Novel Eye Plaque Designs for Brachytherapy of Iris and Ciliary Body Melanoma and the First Clinical Application

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Keywords

Melanoma · Brachytherapy · Eye plaque · Iris-ciliary body

Abstract

Background: While traditional eye plaque brachytherapy can be used for the treatment of iris melanoma, it faces challenges of poor patient tolerability due to cornea-plaque touch caused by radius of curvature mismatch and potential dosimetric inaccuracy from incomplete coverage. We present novel plaque designs and the first clinical application of the plaques for iris melanoma. **Methods:** Two dome-shaped plaques (EP2132 and EP1930) were designed to vault above the cornea to treat tumors of the iris and ciliary body. Image-based treatment planning of the first 2 clinical cases using the EP2132 plaque covered the tumor base plus a 2 mm margin and the involved ciliary body with at least 75 Gy to the tumor apex. **Results:** The tumors decreased in size following treatment. The patients tolerated the treatment well. There was no adverse event associated with the traditional iris plaques, such as decreased vision, pain, corneal edema, glaucoma, or cataract. **Conclusion:** The novel dome-shaped

plaques for the treatment of iris melanoma provide effective dose distribution, improved surgical maneuverability, and increased tolerability for the patient. This plaque model can be used to treat iris melanoma of various sizes, configurations, and locations, including the ciliary body. The need for a customized plaque platform for each patient is minimized.

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Introduction

Iris melanoma is a subtype of uveal melanoma historically thought to have a more indolent natural course compared to melanoma of the ciliary body or choroid [1]. Before 2001, the metastatic rate of iris melanoma was reported to range from 3–5% over 10 years [1, 2]. More recent studies suggest a higher rate of metastasis. A multi-center study from 2012, for example, reported a rate of 10.7% at 5 years [3], and a single-center study of the same year revealed rates of 9 and 11% at 10 and 20 years, respectively [4]. The management of iris melanoma has accordingly shifted towards intervention rather than obser-

Fig. 1. Two novel plaques designed for the treatment of iris melanoma. **a** The EP2132 plaque is circular with a diameter of 21 mm and an opening of 5 mm at the center. It has 32 seed slots in a radial pattern centrally and concentric peripherally. **b** The EP1930 plaque is slightly smaller than EP2132 with 19 mm in diameter and a 2-mm opening at the center. There are 30 concentric seed slots in EP1930. The brown lines indicate seed slots. Note the placement of the eyelets, 4 clock hours apart, for both plaques. The color refers to the online version only.

vation. Treatment options have traditionally included local resection, plaque brachytherapy (PB), proton beam radiation therapy, and enucleation. PB is now widely used [5–9] due to its minimally invasive nature compared to resection or enucleation [7, 10]. Compared to proton therapy, PB delivers less radiation to the orbit and remainder of the globe [11] and leads to fewer post-treatment glaucoma [12–14]. Therefore, except for very large tumors, PB has been the treatment of choice over proton beam therapy for many ocular oncologists [15].

Nonetheless, there are challenges related to treating iris melanoma with PB, including plaque-corneal contact and resultant patient discomfort during treatment, uncertain plaque placement and possibly incomplete dosimetric coverage, and the potential need for plaque customization for each patient. Because the curvature of a standard plaque for choroidal melanoma is usually designed to conform to the sclera, the use of such standard plaques causes cornea-plaque touch and excessive pressure on the cornea [7, 16]. Finger [17] introduced the use of a 0.1-mm-thick amniotic membrane that is placed between the plaque and the cornea to reduce patient discomfort. Custom plaques [11] and modified Collaborative Ocular Melanoma Study (COMS) plaques [18] with boomerang, partial-ring, or fully-circular shapes for individual patients have been used to improve the treatment of iris melanoma. However, they may still maintain the curvature mismatch, leading to patient discomfort, and they may not be ideal when treating tumors extending to the visual axis or when full coverage of the entire region under the entire cornea is indicated. A modified COMS plaque without the central hole that provides full cover-

age has been reported [19] by machining the original COMS silastic insert to fit the cornea curvature. It requires patient-specific custom machinery, which may not be practical at all institutions.

