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Title: The 2013 American Brachytherapy Society (ABS) Guidelines for Plaque Brachytherapy of Uveal Melanoma and Retinoblastoma

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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.
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 for Physicists in Medicine and ABS. Implantation of plaque sources should be performed by subspecialty trained surgeons. Though there exist select restrictions related to tumor-size and location; the ABS-OOTF agreed that most uveal 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, blind painful eyes and those with no light perception vision are unsuitable for brachytherapy. In contrast, only select retinoblastomas are eligible for plaque brachytherapy. Radionuclide available sources currently include assemblies of gold-shells with low-energy photon seeds (iodine-125, palladium-103, cesium-131), or solid ruthenium-106 or strontium-90 beta-emitting plaques. 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.

Conclusions

The American Brachytherapy Society-Ophthalmic Oncology Task Force, comprised of 47 eye cancer specialists from 10 countries, present our current guidelines and methods of plaque brachytherapy for uveal melanoma and retinoblastoma. We point out what is currently accepted as known, unknown as well as a need for standardization, staging and future research.

*Cover Letter

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Sunday, September 8, 13

M. J. Zelefsky, MD
Editor-in-Chief
Brachytherapy
Memorial Sloan-Kettering Cancer Center
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1275 York Avenue, Box 22
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Dear Dr. Zelefsky:

Please consider our manuscript titled, "**The 2013 American Brachytherapy Society (ABS) Guidelines for Plaque Brachytherapy of Uveal Melanoma and Retinoblastoma**," for publication in your journal, ***Brachytherapy.***

When the board of The American Brachytherapy Society asked me form a committee to develop guidelines for ophthalmic plaque brachytherapy, I took this opportunity to greatly expand and internationalize this effort. I hope you will agree that this process has strengthened the guidelines and made them more broadly applicable and valuable.

However, in that each and every author has contributed to this work and the ABS agreed that they should be recognized for their contributions. Therefore, should you find these guidelines worthy of publication, I respectfully request that every authors name be recognized/linked to the article in PubMed and other such services.

Thank you for your time and consideration.

Best regards,

Paul

Paul T. Finger, MD

"This is original work which has never been published before. The author and all co-authors affirm that this manuscript has not been nor will be submitted elsewhere while under consideration by Brachytherapy."

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***List of Abbreviations Used**

List of Abbreviations

ABS - American Brachytherapy Society

OOTF – Ophthalmic Oncology Task Force

PTF – Paul T Finger

FAF – fundus autofluorescence

CT – computed tomography

MRI – magnetic resonance imaging

PET/CT – positron emission tomography / computed tomography

T – tumor

N – node

M –metastasis

TTT – transpupillary thermotherapy

Gy – gray

KeV – kilo-electron volt

^{60}Co – cobalt-60

^{103}Pd – palladium-103

^{125}I – iodine-125

^{106}Ru – ruthenium-106

^{131}Cs – cesium-131

^{90}Sr – strontium-90

VEGF – vascular endothelial growth factor

NCI – National Cancer Institute

NIH – National Institute of Health

DHHS – Department of Health and Human Services

AJCC- American Joint Committee on Cancer

UICC – Union International for Cancer Control

RPT – ruthenium plaque therapy

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.

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enhance their practice.

KEY WORDS: Plaque, brachytherapy, radiation, guidelines, methods, ABS, AJCC, consensus

INTRODUCTION

Brachytherapy has been used to treat intraocular tumors since 1930.[1] Subsequent reports described cobalt-60 (^{60}Co), ruthenium-106 (^{106}Ru), iodine-125 (^{125}I), palladium-103 (^{103}Pd), strontium-90 (^{90}Sr) and cesium-131 (^{131}Cs) plaque sources.[2-12] Despite the international use of ophthalmic brachytherapy for both uveal melanoma and retinoblastoma, 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.[13]

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 to enucleation (removal of the eye) for prevention of metastatic melanoma for a specific cohort of select medium-sized choroidal melanoma.[13] 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. [15] Similarly, Lommatzsch and others have established a long tradition of using ^{106}Ru plaque therapy in Europe.[16-21] This difference in practice currently persists.

