

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-review 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. © 2014 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

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 choroidal 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

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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 indispensable, 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, CA) has become indispensable 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. COMS medium and large uveal melanomas can be treated, after counseling about likely vision outcomes.	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. 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 ¹⁰⁶Ru and ⁹⁰Sr 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 choroidal 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, non-plaque 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 pre-implant 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=D7gm8Tel3a&sig=zmcdrOUS15NVqqfDI_oPFOvhRCA&hl=en&ei=yN7MSfvZDprNIQfnqtXQCQ&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=106Rh&unc=nds>.

recommends (Level 2 Consensus) that vitreous seeding should be absent or within 2 mm of the tumor surface. Either low-energy ¹⁰³Pd, ¹²⁵I (for thicker tumors), or ¹⁰⁶Ru 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 ¹⁰⁶Ru and ⁹⁰Sr 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 ¹²⁵I 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 (¹⁰³Pd and ¹²⁵I) and beta-emitting ¹⁰⁶Ru 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 ¹⁰³Pd and ¹²⁵I plaques, larger physical safety margins are typically used with ¹⁰⁶Ru.

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

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

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.

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		Thickness		Basal diameter		Radiation dose		Local control		Metastasis		Visual acuity
				Mean or median, mo	Mean or median (range)	Mean or median (range)	Mean or median (range)	Apex, mean	Overall, %	5 y	Overall	5 y	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	NA			
Quivey <i>et al.</i> (90)	1996	239	¹²⁵ I	36	5.5 (1.9–11.0)	10.9 (4–18)	70	91.7	82	7.5	12	NA	NA			
Fontenesi <i>et al.</i> (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 <i>et al.</i> (24)	1997	266	¹⁰⁶ Ru	43	4.4 (1.0–13.1)	10.0 (3–23)	100	83	82	11	14	NA	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 <i>et al.</i> (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 <i>et al.</i> (48)	2002	354	¹²⁵ I	60	9.0 (9.8–16)	14.0 (5–21)	80	91	91	24	24	43				
Puusaari <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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). Finally, 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.

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