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MRI-based Treatment Planning and Dose Delivery Verification for Intraocular Melanoma Brachytherapy

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Abstract

Purpose: Episcleral plaque brachytherapy (EPB) planning is conventionally based on approximations of the implant geometry with no volumetric imaging following plaque implantation. We have developed a magnetic resonance imaging (MRI)-based technique for EPB treatment planning and dose delivery verification based on the actual patient-specific geometry,

Methods and Materials: MR images of six patients, prescribed 85 Gy over 96 hours from COMS-based EPB, were acquired prior to and after implantation. Pre- and post-implant scans were used to generate “pre-plans” and “post-plans”, respectively. In the pre-plans, a digital plaque model was positioned relative to the tumor, sclera, and nerve. In the post-plans, the same plaque model was positioned based on the imaged plaque. Plaque position, point doses, percentage of tumor volume receiving 85 Gy (V_{100}), and dose to 100% of tumor volume (D_{min}) were compared between pre- and post-plans. All isodose plans were computed using TG-43 formalism with no heterogeneity corrections.

Results: Shifts and tilts of the plaque ranged from 1.4-8.6 mm and 1.0-3.8 mm, respectively. V_{100} was 97% for four patients. D_{min} for pre- and post-plans ranged from 83-118 Gy and 45-110 Gy, respectively. Point doses for tumor apex and base were all found to decrease from the pre-

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implant to the post-implant plan, with mean differences of $16.7 \pm 8.6\%$ and $30.5 \pm 11.3\%$, respectively.

Conclusions: By implementing MRI for EPB, we eliminate reliance on approximations of the eye and tumor shape and the assumption of idealized plaque placement. With MRI, one can perform pre- as well as post-implant imaging, facilitating EPB treatment planning based on the actual patient-specific geometry and dose delivery verification based on the imaged plaque position.

Keywords

ocular; melanoma; brachytherapy; magnetic resonance imaging; dosimetry

Introduction

Melanoma of the uveal layer, which includes the choroid, ciliary body, and the iris, is the most common primary intraocular cancer¹. Treatment options include enucleation and globe-sparing irradiation techniques such as charged particle therapy, stereotactic radiotherapy, and more commonly, episcleral plaque brachytherapy (EPB)². Iodine-125 (I-125) EPB was evaluated by the Collaborative Ocular Melanoma Study (COMS) trial for medium-sized tumors and was found to be as effective as enucleation in terms of disease-specific and overall survival, with the additional benefits of eye and some vision preservation³.

A COMS-based approach for treating uveal melanoma patients via EPB with I-125 seeds is used at our institution; outcomes for over 500 patients treated between 1996 and 2011 have been reported by Badiyan et al⁴. This approach utilizes ophthalmic information, i.e., ultrasound (U/S) A- and B-mode imaging, fundus photographs, and retinal diagrams, to create a two-dimensional (2D) representation of the tumor and its relationship to critical structures on a standard model of the eye. The ophthalmic information provides the tumor apex height, basal dimensions, distances to critical structures, tumor shape and its location in the eye. The tumor is typically represented on the 2D standard eye model diagram as an oblate spheroid shape of apical height and width. The plaque is generally represented as being positioned symmetrically about the tumor, and appositioned to the sclera which is defined to have a uniform thickness of 1 mm. Points of interest (POIs), e.g., tumor apex, prescription depth, optic disc, fovea, and lens, are identified on the cross-sectional diagram of the standard eye, and the coordinates of these points are calculated in the eye-plaque coordinate frame, where all points lie in a single plane. Isodoses are calculated using a radiation therapy treatment planning system and displayed relative to the points of interest by manually super-imposing a transparency printout of the isodose lines onto the cross-sectional diagram. With this approach, the information used for EPB treatment planning does not utilize volumetric imaging methods that are standard of care for the radiation therapy of other tumor sites. A limitation of the 2D method is that the resulting dosimetry is based on a generalized approximation of the treatment geometry that may not accurately represent the patient-specific geometry of the tumor and of the ocular anatomy, e.g., mushroom-shaped versus the more classic dome-shaped tumors, scleral thickness, and proximity of tumor to optic nerve sheath.