The guidelines defined herein will exclude general aspects recently published by the American Association for Physicist in Medicine (AAPM) and the American Brachytherapy Society (ABS).[22,23] The AAPM Task Group-129 (TG-129) has recently provided medical 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.[23] Therein, comparative dosimetry revealed that the lower energy photons from ^{103}Pd irradiation were more rapidly absorbed within the target zone (hypothetical tumor and 2 mm surround) with less irradiation to most normal ocular structures. The second AAPM TG-129 report was published with the ABS and offers preferred methods for dose calculation, plaque handling and quality assurance.[22] That 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, United States of America, Russia and Sweden. Charged with developing modern guidelines for the use of plaque brachytherapy for uveal melanoma and retinoblastoma, 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 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, 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, California, USA) of the subjects explored herein were sent to the participating eye cancer specialists. The results of the literature review and survey was adapted to the journal, Brachytherapy'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 prior to submission for publication.

Many important recommendations of the ABS-OOTF were graded using levels of consensus modified from the 2003 ABS levels of Nag et al (Table 1).[24]

ABS-OOTF Recommended Methods

The ABS-OOTF recommends that plaque procedures be performed in specialized medical centers with expertise in ophthalmic brachytherapy (Level 1 Consensus). Further, 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.[22,23] 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 retinoblastoma is complex. However, modern methods have greatly improved the accuracy of clinical diagnosis. Though patient history and physical examination (slit-lamp, ophthalmoscopy) are indispensible, state of the art ophthalmic oncology

services also utilize high and low-frequency ultrasound imaging, photography, intraocular angiography, fundus autofluorescence imaging (FAF), optical coherence tomography (OCT), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) and biopsy. In addition, wide-field fundus photography (RetCam, Clarity Medical Systems, Pleasanton, California, USA) has become indispensible for the diagnosis, staging and for monitoring the effects of retinoblastoma treatment. Though beyond the scope of this work, multimodality ophthalmic imaging plays an increasingly integral role in tumor diagnosis and follow up. While 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 the 2003 ABS guidance (Table 2).[24] Reports now include brachytherapy for most uveal melanomas. This includes iris, ciliary body, choroidal, subfoveal, juxtapapillary and circumpapillary melanomas.[25-33] The reported literature also includes treatment of small and large tumors as well as those with limited extrascleral extension.[34-38] 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, blind painful eyes and those with no light perception vision. The ABS-OOTF recognizes that there will be instances where 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 diagnosis of "small" American Joint Committee on Cancer (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 prior to intervention.[39-42] This is particularly applicable for tumors near the fovea and optic nerve, or monocular patients where treatment is likely to cause radiation related vision morbidity.[25,43-45] 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 intra-operative tumor transillumination. This (in turn) makes definition of the targeted zone and plaque placement particularly difficult. 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 pathology, genetic and molecular biologic analysis.[46,47] 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.[48]

4) Brachytherapy for tumors near, touching or surrounding the optic disc is also controversial.[25] 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 to 6 mm. Thus, if a round plaque is perfectly placed against the retrobulbar optic nerve sheath, its posterior extent will be 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 2005, slotted plaques were devised with 8-mm openings.[25] Slots allow the optic nerve sheath to enter the plaque, thus more posteriorly locate the seed sources and move the targeted zone 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 complete the targeted zone.

However, the ABS-OOTF also recognizes that the penumbra at the edge of beta (^{106}Ru and ^{90}Sr) plaques is relatively sharp compared to the low energy gamma of ^{125}I and ^{103}Pd plaques.[22,33,49,50] Thus, tumor tissue within the slot is likely to receive less radiation with slotted ^{106}Ru and ^{90}Sr plaques compared to ^{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 prior to treatment.[51] However, staging methods vary throughout the world. They range from relatively non-specific hematologic surveys, chest x-rays, ultrasonographic or radiographic imaging of the abdomen (MRI or CT) to total body positron emission tomography/computed tomography (PET/CT).[51,52] 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 that early detection of metastatic melanoma often allows for adjunctive systemic therapy. 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 where 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 where 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 retinoblastoma.[20,53] More frequently, radioactive plaques are used after local treatment failure (after cryotherapy, chemotherapy (systemic or ophthalmic artery perfusion), transpupillary thermotherapy (TTT), external beam radiation therapy or a combination thereof).[54] For example, a specific indication for plaque treatment may be found in cases were there is residual macular Rb following optimal chemoreduction. In these cases, TTT laser 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 eyes equator and found in unilaterally affected children. For secondary treatment, residual or recurrent tumors are treated irrespective of location. However, in consideration of unusual tumor locations, anterior segment involvement is typically an indication for enucleation and there exist no reports of slotted plaque therapy for juxtapapillary retinoblastoma. Reflecting a generalized effort to avoid, EBRT, non-plaque brachytherapy implants have been used for orbital recurrence of retinoblastoma.[55,56]