In this study, we report 2 novel designs of dome-shaped plaques (Eye Physics model EP2132 and EP1930) aimed at solving the problem of unpredictable comfort, coverage, and cost. These new plaques vault over the cornea to treat tumors of the iris and ciliary body with up to 360° uniform dosimetric coverage. They provide more seed slots than COMS plaques. The potential seed arrangement permutation offers flexible tumor coverage and eliminates the need for custom hardware for each patient. The first clinical cases, surgical method, and outcome using the EP2132 plaque with image-based treatment planning are presented.

Materials and Methods

Two dome-shaped plaques, EP2132 (Fig. 1a) and EP1930 (Fig. 1b), were designed using Plaque Simulator Version 6 (Eye Physics LLC, Los Alamitos, CA, USA), exported to a stereolithography (.stl) file and prototyped using a Formlabs 3D printer (Somerville, MA, USA) with a 0.001-inch resolution and direct castable blue resin. The castable resin prototype was then used to produce the plaque in 18-karat gold with better than 0.2-mm accuracy. The core design for the seed slots is the same as for other Eye Physics plaques. EP2132 and EP1930 each features 3 suture eyelets 120° apart for improved stability and accuracy when suturing to the sclera.

The EP2132 plaque is circular with a diameter of 21 mm with a 5-mm opening at the center for cornea oxygenation. The thickness of the plaque is 2 mm. The central hole lies in axial alignment with the pupil. The plaque has 32 seed slots in a radial pattern cen-

trally and a circular pattern in the periphery for flexible dose coverage of the iris and ciliary body. The EP1930 plaque is circular with a diameter of 19 mm and an opening of 2 mm at the center. Thirty seed slots lie in a concentric circular pattern. The seed patterns of the plaques are intended for different size eyes and dose coverage anterior and posterior to the limbus. EP1930 provides more seed slots for anterior coverage. The central opening size is as large as practical for each seed pattern.

The radius of curvature of the novel plaques is 9 mm, which contrasts with that of COMS plaques that is 12.3 mm. It is the reduced radius of curvature of the new plaques combined with the large diameter of 19 mm (EP1930) or 21 mm (EP2132) that creates the vault between the plaque and the ocular surface. For comparison, the radius of curvature of the cornea is 7.5 mm, and the corneal diameter is 12 mm.

Fig. 2. Multimodal imaging of the iris melanoma in Case 1 (a–c) and Case 2 (d–f). **a** Slit-lamp photograph shows the inferotemporal iris melanoma with a central nodule that extends into the pupillary axis. **b** High-frequency ultrasound biomicroscopy demonstrates the axial height of the tumor. **c** Anterior segment fluorescein angiography shows leakage of fluorescein in the vessels associated with the iris melanoma. **d** Slit-lamp photograph of Case 2 showing iridociliary melanoma in the superotemporal quadrant. **e** Gonioscopy shows the location of the tumor deep in the angle. **f** B-mode ultrasonography shows the ciliary body involvement.

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Fig. 3. Pretreatment planning for Case 1 (a–c) and Case 2 (d–f). **a** The retinal diagram demonstrates an overlaid slit-lamp photograph, the plaque, seed placement pattern, and isodose lines. The tumor outline is delineated by the brown contour. The seeds are shown as light blue bars. The thick cyan isodose line indicates the coverage by the prescribed 75 Gy. **b** A dose-area histogram on the retinal spherical surface demonstrates the coverage of the tumor base plus margin and the doses to the critical retinal structures. **c** A dose-volume histogram shows 3D dosimetry to the tumor, lens, and the entire eye. **d** Isodose map for Case 2 with an overlaid slit-lamp photograph. The majority of the iridociliary melanoma is posterior to the limbus. **e** Tumor-meridian view of the eye with the EP2132 plaque. **f** Tumor-meridian view of the eye with the COMS22 plaque showing substantial overlap of the plaque's seed carrier with the cornea. Colors refer to the online version only.

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(For figure see next page.)

Fig. 4. Intraoperative photographs illustrating the procedure of implanting the plaque covering the cornea. After 360° of perilimbal peritomy (a), amniotic membrane was placed over the cornea (b). The plaque was placed over the cornea and then sutured into place

using the 3 eyelets (c). The conjunctiva was draped over the plaque and then suture closed (d). There was no tension on the eyelids upon closure (e). Temporary tarsorrhaphy of the eyelids was performed (f).