A three-dimensional (3D) representation of the eye was generated by the Plaque Simulator (PS) software, developed by Astrahan et al⁵. The PS software generates an interactive, translucent, 3D model of a patient's eye and tumor based on composite information from multiple imaging sources, i.e., computed tomography (CT) or magnetic resonance imaging (MRI) to determine the dimensions of the eye, U/S imaging to determine the dimensions of the tumor, and fundus photographs that are mapped onto the retinal and tumor surfaces. However, the 3D information provided by the PS software is limited since it does not directly use the volumetric image data to represent the patient's ocular anatomy and tumor.

Others have developed a 3D-based approach using conventional treatment planning systems and CT imaging to generate a reference eye geometry for EPB isodose planning⁶⁻⁸. Gagne et al. described how funduscopy images are used to aid the contouring of normal tissue volumes on the CT including the ciliary body, cornea, eyelid, lacrimal gland, lens, and optic nerve, as well as identifying dose points for the foveola and optic disc. However, due to the poor soft tissue contrast of CT, the tumor contour was still limited to an ellipsoidal shape based on tumor apex and basal dimensions provided by the ophthalmic examination.

An alternative to CT is the use of MRI for volumetric imaging of uveal melanomas because MRI has excellent soft tissue contrast⁹⁻¹¹. Daftari et al. found that 3D T₂-weighted fast spin echo MR imaging at 1.5-T yielded accurate volumetric measurements and additional information regarding tumor shape compared to more conventional imaging techniques, e.g., U/S and transscleral illumination⁹. In addition, MRI does not suffer from severe streaking artifacts that can obscure the ocular anatomy, as with CT, due to the low magnetic susceptibility of the gold alloy plaque. Thus, MRI has a unique advantage over CT in that one can image with the plaque in place which allows for treatment dose verification¹². MR imaging of the implanted plaque at 1.5-T was proposed by Houdek et al. in 1989 and evaluated for one patient, demonstrating the feasibility of post-implant MR imaging for 3D visualization of the ocular anatomy, tumor, and plaque position with adequate spatial resolution¹². However, other than verification via U/S by the ophthalmologist immediately after plaque implantation, the acquisition of volumetric image datasets of the implant is not commonly done for EPB, unlike other tumor sites receiving brachytherapy, e.g. post-implant CT or MR imaging of permanent prostate seed implants. Thus, EPB dosimetry has been historically based on approximated treatment geometries generated from pre-implant imaging information. In this work, we describe the implementation of MR imaging for EPB, eliminating both the reliance on approximations of the ocular anatomy and tumor shape as well as the assumption of idealized plaque placement. We demonstrate how pre- and post-implant MR imaging can facilitate EPB treatment planning based on the actual patient-specific geometry and dose delivery verification based on the imaged plaque position. Furthermore, we demonstrate how all of this can be accomplished using a conventional treatment planning system (TPS).

Methods and Materials

Six patients were enrolled in a prospective clinical trial approved by the Washington University Human Research Protection Office to evaluate the utility of pre- and post-implant MRI. Patients were prescribed 85 Gy over 96 hours from COMS-based EPB with I-125

seeds. The plaque size and prescription depth were based on tumor basal dimensions and apex heights, respectively, as determined by U/S imaging and fundus photography. The seed activity to deliver 85 Gy at a prescribed depth along the central axis of the plaque was calculated based on TG-43 isotropic point source formalism, where all activated seeds were set to uniform strength¹³. In the case of notched plaques, certain seeds were set to zero strength to simulate the location of the notch.

For all patients, MRI was performed on a 1.5-T scanner (Intera, Philips Medical Systems, Inc., Cleveland, Ohio) in two sessions, i.e., about one week prior to implantation and post-implantation with the plaque in place. Plaque implants were generally done on Fridays, with removal on the following Tuesdays. The earliest and most convenient time for post-implant imaging, accounting for patient recovery and admission following the implant procedure, as well as considering the hours of operation of the MRI scanner, was judged to be Monday. The timing of the post-implant should be considered on an institutional basis.