Systemic evaluations for retinoblastoma vary widely but typically consist of orbital and

intracranial MRI imaging. Due to its ionizing radiation component, CT imaging is employed only when MRI is not available. 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.[57,58] However, fewer eyes are being enucleated due to chemoreduction with subsequent alternative treatments and the recent use of selective ophthalmic arterial perfusion for advanced intraocular disease. Both these techniques likely result in down-staging, where histopathologic markers for metastasis may disappear leaving only clinical staging.[58-60] Therefore, prior to plaque therapy being considered, the ABS-OOTF recommends (Level 2 Consensus) that children whose retinoblastomas may have had access to aqueous outflow passages, massive (> 3mm) involvement of the choroid, post-laminar invasion of the optic nerve, extraocular extension and bilateral disease 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). In order 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 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 treating eye cancer specialists. Each tumor should be staged according to the latest American Joint Committee on Cancer or equivalent Union for International Cancer Control staging system (currently the 7th

edition).[61,62]

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 computed tomography nor magnetic resonance imaging currently offer superior tumor measurements.

The medical physicist transfers this information to a computerized treatment planning system. Though 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.[23] 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.[22,23]

Radionuclide Selection

The ABS-OOTF found that ^{125}I and ^{103}Pd plaques are used by 3 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 retinoblastoma 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, opposite eye wall) of available radionuclide sources prior to 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 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. Further, 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.[6,17,19-21,37,38,63,42] Dose prescriptions for uveal melanoma typically range from 70 to 100 Gy to the tumors apex. Two ABS-OOTF centers report employing 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 employed 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 that it may affect local control, dose rates should not be less than

0.60 Gy/h for iodine-125 or palladium-103 plaques.[64] 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 Zeigler Corp., Berlin, Germany) typically restrict tumor apical height less than a mean 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 Laboratory, Rochester, Minnesota, USA) 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 utilize ^{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 survey of ABS-OOTF centers, brachytherapy for uveal melanoma treatment durations typically range from 5 to 7 days.

Retinoblastoma Brachytherapy Practice Patterns

Eligible retinoblastomas are typically less than 15 mm in base and no more that 10 mm in thickness.[20,53,54,65-67] Some describe Group B (International Classification) as being the most

commonly applicable stage. The ABS-OOTF 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) have been employed. Using low energy plaques, a solitary retinoblastoma is typically treated with a dose of 40 - 50 Gy to the tumor apex over 3 to 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 noted that a history of or synchronous treatment with chemotherapy potentiates radiation-related intraocular vasculopathy (retinopathy and optic neuropathy). [65] In these cases, he advocated reduced apical ^{125}I prescription doses 20-25 Gy or allowing several months between chemotherapy and brachytherapy.[65]

PLAQUE SURGERY

Survey of ABS-OOTF centers suggests that brachytherapy using both low energy photon-emitting sources (^{103}Pd, ^{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 surgeon 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 trans-ocular 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. The ABS-OOTF defines “normal plaque position” (Level 1 Consensus) that the targeted zone includes the tumors base and safety margin. The ABS-OOTF survey found that in comparison to ^{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) with intraoperative ophthalmic ultrasound verification is employed.[68,69] 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.[70]

In all cases, the plaque is sutured as to cover the marked, episcleral target zone. Then the extraocular muscles and conjunctiva are re-attached as not to disturb brachytherapy. When utilizing plaque with low-energy seeds, the eye is typically covered with a lead patch shield. Typically, after 5 to 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 re-attached 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 prior to conjunctival closure.[71]

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 to 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 that typically occurs within the first 3 years follow up (see radiation

complications below).[8,38,44,45,72] 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 re-examined for evidence of metastatic disease and second non-ocular primary cancers.[51,52,73] 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.

