Paediatr Genet* 1987;8:95–99.
[82] Bunin GR, Felice MA, Davidson W, *et al*. Medical radiation exposure and risk of retinoblastoma resulting from new germline RB1 mutation. *Int J Cancer* 2011;128:2393–2404.
[83] Finger PT, Harbour JW, Karcioglu ZA. Risk factors for metastasis in retinoblastoma. *Surv Ophthalmol* 2002;47:1–16.
[84] Sastre X, Chantada GL, Doz F, *et al*. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. *Arch Pathol Lab Med* 2009;133:1199–1202.
[85] Abramson DH, Dunkel IJ, Brodie SE, *et al*. Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). *Ophthalmology* 2010;117:1623–1629.
[86] Dimaras H, Kimani K, Dimba EA, *et al*. Retinoblastoma. *Lancet* 2012;379:1436–1446.
[87] Uveal Melanoma. In: Edge SE, Byrd DR, Compton CC, *et al*, editors. *AJCC cancer staging manual 7th edition*. 7th ed. New York; London: Springer; 2009. p. 547–559.
[88] Retinoblastoma. In: Edge S, Byrd DR, Compton CC, *et al*, editors. *The AJCC cancer staging manual*. 7th ed. New York, NY: Springer; 2009. p. 561–568.
[89] Damato B, Patel I, Campbell IR, *et al*. Visual acuity after ruthenium-106 brachytherapy of choroidal melanomas. *Int J Radiat Oncol Biol Phys* 2005;63:392–400.
[90] Quivey JM, Augsburger J, Snelling L, *et al*. ^{125}I plaque therapy for uveal melanoma. Analysis of the impact of time and dose factors on local control. *Cancer* 1996;77:2356–2362.
[91] Kiratli H, Bilgic S, Atahan IL. Plaque radiotherapy in the management of retinoblastoma. *Turk J Pediatr* 1998;40:393–397.
[92] Temming P, Lohmann D, Bornfeld N, *et al*. Current concepts for diagnosis and treatment of retinoblastoma in Germany: Aiming for safe tumor control and vision preservation. *Klin Padiatr* 2012;224:339–347.
[93] Harbour JW, Murray TG, Byrne SF, *et al*. Intraoperative echographic localization of iodine 125 episcleral radioactive plaques for posterior uveal melanoma. *Retina* 1996;16:129–134.
[94] Chang MY, Kamrava M, Demanes DJ, *et al*. Intraoperative ultrasonography-guided positioning of iodine 125 plaque

brachytherapy in the treatment of choroidal melanoma. *Ophthalmology* 2012;119:1073−1077.

[95] Finger PT. Finger's amniotic membrane buffer technique: Protecting the cornea during radiation plaque therapy. *Arch Ophthalmol* 2008; 126:531−534.

[96] Semenova E, Finger PT. Amniotic membrane corneal buffering during plaque radiation therapy for anterior uveal melanoma. *Ophthalmic Surg Lasers Imaging Retina* 2013;44:477−482.

[97] Kujala E, Makitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003; 44:4651−4659.

[98] Chin K, Finger PT, Kurli M, *et al*. Second cancers discovered by (18)FDG PET/CT imaging for choroidal melanoma. *Optometry* 2007;78:396−401.

[99] Hawkins BSCollaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol* 2004;138:936−951.

[100] Finger PT. Radiation therapy for orbital tumors: Concepts, current use, and ophthalmic radiation side effects. *Surv Ophthalmol* 2009; 54:545−568.

[101] Finger PT, Tena LB, Semenova E, *et al*. Extrascleral extension of choroidal melanoma: Post-enucleation high-dose-rate interstitial brachytherapy of the orbit. *Brachytherapy* 2013; [Epub ahead of print].

[102] Bechrakis NE, Hocht S, Martus P, *et al*. Endoresection following proton beam irradiation of large uveal melanomas. *Ophthalmologe* 2004;101:370−376.

[103] Damato BE, Paul J, Foulds WS. Risk factors for residual and recurrent uveal melanoma after trans-scleral local resection. *Br J Ophthalmol* 1996;80:102−108.

[104] Chan HS, DeBoer G, Thiessen JJ, *et al*. Combining cyclosporin with chemotherapy controls intraocular retinoblastoma without requiring radiation. *Clin Cancer Res* 1996;2:1499−1508.

[105] Desjardins L, Chefchaouni MC, Lumbroso L, *et al*. Functional results of retinoblastoma treatment with local treatment used in isolation or associated with chemotherapy. *J Fr Ophtalmol* 2005;28:725−731.