Prior to the MR imaging of patients with the implanted plaque, phantom images were acquired using T₂-weighted (T2W), T₁-weighted (T1W), and proton-density weighted (PDW) sequences to develop a technique for imaging of the plaque. A gel phantom embedded with notched and non-notched eye plaques of different sizes, and then pierced with titanium needles to serve as registration landmarks, was imaged using both CT and MR imaging. This was initially done to follow published guidelines regarding the commissioning of MRI of brachytherapy applicators, i.e., titanium applicators for gynecologic brachytherapy, which have recommended the acquisition of CT as well as MRI scans of phantoms using clinical sequences to assess the level of artifact and distortion introduced by the applicator¹⁷. A unique challenge when applying this common approach for assessing imaging artifact to EPB is the severe, streaking metal artifact in the CT images, limiting the value of the CT in providing a reference geometry for the plaque. However, during our phantom imaging, we observed that the MR image datasets, e.g., the T2W, T1W, and PDW image datasets, could be evaluated directly and separately from the CT images to assess geometric distortions based on the known dimensions of the plaque. Because the images were acquired in the same imaging session, the datasets upon import into the TPS (Eclipse BrachyVision, Varian Medical Systems, Palo Alto, CA) were automatically registered based on their shared frame of reference, facilitating comparison of the imaged plaque geometry between the datasets.

Based on the phantom imaging, a multi-sequence MR imaging technique combining T2W, T1W, and PDW sequences was developed and fine-tuned to facilitate visualization of the ocular anatomy, tumor, and plaque. Patients were imaged supine with the head coil in place. Imaging extents were set in the superior-inferior direction from the top of the head to just below the pons, and in the anterior-posterior direction from the nose to just posterior to the brainstem, and in the lateral direction to capture both globes of the eyes. Patients were asked to focus their eyes overhead on a decal of two dots located inside the bore on the top and to minimize blinking for the duration of the scans. The pre- and post-implantation MRI datasets were exported to the radiation therapy TPS, mentioned above.

Once MR images were imported into the TPS, a 3D virtual model of the seed-loaded plaque was selected based on the prescribed plaque size, where these 3D models were created previously as part of commissioning of the process within the treatment planning system for all COMS plaque sizes (12 mm, 14 mm, 16 mm, 18 mm, 20 mm, and 22 mm). The seed groups were created in the TPS for all plaque sizes based on TG-129 seed center coordinates¹⁴. To model the plaque applicator in the TPS, the different-sized silastic inserts were imaged (0.67 mm slice thickness, in-plane resolution of $0.098 \text{ mm} \times 0.098 \text{ mm}$, spiral pitch of 0.4, 50 mm reconstruction FOV, 120 kVp, 70 mAs) on a CT scanner (Brilliance 64-slice CT, Philips Medical System, Inc., Cleveland, OH). The boundaries of the imaged silastic inserts were digitized in the TPS as surrogates for the gold alloy plaques which, if imaged on CT, would have yielded severe streaking artifacts. Thus, the TPS was “pre-loaded” with a library of applicators and corresponding seed groups for each COMS plaque size.

Once the appropriate 3D model of the seed-loaded plaque was selected, “pre-plans” and “post-plans” were generated on the pre- and post-implant MRI scans, respectively. In the pre-plans, the position of the virtual 3D plaque model was represented by centering the plaque as much as possible relative to the tumor while accounting for nerve interference, and placing the origin of the plaque coordinate system, as defined by TG-129, within 1 mm of the outer surface of the sclera¹⁴. If the ophthalmologist prescribed a notched plaque, this was accounted for in the position of the digital plaque. In the post-plans, the 3D plaque model was positioned based on the signal void of the imaged plaque. Tumor and normal tissues (globe, lens, and optic nerve) were contoured, and points of interest (fovea, lens, optic disc, tumor apex, tumor base, and prescription depth) were defined on the pre- and post-implant images. The prescription depth, provided by the ophthalmologist, was defined along the central axis of the plaque. All remaining points of interest were defined relative to the patient anatomy. The tumor apex height, provided by the ophthalmologist, was defined as the deepest depth of the tumor. The tumor apex point was defined at the apex height. The tumor base point was located at the tumor base, directly opposite from the apex point, and along the inner sclera. The lens point was the centroid of the lens, the optic disc point was the center of the disc on the inner sclera, and the fovea was defined as the focal point on the inner sclera directly opposite the lens. The pre-calculated seed activity was entered into the TPS and isodoses were computed using the TG-43 formalism with no heterogeneity corrections (dose calculation grid at $1.0 \text{ mm} \times 1.0 \text{ mm} \times 1.5 \text{ mm}$)¹³. Point doses, percentage of tumor volume receiving 85 Gy (V_{100}), and dose to 100% of tumor volume ($D_{\min}$) were compared between pre- and post-plans. Lastly, differences in plaque position between the pre- and post-images were evaluated. The tilt of the plaque in the post-implant plans was defined as the maximum distance from the outer sclera to the inner edge of the plaque, where zero tilt was assumed in the pre-implant plans. The shift between plaques was determined using the differences in centroid location of isodose clouds contained within the plaque (~200 Gy) on registered pre- and post-images, where registration was based on tumor and ocular anatomy.