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. Pre-enucleation external beam radiation therapy (PERT) has not been widely performed since the COMS large-melanoma study found no statistically significant survival advantage.[52,74] In contrast, most centers continue to apply post-exenteration radiation therapy in cases where there is residual orbital melanoma and retinoblastoma.

Local resection (internal evacuation or external lamellar sclerouvectomy) is employed to remove select (typically select medium-sized or large) uveal melanoma but not retinoblastoma. Some centers irradiate the uveal melanoma prior to endoresection or place a radioactive plaque over the tumors base after transscleral resection.[75] 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 radiotherapy may reduce the risk of local tumor recurrence.[76] However, we also recognize there exist no prospective comparative or case-matched studies examining the relative risks and benefits of resection techniques compared to primary brachytherapy or

enucleation.

Retinoblastoma of stage AJCC T4 or International Classification D and E are not candidates for brachytherapy and are typically treated by enucleation.[67] The ABS-OOTF achieved Level 1 Consensus that primary enucleation prior to extraocular extension, optic nerve invasion and or massive choroidal infiltration offers greater than 95% primary tumor free survival.[57,58,67] While retinoblastomas 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, external beam radiation therapy should be avoided due to secondary carcinogenesis and orbital bone dysplasia.[77,78] Preferred practice patterns for treatment of retinoblastoma are even more complex and beyond the scope of this review.[79]

ALTERNATIVE RADIATION THERAPY TECHNIQUES

Proton therapy was pioneered at the Harvard Cyclotron Laboratory and by researchers at the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital.[80] Since that time, at least 12 additional institutions around the world have embraced this technique with numerous additional centers under construction.[81-83] These centers typically use a proton radiobiologic effectiveness value of 1.1 compared to ^{60}Co. For uveal melanoma, doses of approximately 60 Gy are delivered in four (15 Gy) daily fractions. Though there exists no significant alpha/beta dose comparison high-dose-rate proton beam versus low dose rate plaque brachytherapy, the ABS-OOTF recognizes (Level 1 Consensus) that both the dose rates and dose volumes differ. Further, 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 treatment of posterior choroidal melanomas, radiation must travel through the sclera prior to entering the tumor and through the eye prior to exiting through normal anterior ocular tissues.[23] Primarily due to dose gradient and side-scatter effects, plaque brachytherapy delivers comparatively more radiation to subjacent sclera and adjacent ocular structures.

The ABS-OOTF recognizes (Level 1 Consensus) that in 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 in comparison to proton beam. This relative dose sparing may explain why clinical studies have revealed more anterior segment complications and secondary enucleations after charged-particle therapy.[81,84-88]

External beam radiation techniques are also complicated by mobile target volume (eye movement). Consider that 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), the potential mobility of the eye and its target volume makes dose-deposition less predictable. 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. Lastly, proton beam facilities are vastly more expensive (Table 4).[89,90]

The ABS-OOTF survey indicates that proton beam has been employed 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, then removed by internal resection.[75] 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, dose and dose rate. Further, until acceptance of the AJCC staging system, their existed no universal method to report the size of uveal melanomas. Further, there is no uniform method of reporting with respect to follow up duration, visual acuity, local control or metastasis. Herein, we have assembled a non-inclusive table of representative case series with >100 treated patients (Table 5).

Select observations derived from Table 5 include: the radionuclides ^{125}I and ^{106}Ru are best represented and on average the data is over 10 years old. Note that a mean 341 patients were 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 was 83 Gy and 80 Gy respectively (range 70 Gy to 100 Gy). Similarly, reported and 5-year local control rates averaged 89.5% (range 69.9% to 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.[35] Lastly, visual acuity results varied widely.

Visual acuity outcomes are difficult to compare in that they depend on many factors including but not limited to: pre-existing exudative retinal detachments, subfoveal 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.[91-93] 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.[92] Clinical findings include transudation of intravascular components (blood, serum, 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 results 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).

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.[94-98] Therapy is used to suppress transudation, thus ameliorate edema and counter neovascularization. However, while these techniques are widely used, the ABS-OOTF recognizes that no published prospective-randomized or large-scale studies examining 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.[99,100] Treatment converted slow ischemia within and anterior to the targeted zone 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.[8,101,102] 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 of the aforementioned side effects can result loss of vision and quality of life.