[106] Gragoudas ES, Goitein M, Verhey L, *et al*. Proton beam irradiation of uveal melanomas. Results of 5 1/2-year study. *Arch Ophthalmol* 1982;100:928−934.

[107] D'Hermies F, Meyer A, Morel X, *et al*. Neovascular glaucoma following proton-beam therapy. Case report. *J Fr Ophtalmol* 2001;24:95−101.

[108] Egger E, Zografos L, Schalenbourg A, *et al*. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys* 2003;55:867−880.

[109] Damato B, Kacperek A, Chopra M, *et al*. Proton beam radiotherapy of choroidal melanoma: The Liverpool-Clatterbridge experience. *Int J Radiat Oncol Biol Phys* 2005;62:1405−1411.

[110] Kim MK, Char DH, Castro JL, *et al*. Neovascular glaucoma after helium ion irradiation for uveal melanoma. *Ophthalmology* 1986; 93:189−193.

[111] Hungerford JL, Foss AJ, Whelahan I, *et al*. Side effects of photon and proton radiotherapy for ocular melanoma. *Front Radiat Ther Oncol* 1997;30:287−293.

[112] Cassoux N, Cayette S, Plancher C, *et al*. Choroidal melanoma: Does endoresection prevent neovascular glaucoma in patient treated with proton beam irradiation? *Retina* 2013;33:1441−1447.

[113] Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology* 1999;106:1579−1587.

[114] Boyd SR, Gittos A, Richter M, *et al*. Proton beam therapy and iris neovascularisation in uveal melanoma. *Eye (Lond)* 2006;20: 832−836.

[115] Nakagawa Y, Yoshihara H, Kageji T, *et al*. Cost analysis of radiotherapy, carbon ion therapy, proton therapy and BNCT in Japan. *Appl Radiat Isot* 2009;67:S80−S83.

[116] Anonymous. Proton therapy appears to be less cost-effective. *Cancer Discov* 2013;3:OF2.

[117] Osman IM, Abouzeid H, Balmer A, *et al*. Modern cataract surgery for radiation-induced cataracts in retinoblastoma. *Br J Ophthalmol* 2011;95:227−230.

[118] Archer DB, Amoaku WM, Gardiner TA. Radiation retinopathy—clinical, histopathological, ultrastructural and experimental correlations. *Eye (Lond)* 1991;5:239−251.

[119] Finger PT. Anti-VEGF bevacizumab (Avastin) for radiation optic neuropathy. *Am J Ophthalmol* 2007;143:335−338.

[120] Arriola-Villalobos P, Donate-Lopez J, Calvo-Gonzalez C, *et al*. Intravitreal bevacizumab (Avastin) for radiation retinopathy neovascularization. *Acta Ophthalmol* 2008;86:115−116.

[121] Finger PT. Radiation retinopathy is treatable with anti-vascular endothelial growth factor bevacizumab (Avastin). *Int J Radiat Oncol Biol Phys* 2008;70:974−977.

[122] Finger PT, Chin KJ. Intravitreous ranibizumab (Lucentis) for radiation maculopathy. *Arch Ophthalmol* 2010;128:249−252.

[123] Finger PT, Chin KJ. High-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy. *Eur J Ophthalmol* 2013;23: 850−856.

[124] Finger PT, Kurli M. Laser photocoagulation for radiation retinopathy after ophthalmic plaque radiation therapy. *Br J Ophthalmol* 2005;89:730−738.

[125] Materin MA, Bianciotto CG, Wu C, *et al*. Sector laser photocoagulation for the prevention of macular edema after plaque radiotherapy for uveal melanoma: A pilot study. *Retina* 2012;32: 1601−1607.

[126] Radin PP, Lumbroso-Le Rouic L, Levy-Gabriel C, *et al*. Scleral necrosis after radiation therapy for uveal melanomas: Report of 23 cases. *Graefes Arch Clin Exp Ophthalmol* 2008;246:1731−1736.

[127] Barman M, Finger PT, Milman T. Scleral patch grafts in the management of uveal and ocular surface tumors. *Ophthalmology* 2012;119:2631−2636.

[128] Bechrakis NE, Bornfeld N, Zoller I, *et al*. Iodine-125 plaque brachytherapy versus transscleral tumor resection in the treatment of large uveal melanomas. *Ophthalmology* 2002;109:1855−1861.