Results

Pre-implant MRI Technique

Fine-tuning of the MR imaging parameters to provide adequate visualization of the tumor and ocular anatomy for pre-implant isodose planning yielded the following acquisition protocol. For the T2W turbo spin echo (TSE) sequence, 1.5 mm axial slices with no gap were acquired, echo time (TE) was 75 ms, repetition time (TR) was “shortest”, flip angle (FA) was 90°, acquisition bandwidth was set to 438 Hz/pixel, and the number of averages was 3. The T1W-MRI was a 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence, 1.2 mm axial slices were acquired. The TE, TR, FA, acquisition bandwidth, and the number of averages were 4.0 ms, 8.5 ms, 8°, 171 Hz/pixel, and 1, respectively. The inversion time (TI) was 1000 ms. For both sequences, the in-plane voxel size was 1 mm × 1 mm. The scan time was approximately 4-5 minutes per sequence.

We found that a multi-sequence technique using both T1W- and T2W-MRI was necessary in order to image different aspects of the ocular melanoma and surrounding anatomy. For example, as shown in Figures 1a-1b for Patient 1, T1W-MRI demonstrates better contrast between the tumor and the vitreous eye compared to T2W-MRI, which can affect estimation of tumor extension into the eye and tumor apex height. However, one caveat of using T1W-MRI alone is that it may over-estimate the lateral extent of the tumor by including retinal detachment, as shown in Figures 1c-1d for Patient 3. We observed that on T1W-MRI the tumor as well as any retinal detachment appeared hyper-intense and merged together in contrast to the globe of the eye which appeared hypo-intense. On T2W-MRI, the tumor alone appeared hypo-intense with no enhancement of the retinal detachment in the globe of the eye which appeared hyper-intense. As a result, we performed pre-implant planning using T2W-MRI as the primary dataset for virtual plaque positioning along the tumor base fused with T1W-MRI to help define the tumor depth.

Post-implant MRI Technique

Phantom imaging of the plaques, which appeared hypo-intense in all datasets, indicated that the T2W-MRI sequence yielded the most distorted images followed by T1W-MRI and then PDW-MRI. For the latter two sequences, the measured plaque diameter was within 1 mm of expected, and the centers of the plaques were aligned to within 1 mm between datasets, with most of the distortion, if any, observed along the lip collimation of the plaque. Fine-tuning of the MR imaging parameters to provide adequate visualization of the tumor and ocular anatomy, in addition to the plaque, was accomplished with the clinical patient scans, as summarized below.

For post-implant imaging of EPB patients, T1W- and T2W-MRI were acquired using the same acquisition parameters as described above for pre-implant imaging. In agreement with phantom imaging tests, T2W-MRI for patient imaging was very susceptible to metal artifacts, yielding distortion mostly along the lip collimation of the plaque and in the tissues immediately adjacent to the plaque, rendering T2W-MRI as the least useful sequence for post-implant imaging. In agreement with phantom imaging tests, T1W-MRI for patient imaging was less susceptible to metal artifact than T2W-MRI. Patient imaging also showed