Case Presentations

Case 1

A 49-year-old Caucasian female with an iris nevus of the right eye was observed since 2012. The initial measurements were $8 \times 3.8 \times 1.6$ mm. She developed recurrent episodes of hyphema associated with decreased vision 4 years later. Upon initial evaluation by an ocular oncologist, the mass was noted to have grown, measuring $8 \times 4 \times 3$ mm (Fig. 2a). The central nodule of the melanoma had doubled in size in the 4-year time frame and extended medially into the pupillary axis (Fig. 2b). Iris fluorescein angiography showed diffuse, multifocal hyperfluorescence and late leakage (Fig. 2c).

Plaque planning involved the use of computed tomography imaging to construct a patient-specific eye model [20]. The tumor was contoured using slit-lamp photography (Fig. 3a). Three-dimensional treatment planning was performed using Plaque Simulator version 6.5 for EP2132. The brown contour delineated the tumor. Thirteen Iodine-125 seeds were used to deliver therapeutic radiation to the tumor. With the suture eyelets of the plaque placed at 4, 8, and 12 o'clock in the perilimbal sclera 5.0 mm from the limbus, 7 seeds in the center of the plaque covered the tumor, and 6 seeds in the plaque periphery covered the ciliary body. The seeds are demonstrated as light blue bars in Figure 3a (the color refers to the online version only).

The dose calculations were performed using a linear source model with anisotropy correction according to AAPM TG43 [21]. Slot collimation was enabled in the Plaque Simulator software [22], which activated ray tracing of the collimation of primary radiation by the rectangular slot surrounding each seed. Partial exposure was enabled, which calculated the fraction of primary radiation from a linear source that does not pass through the shell. The doses were calculated under the infinite homogeneous water assumption according to AAPM TG129 [23]. Figures 3b and c show the dose area histogram on the retinal spherical surface and the dose volume histogram, respectively. The planned dose to the tumor apex was 85 Gy. At least 75 Gy covered the tumor base with an additional margin of 2 mm. The doses to the cornea apex, center of the crystalline lens, center of the optic disc, and fovea were 94, 57, 6, and 6 Gy, respectively. About half of the cornea received over 75 Gy, but the dose to the superonasal sector of the cornea – the quadrant farthest from the tumor – was gradually reduced to 30 Gy.

Figure 4 details the surgical procedure of plaque application. A 360-degree limbal peritomy was made, and Tenon's capsule was carefully dissected in all quadrants to reveal the bare sclera around the corneal limbus (Fig. 4a). Amniotic membrane was applied to the cornea with tissue glue for corneal protection (Fig. 4b). The plaque was placed over the eye with the base of the plaque in contact with the bare sclera around the cornea (Fig. 4c). Using a 5-0 nylon suture, the eyelets were sutured to the sclera in the pre-planned orientation. The plaque did not have contact with the cor-

Fig. 5. Side-by-side view of the iris melanoma cases before and after PB in Case 1 (a–d) and Case 2 (e, f). **a** The inferotemporal iris melanoma had a highly vascular core that dramatically reduced in size after PB (**b**). High-frequency B-mode ultrasonography prior to PB demonstrates a reduction in the axial height of the tumor's central core from 3 mm (**c**) to 1.8 mm at 4 months from brachytherapy (**d**). **e** The pre-PB slit-lamp photograph of the iridociliary melanoma. **f** One month after PB, the tumor appears smaller and less pigmented.

nea. A Gunderson flap was fashioned by completely draping the conjunctiva over the plaque (Fig. 4d). At the end of the procedure, the eyelids easily came together without tension (Fig. 4e). The eyelids were surgically closed by placing a temporary tarsorrhaphy with bolsters (Fig. 4f). Four days later, the tarsorrhaphy was taken down and the plaque was surgically removed.

Case 2

A 72-year-old male with superotemporal iridociliary melanoma measuring $3.5 \times 3 \times 3$ mm (Fig. 2d–f) underwent PB using EP2132. The dose calculation and plaque planning were performed using identical methods as in Case 1. Figure 3d shows the isodose map overlaid with the slit-lamp photograph. Most of the tumor was posterior

to the limbus, and the entire limbus was included in the treatment due to angle seeding of the tumor. Eight seeds were placed on the inner circle of the peripheral seed slots of the plaque to cover the entire limbus, and 4 additional seeds (3 anterior and 1 posterior) were placed at 12 to 3 clock hours to ensure tumor coverage with 85 Gy reaching >4 mm posterior to the limbus. Figures 3e and f show the tumor-meridian view of the eye with the EP2132 and COMS22 plaques, respectively. EP2132 ensures full-dose coverage without plaque-cornea contact. It is, however, impractical to plan accurately with COMS22 due to the significant overlap of the plaque's seed carrier with the cornea. The surgical method of plaque implantation was identical to that of Case 1, although amniotic membrane was not applied.