STAGING OF RADIATION SIDE EFFECTS

The ABS-OOTF recognizes that there exists no comprehensive staging system for the ophthalmic side effects of radiation therapy. Though 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, NCI, NIH, DHHS (http://ctep.cancer.gov), the ABS-OOTF recommends that a radiation specific ophthalmic side effect staging system 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 be performed by skilled plaque surgeons in experienced subspecialty centers. We agreed that the recent joint AAPM/ABS TG-129 published guidelines for plaque construction, dosimetry and quality assurance be read and widely employed at active centers.[22,23] We also concurred that many radionuclide sources can be employed, but only ^{125}I, ^{103}Pd and ^{106}Ru are used in 3 or more ABS-OOTF centers. While there exist tumor thickness restrictions for ^{106}Ru and ^{90}Sr, taller tumors can be treated with ^{125}I or ^{103}Pd techniques.[7,11,22,49]

Overall, the ABS-OOTF expanded general indications for uveal melanoma patient selection. Lastly, we found that plaque brachytherapy is not commonly used for retinoblastoma. However, indications include small anterior tumors in unilateral cases, for salvage after chemoreduction with subsequent alternative therapies and in select cases where macular laser will likely cause

loss of vision.

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 de-escalation study or a thickness-based sliding scale in treatment of uveal melanoma? Can there be international standards for dosimetry to determine the relative efficacy (alphas and betas) 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 treatment of juxtapapillary and circumpapillary tumors? With regards to retinoblastoma, are there oncogenic risks of plaque brachytherapy? What are the optimal parameters for tumor selection and radiation dose (if used before or after chemotherapy)? The ASB-OOTF hopes future research will answer some of these questions.

The ABS-OOTF recommends that the eye cancer community use universal AJCC –UICC staging to define tumor size, location and associated variables.[61,62] This would enable multi-center communication, comparative analysis and patient education. It 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.

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. For the first time, the ABS-OOTF includes eye cancer specialists from North American, Russia, Asia and Europe. 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.

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Table Legends

Table 1: ABS-OOTF Levels of Consensus

ABS – OOTF = American Brachytherapy Society–Ophthalmic Oncology Task Force

Table 2: Changes in General Guidelines for Treatment of Uveal Melanoma

AJCC =7th edition, American Joint Commission on Cancer [62]

* ^{106}Ru and ^{90}Sr plaques are less accommodating for nodular extrascleral extension.

Table 3: Radiobiological characteristics of radionuclides used for episcleral brachytherapy.

Photon emissions less than 5 KeV were removed from calculations of mean energy and tenth value layers (TVLs)

Table 4: Comparison of Plaque and Proton Therapy

^{103}Pd = palladium-103, ^{125}I = iodine-125, ^{106}Ru = ruthenium-106

Table 5: Review of Uveal Melanoma Clinical Case Series

Author = first author, Year = year of publication, Pts. = numbers of patients, Follow-up = months, Dose = Gy, Tumor dimensions = mm, Local control and metastasis = % References used.

Table 6: Classification for Radiation Retinopathy

DA = disc areas, OCT = optical coherence tomography, ICG = indocyanine green angiography, FAG = fluorescein angiography, vision loss must be related to associated sign(s). This table is modified from an original classification.[99]

*Title Page

The 2013 American Brachytherapy Society (ABS) Guidelines for Plaque Brachytherapy of Uveal Melanoma and Retinoblastoma

The American Brachytherapy Society Ophthalmic Oncology Task Force

Running Title: ABS-OOTF- ABS Plaque Brachytherapy Guidelines

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Abstract = 250 words

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Table(s)

Table 1. ABS-OOTF 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 nor specific recommendation.

ABS – OOTF = American Brachytherapy Society–Ophthalmic Oncology Task Force

Table 2: Changes in General Guidelines for Treatment of Uveal Melanoma

2003 ABS Recommendations	2013 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, 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, 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,* basal diameters that exceed the limits of brachytherapy, blind painful eyes and those with no light perception vision are not suitable for plaque therapy.

AJCC =7th edition, American Joint Commission on Cancer

* ^{106}Ru and ^{90}Sr plaques are less accommodating for nodular extrascleral extension.

Table 3. Radiological characteristics of radionuclides used for episcleral brachytherapy. Photon emissions less than 5 keV were removed from calculations of mean energy and tenth-value layers (TVLs).