that because the tumor appeared hyper-intense in T1W-MRI, this made the tumor more discernable against the hypo-intense plaque. Because of previous evidence indicating that PDW-MRI with very short echo times is less sensitive to metal artifact compared to T2W-MRI, PDW-MRI was specifically added to the post-implant MRI protocol only for improved visualization of the plaque^{15,16}. For the PDW TSE sequence, 1.5 mm axial slices with no gap were acquired, TE was “shortest”, TR was set to [3000 – 6000] ms, FA was 90°, acquisition bandwidth was 877 Hz/pixel, and number of averages was 1. The scan time was about 3.5 minutes. In agreement with phantom imaging tests, PDW-MRI did help reduce the distortion of the plaque and make the boundaries more discernable in the image, making it easier to evaluate any tilting of the plaque. However, patient imaging also indicated that PDW-MRI led to reduced soft tissue contrast making it difficult to delineate structures within the eye, including the tumor. Thus, PDW-MRI should be acquired for improved visualization of the plaque and acquired in conjunction with T1W-MRI for improved visualization of the tumor and ocular structures. As a result, we performed post-implant planning on the post-implant T1W-MRI as the primary dataset fused to the post-implant PDW-MRI if needed to define the plaque boundaries better, and fused to the pre-planning T2W-MRI if needed to help define tumor boundaries in areas with retinal detachment. In some cases, because of the awkward orientation of the implanted plaque relative to the axial plan, we acquired additional PDW-MRI scans with 1 mm × 1 mm resolution in a plane that approximately bisected the plaque. This was to improve the resolution of the lip collimation of the plaque relative to the outer sclera. Examples of post-implant T2W-, T1W-, and PDW-MRI are available in the Online-only Supplementary Materials for Patient 5.

Planned Versus Administered Implant Geometries and Dosimetry

The tumor basal dimensions, tumor apex height, prescribed plaque size, and prescription depth are summarized in Table I, along with the shifts and tilts of the plaque. The doses to all points of interest are summarized in Table II. Point doses for tumor apex and base were all found to decrease from the pre-implant to the post-implant plan, with mean differences of $16.7 \pm 8.6\%$ and $30.5 \pm 11.3\%$, respectively. The change in point doses for critical structures (fovea, lens, and optic disc) was dependent on the direction of the change in plaque position relative to the structures. Differences of 1% or less were generally observed in the dose at the prescription depth because this point was defined relative to the central axis of the plaque, and, consequently, moved with the plaque. Below, we describe in more detail the impact of these shifts and tilts on V_{100} and $D_{\min}$ for the six patients.

For Patient 2, whose plaque was shifted by 2.4 mm and tilted by about 4 mm (the largest tilt observed in this study) the dose to tumor apex decreased by 17%; however, the V_{100} remained at 100% and the $D_{\min}$ remained above 85 Gy. This was because the prescription depth was at least 1 mm beyond the tumor apex with at least 2 mm of margin between the plaque and tumor edges. For Patients 3 and 6, with similar margins on prescription depth and plaque size, the V_{100} in the post-plans exceeded 98.0% and the $D_{\min}$ remained at or above 80 Gy. For Patient 4, who had a notched plaque, the V_{100} in the post-plan dropped to 97.2% and the $D_{\min}$ decreased to 73 Gy due to the plaque being tilted away from the sclera by the optic nerve.

The most adverse dosimetric effect on V_{100} and on D_{min} was observed for Patient 1 who had a tumor situated in the inferior side of the right eye at 6 o'clock, posterior to the equator, with approximately 2 mm between the posterior edge of the tumor and the edge of the optic disc. The intraocular tumor location is based on a retinal diagram using treatment positions described by Rivard et al⁸. For this patient, less than 1 mm margin was added to the prescription height, and a non-notched plaque was implanted. The proximity of the optic nerve prevented the plaque from being centered on the tumor or flush with the sclera (see Figure 2), yielding a shift and tilt of 3.9 mm and 1.6 mm, respectively, from the planned plaque placement. As a result, the V_{100} decreased from 100% to 57.3%, and the D_{min} decreased from 89 Gy to 45 Gy when comparing the pre-implant MRI to the post-implant MRI.