Results

Case 1

The patient reported minimal discomfort during the implantation period of 4 days. Ophthalmic examinations performed at 14 days and 4 months after plaque implantation revealed absence of secondary neovascularization of the iris or angle, corneal edema, keratopathy, posterior synechiae, or cataract. There was decreased vascularity of the tumor surface and no recurrence of hyphema. The tumor nodule had decreased from the pre-PB (Fig. 5a, b) height of 3.0–1.8 mm after treatment (Fig. 5c, d). The patient's preoperative distance visual acuity was 20/20 and 20/25 at 4 months following PB. She continues to be monitored for potential radiation- and tumor-associated adverse effects and undergoes routine systemic metastasis surveillance.

Case 2

The patient reported minimal discomfort during the treatment period of 4 days. At the time of plaque removal, the patient was noted to have corneal epithelial defect. He was prescribed erythromycin. At the 1-month follow up, his best-corrected vision was 20/40 – compared to his preoperative vision of 20/30, and the corneal epithelial defect had resolved. The tumor decreased from pre-PB dimensions of 3.5×3 to 3×1 mm (Fig. 5e, f). There were no radiation-associated adverse effects.

Discussion

For the treatment of iris or iridociliary melanoma, the novel plaques were specifically designed with a smaller radius of curvature than that of the conventional COMS and EP plaques, while maintaining a large diameter. Such dimensions preclude contact between the plaque and cornea, improving patient comfort, plaque positioning accuracy, and plaque stability during the treatment period. This design allows for a uniform surgical approach and decreases the demand for resources required to produce customized plaque for each patient, hence minimizing cost. The new designs also provide more seed placement options due to their hemispheric configuration rather than a simple two-dimensional ring around the limbus as seen in modified COMS plaques. They therefore offer up to 360° coverage of the anterior segment between the cornea and lens and near the corneal limbus, broadening their application for nearly any size and anatomic location of iris or iridociliary melanoma.

Additionally, in contrast to the COMS plaques, the EP plaques do not use a separate seed carrier and thus eliminate seed placement uncertainty that comes with mobile and flexible seed carriers. The seed slots built into the EP plaques are designed to collimate each radiation source, effectively shielding laterally directed primary radiation that does not contribute to tumor treatment. Therefore, the plaques are overall thinner than COMS plaques and yield a more homogenous dose distribution between the plaque and tumor apex in addition to the reduction in the radiation dose beyond the target.

The central opening of each plaque improves oxygenation of the cornea and thus preserves the integrity of the cornea throughout treatment. Notable differences between the two plaques include the size of the central opening and the overall diameter. EP1930 with the smaller opening allows for more coverage of the anterior and central tumor, but its smaller overall size may be more desirable in an eye with limited conjunctival laxity for the construction of Gunderson flap during plaque application. In contrast, the larger EP2132 is more appropriate for tumors involving the ciliary body. The combination of the dosimetric need for the target tumor and the conjunctival laxity of the recipient eye may ultimately dictate the choice of one plaque over another. Despite the slight differences, the surgical technique for the application of the two plaques is identical. The use of amniotic membrane on the cornea is optional, as demonstrated by Cases 1 and 2 that had the same postoperative vision and corneal surface outcomes.

One potential for dosimetric error of the new plaque designs comes from air gaps that can form between the plaque and cornea. Because the inverse-square law rather than attenuation is dosimetrically dominant at short distances from the seeds, however, accounting for the air gap is clinically insignificant in dosimetry compared to assuming overall homogeneous water. Our calculations show that the dose difference is within 1.5% when accounting for the air gap versus assuming the air gap as water.

In summary, the novel plaque designs described herein offer several advantages over COMS or modified COMS plaques – comfort for the patient, coverage of the tumor, cost minimization, broad applicability, and uniformity of the surgical method. More outcome studies are needed to elucidate the efficacy and tumor control with the new plaque design in the treatment of iris melanoma.

Statement of Ethics

The photographs of the patient were taken after obtaining written informed consent from the patient. The provisions of the Declaration of Helsinki for research involving human subjects were followed. No animal research was conducted as part of this work.

Disclosure Statement

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