Photon emitters	[1] Half-life	[1] Mean photon energy (keV)	[2] Water TVL (mm)	[3] Pb TVL (mm)
^{125}I	59.4 days	28.4	55	0.059
^{103}Pd	16.99 days	20.7	30	0.026
^{131}Cs	9.69 days	30.4	62	0.070
Beta emitters	[1] Half-life	[1] Endpoint beta energy (MeV)	CSDA range in water (mm) [5]	
$^{106}Ru/^{106}Rh$	371.8 days	3.541 [4]	17	
^{90}Sr	28.8 years	0.546 [6]	1.9	

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

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

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

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

[5] 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=zmcdrOUSl5NVqqfDl_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

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

Table 4: Comparison of Plaque and Proton Therapy

PLAQUE	**PROTON**
Surgical Insertion and Removal	Surgical Clip Implantation
Continuous Low Dose Rate Treatment 5 – 7 Day (^{125}I, ^{103}Pd) 3-7 Day (^{106}Ru)	4 Daily High Dose Rate Fractions
Mobile Radiation Field	Static Radiation Field
Fewer Anterior Segment Complications Posterior Segment Complications	More Anterior Segment Complications Posterior Segment Complications
Less Expensive	More Expensive

^{103}Pd = palladium-103, ^{125}I = iodine-125, ^{106}Ru = ruthenium-106

Table 5: Review of Uveal Melanoma Clinical Case Series

Author	Year	Pts.	Radionuclide	Follow up	Thickness	Basal Diameter	Radiation Dose	Local Control	Local Control	Metastasis	Metastasis	Visual Acuity
		No.		Mean or Median	Mean or Median	Mean or Median	Apex	Overall	5-year	Overall	5-year	Final %
				months	(range)	(range)	Mean	%				>20/200
Lommatzsch [3]	1987	309	ruthenium-106	80	3.7 (1.2-11.8)	9.7 (4.5-21.5)	100	69.9	84	12.9	NA	NA
Quivey [64]	1993	239	iodine-125	36	5.5 (1.9-11.0)	10.9 (4-18)	70	91.7	82	7.5	12	NA
Fontenesi [15]	1993	144	iodine-125	46	Small n=15, Medium n=84, Large n=45	NA	75	97.7	94.4	2.7	2	71.3
Seregard [21]	1997	266	ruthenium-106	43	4.4 (1.0-13.1)	10.0 (3-23)	100	83	82	11	14	NA
COMS [13]	2001	657	iodine-125	96	4.8 (2.5-10.0)	11.4 (up to 16)	85	NA	NA	9	9	63
Bechrakis [103]	2002	152	iodine-125	30.1	9.0 ± 1.1	14.6 ± 2.4	98 ± 18	88.8	NA	11.1	NA	5.6
Shields [35]	2002	354	iodine-125	60	9.0 (9.8-16)	14.0 (5-21)	80	91	91	24	24	43
Puusaari [36]	2003	97	iodine-125	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 [83]	2005	458	ruthenium-106	47	3.2 (0.7-7.0)	10.6 (5-16.6)	80	97	97.9	8.1	NA	57
Finger [6]	2009	400	palladium-103	51	3.8 (1.5-12.3)	10.5 (5-19.9)	73	97	NA	6	7.3	79
Mean	2003	341		52.9			84	91.9	91.2	14	17.9	48.3
Median	2002	354		47			82.5	92.9	92.5	11	14	48

Tumor measurements = milimeters , Followup = months, Pts. No. = number of patients,
%<20/200 = those with better than 20/200 vision, NA = not available

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 micro-aneurysms	None	Extramacular	Ophthalmoscopy / FAG	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	FAG	mild
2	Above findings	None	Macular	Both	moderate
3	Any combination of the above plus				
	Retinal neovascularization	Vision loss	Extramacular	FAG	severe
	Macular edema - New onset	Vision loss	Macular	FAG / OCT	severe
4	Any combination of the above plus				
	Vitreous hemorrhage	Vision loss	Vitreous	Ophthalmoscopy	severe
	Retinal ischemia (>or = 5DA)	Vision loss	Both	FAG	severe

DA = disc areas, OCT = optical coherence tomography, ICG = indocyanine green angiography, FAG = fluorescein angiography, vision loss must be related to associated sign(s). This table is modified and updated from an original classification. [99]