Patient 5 had a tumor situated in the superior side of the left eye at 12 o'clock, posterior to the equator, with approximately 0 mm between the posterior edge of the tumor and the edge of the optic disc. For this patient, a notched plaque was used to account for nerve interference, however there was less than 1 mm margin between the tumor apex and prescription height. For this patient's implant, the plaque was placed more medially (at 10 o'clock) than what was planned (at 12 o'clock) and, as a result, was not centered on the tumor, yielding a shift of 8.6 mm (the largest shift observed in this study) from the planned plaque placement (see Figure 3). The asymmetric plaque placement led to a decrease in V_{100} from 99.8% to 80.9%, and a decrease in D_{min} from 83 Gy to 56 Gy from the pre-implant MRI to the post-implant MRI.

Discussion

COMS EPB dosimetry has been historically based on approximated, rather than actual, treatment geometries generated from pre-implant imaging information where the tumor is typically represented as an oblate spheroid shape relative to a reference eye geometry, and isodoses are calculated assuming ideal placement of the plaque, i.e., perfect apposition of the plaque to the sclera and symmetric positioning of the plaque relative to the tumor⁵⁻⁸. In contrast to what is done for the brachytherapy isodose planning of other disease sites, e.g. cervix or prostate, there is typically no volumetric imaging of the implanted applicator geometry for COMS EPB patients. CT imaging of the implanted plaque geometry suffers from severe metal artifacts and inadequate soft tissue contrast, preventing visualization of the plaque, ocular tissues, and tumor. With MRI of EPB patients, anatomic and tumor information can be obtained on a patient-specific basis, implant dosimetry can be performed using the actual plaque geometry, and furthermore, all of this information can be visualized in 3D. Here we describe the implementation of an MRI-based technique to perform pre- and post-implant imaging for EPB treatment planning, allowing estimation of the implant geometry and dosimetry prior to plaque implantation, as well as verification of the administered implant geometry and dosimetry prior to plaque removal. To our knowledge, this is the first published work to demonstrate how MRI-based methods can be used to evaluate the effects of any discrepancies between estimated and administered implant geometries on tumor coverage for EPB patients.

Based on our findings, pre-implant EPB dosimetry should be performed using T2W-MRI as the primary dataset for estimating the plaque position relative to the tumor base, and fused with T1W-MRI to help define the tumor depth. Post-implant EPB dosimetry should be performed using T1W-MRI as the primary dataset because of the severe metal artifact observed with T2W-MRI. The post-implant T1W-MRI can be fused to a post-implant PDW-MRI, if needed, to reduce the effects of metal artifacts and better define the plaque position. If there is retinal detachment, the post-implant T1W-MRI can be fused to the pre-planning T2W-MRI to better define the lateral extent of the tumor.

Our imaging technique is based on a 1.5-T MRI unit, similar to Daftari et al. and Houdek et al., and may not readily apply to higher magnetic field strengths (i.e., 3-T) due to increased image distortions and susceptibility artifacts^{9,12}. To evaluate the effects of the plaque on image quality for a particular MRI unit, we recommend that phantom images of the plaques be acquired using the proposed clinical imaging sequences prior to the implementation of MR imaging for EPB patients, similar to what was done at our institution. Our phantom studies were confirmed with what we observed clinically, i.e., that T2W-MRI sequences led to the most distorted images of the plaque followed by T1W-MRI and then PDW-MRI as the least distorted. For the latter two sequences, the measured plaque diameter in the phantom images was within 1 mm of expected, and the centers of the plaques were aligned to within 1 mm between datasets, with most of the distortion, if any, observed along the lip collimation of the plaque (as demonstrated by images for Patient 5 in the On-line only Supplementary Material). We estimated that this distortion along the lip collimation may lead to a discrepancy of approximately 1 mm in the apposition of the plaque against the sclera, potentially yielding errors of 10%-20% at prescription depths of at least 5 mm with larger errors for shallower depths from the plaque, e.g., at the tumor base, due to the higher dose gradients closer to the plaque¹⁸. Thus, to improve resolution of the plaque collimation against the sclera, we acquired PDW images in a plane that bisected the plaque in order to obtain images with 1 mm × 1 mm resolution along this plane. Fine-tuning of the MR imaging parameters to provide adequate visualization of the tumor and ocular anatomy, in addition to the plaque, was accomplished with the clinical patient scans. With the introduction of metal artifact reduction sequences on commercially available MR units, there is potential for future improvement of image quality for post-implant imaging¹⁹.

With our approach, the pre-implant MRI-based plan can be used as a pre-operative tool to evaluate the estimated plaque position by assessing the tumor's location relative to critical structures and whether there are any potential issues with plaque placement. As an example, the non-notched plaque was not placed as closely against the nerve as was planned for Patient 1 leading to an under-dose of the tumor. Perhaps visualization of the tight placement of the virtual plaque in the pre-implant images by the ophthalmologist would have suggested the use of a non-notched plaque to provide better prescription dose coverage of the tumor. As another example, the plaque was placed more medially than what was planned for Patient 5 leading to an under-dose of the tumor. Perhaps visualization of the virtual plaque placement in the pre-implant images by the ophthalmologist either prior to or during the implant procedure would have helped guide the plaque localization approach to maximize prescription dose coverage. Thus, the pre-implant plan can be a useful tool, especially for the ophthalmologist, to investigate the effect of optic nerve interference, to pre-plan the

plaque localization approach, and determine whether changes should be made to the prescribed treatment geometry, i.e., use of a notched versus non-notched plaque.

With our approach, the post-implant MRI-based plan can be used to detect and assess any discrepancies that may occur between the planned (i.e., ideal) and administered plaque geometries. Our study did detect such discrepancies, but such changes did not always negatively impact the dosimetry due to added margins along the tumor height and basal dimensions, as shown for Patients 2, 3, 4, and 6. Based on these findings, we recommend the implementation of more robust planning/prescription guidelines to address uncertainties in plaque placement, e.g., prescribe to a depth at least 1 mm beyond the tumor apex height, select a plaque size that provides at least 2 mm margin circumferentially between the tumor basal boundaries and the plaque, and ensure that at least a 2 mm margin exists between the tumor edge and optic nerve sheath for non-notched plaques, otherwise prescribe a notched plaque. Similarly, Gagne et al. concluded that the tumor margins recommended by the American Brachytherapy Society in 2003 may be inadequate for prescription dose coverage given the radiation characteristics and placement uncertainties of COMS plaques, and that better coverage may be achieved using a basal expansion of 3 mm or greater and/or prescribing beyond the tumor apex²⁰.

Plaque placement uncertainties should be expected, especially for tumors located near the disc and fovea where surgical access and visualization can be hindered by the ocular anatomy, and apposition of the plaque to the sclera can be obstructed by the optic nerve sheath, inferior oblique muscle, and posterior ciliary vessels and nerves¹⁸. The occurrence of plaque tilt is the highest for posterior tumors near the fovea and optic disc, which are also generally known to have higher local failure rates¹⁸. Once the plaque is implanted, these structures can become congested or swollen over the implant duration, tilting the plaque away from the sclera. In a study of 162 patients, Almony et al. showed that, even with good apposition of the plaque (< 1 mm tilt) at time of implant for 81% of these patients, tilting of the plaque by more than 1 mm was detected at time of implant removal (96 hours later) for 53% of patients due to pre-scleral hematoma, inferior oblique muscle, optic nerve sheath, posterior ciliary nerves and vessels, or other indeterminate factors¹⁸. Almony et al. reported local failure occurred in only 3 patients (2%), all of whom had tilt of 1.95 mm or greater at plaque removal.

The decision to invest resources into acquiring both pre- and post-implant MR images for eye plaque brachytherapy patients should be considered on an institutional basis. For example, an institution may decide to implement pre-implant MR image planning along with robust planning/prescription guidelines to account for possible shifts and tilts of the implanted plaque for all EPB patients, but reserve post-implant MRI to verify plaque placement for cases involving more posterior tumors located near the disc and fovea. For those institutions with resources to obtain MR images of EPB patients post-implant on a more routine basis, dosimetric verification for EPB can potentially be beneficial for the evaluation of the effects of the administered implant geometry on toxicity and ultimately on tumor control. Future work will include expanding our pre- and post-implant MRI protocol to more EPB patients with long follow-up times to determine an association between plaque tilt/shift and tumor control. This work will also include the collection of dose-volume data to

eventually replace the point-based dosimetry that has been tracked historically, but shown to be extremely sensitive to the high dose gradients observed for EPB. With post-implant MRI and dose-volume data, one may be able to predict when a patient may experience complications, e.g., retinopathy or optic neuropathy, or may need additional therapy, e.g., leave the plaque in longer or perform adjuvant transpupillary thermotherapy^{4,18}.

All plaque dosimetry in this study was performed by modeling the different plaque geometries in a conventional treatment planning system using TG-43-based homogenous dose calculation¹³. However, it may be possible to refine our approach further by performing heterogeneous dose calculation on the MR images^{21,22}. Use of homogenous calculations was considered to be acceptable for the current study based on the fact that the comparison of pre- and post-plans was based on the same dosimetry method.

Conclusions

In this work, we describe the implementation of MR imaging for EPB, eliminating both the reliance on approximations of the ocular anatomy and tumor shape as well as the assumption of idealized plaque placement. We demonstrate how pre- and post-implant MR imaging can facilitate EPB treatment planning based on the actual patient-specific geometry and dose delivery verification based on the imaged plaque position. Furthermore, we demonstrate how all of this can be accomplished using a conventional treatment planning system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

For Patient 1, the T1W-MRI (a) demonstrates better contrast between the tumor (indicated by arrows) and the vitreous eye than the corresponding slice in the T2W-MRI (b) affecting estimation of tumor extension into the eye and tumor apex height. For Patient 3, the T1W-MRI (c) includes retinal detachment and should be viewed in conjunction with the corresponding slice in the T2W-MRI (d) to avoid over-estimation of the lateral extent of the tumor (indicated by arrows).

Figure 2:

An axial image slice from the pre-implant T1W-MRI for Patient 1 (a). The approximate image slice location in the post-implant T1W-MRI (b). The prescription isodose is displayed in yellow on each image slice. The tumor, appearing hyper-intense, is encompassed by the prescription isodose on the image slice in the pre-implant MRI (a) but not in the post-implant MRI (b) due to optic nerve interference.

Figure 3:

Coronal image slices from the pre-implant T1W-MRI (a) and from the post-implant T1W-MRI (b) for Patient 5. The prescription isodose is displayed in yellow, and the tumor contour is displayed in red on each image slice. For this patient's implant, a notched plaque was placed more medially (at 10 o'clock) than what was planned (at 12 o'clock) leading to an under-dose of the tumor.

Table I.

Summary of Implant Geometries

Patient	Tumor Basal Dimensions [mm × mm]	Tumor Apical Height [mm]	Prescription Depth (mm)	Plaque Size [mm]	Shift (mm)	Tilt (mm)
1	8.7×8.39	3.39	4	14	3.9	1.6
2	15.41×16.88	7.85	9	22	2.4	3.8
3	7.51×9.4	5.18	6.18	14	2.1	2.3
4	11.73×9.62	3.83	5	18 (notched)	1.6	1.8
5	10.34×9.57	9.2	10	18 (notched)	8.6	1
6	8.31×9.94	6.44	7.5	14	1.4	1

Summary of Tumor Prescription Coverage and Point Doses for Pre- and Post-implant MRI-based Isodose Plans

Table II.

<u>Patient</u>	V100 (%)		Dmin (Gy)		Apex Dose (Gy)		Base Dose (Gy)		Optic Disc (Gy)		Fovea (Gy)		Lens (Gy)		Prescription Depth (Gy)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	100.0	57.3	89	45	74	56	221	117	61	34	93	38	9	9	86	86
2	100.0	100.0	117	86	106	88	438	314	50	37	64	47	44	45	90	90
3	100.0	98.1	118	77	103	75	428	252	75	65	96	78	16	13	84	84
4	100.0	97.2	95	73	92	86	224	184	92	63	50	38	16	15	86	85
5	99.8	80.9	83	56	84	71	465	341	167	94	172	89	34	36	85	85
6	100.0	100.0	117	110	106	100	554	433	26	27	20	20	62	49	83	84