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Assessment of targeting accuracy of a low-energy stereotactic radiosurgery treatment for age-related macular degeneration

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Abstract

Age-related macular degeneration (AMD), a leading cause of blindness in the United States, is a neovascular disease that may be controlled with radiation therapy. Early patient outcomes of external beam radiotherapy, however, have been mixed. Recently, a novel multimodality treatment was developed, comprising external beam radiotherapy and concomitant treatment with a vascular endothelial growth factor inhibitor. The radiotherapy arm is performed by stereotactic radiosurgery, delivering a 16 Gy dose in the macula (clinical target volume, CTV) using three external low-energy x-ray fields while adequately sparing normal tissues. The purpose of our study was to test the sensitivity of the delivery of the prescribed dose in the CTV using this technique and of the adequate sparing of normal tissues to all plausible variations in the position and gaze angle of the eye. Using Monte Carlo simulations of a 16 Gy treatment, we varied the gaze angle by $\pm 5^\circ$ in the polar and azimuthal directions, the linear displacement of the eye ± 1 mm in all orthogonal directions, and observed the union of the three fields on the posterior wall of spheres concentric with the eye that had diameters between 20 and 28 mm. In all cases, the dose in the CTV fluctuated $< 6\%$, the maximum dose in the sclera was < 20 Gy, the dose in the optic disc, optic nerve, lens and cornea were < 0.7 Gy and the three-field junction was adequately preserved. The results of this study provide strong evidence that for plausible variations in the position of the eye during treatment, either by the setup error or intrafraction motion, the prescribed dose will be delivered to the CTV and the dose in structures at risk will be kept far below tolerance doses.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in those older than 50 in developed countries (Jager *et al* 2008). In 2000, 8.5 million people in the United States (14% prevalence) 55 years of age and older had intermediate or advanced AMD (Bressler *et al* 2003). There are two forms of AMD, dry and wet. In the dry form, vision deteriorates slowly and deposits known as drusen accumulate on the retina. No treatment has been approved by the Food and Drug Administration for dry AMD, though nutritional intervention may be effective (AREDS 2001). The wet form, on the other hand, is characterized by the rapid growth of capillaries in the retina that leak blood and fluid, causing scarring and damage to retinal cells. Frequently centered on the fovea, this neovascularization can result in rapid and permanent loss of central vision. Although there is currently no cure, wet AMD is commonly treated with an injection of a vascular endothelial

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(Some figures in this article are in colour only in the electronic version)

growth factor (VEGF) inhibitor such as ranibizumab into the eye. Injection of VEGF inhibitors has been shown to decrease both neovascularization and fluid accumulation in the retina, and vision can be improved and maintained (Rosenfeld *et al* 2006a, 2006b). However, while the results have been promising, the injections are costly and invasive and must be repeated regularly to arrest deterioration of vision (Brown *et al* 2008).

As wet AMD is a neovascular disease, it is responsive to radiation therapy. The positive effects of radiation are likely due to the inhibition of rapidly growing vascular endothelial cells, disruption of cytokines and reduction of the inflammatory response (Finger *et al* 1998). Patient outcomes after external beam radiotherapy have been mixed for both photon radiotherapy (Avila *et al* 2009b) and proton radiotherapy (Moyers *et al* 1999, Yonemoto *et al* 2000, Zambarakji *et al* 2006). Moyers *et al* reported on the potential improvement on sparing of normal tissues by using narrow proton beams instead of photon beams. More consistently favorable results have been obtained with high-dose-rate brachytherapy, which is given in highly localized single, large fractions (Jaakkola *et al* 2005). A technique involving a single epiretinal application of a strontium-90 source directly to the fovea has been particularly effective (Avila *et al* 2009a). In addition to maintaining or improving patient vision, it has shown a dramatic reduction (or elimination) in the need for anti-VEGF injections. This technique has been applied with and without VEGF inhibitors. However, the strontium-90 source is placed onto the choroidal neovascularization via core vitrectomy, which can have adverse effects.

Recently, an external beam treatment has been developed by Oraya Therapeutics, Inc. (Newark, CA) that delivers a radiosurgical dose in the macula (i.e. clinical target volume, CTV) using narrow, low-energy (superficial at 100 kVp) x-ray fields that largely spare the optic disc, optic nerve, cornea, lens and brain and keep the maximum dose in the sclera well below tolerance doses. This novel radiation treatment technique is particularly convenient for the patient, as it is non-invasive, involves no sedation, and requires only a single sitting. Previous studies have characterized the radiation fields (Lee *et al* 2008) used and the radiation safety of the patients during the procedure (Hanlon *et al* 2009). However, to date, the dosimetric impact of variations in the position and orientation of the eye during treatment is not known.

The purpose of this study was to investigate the sensitivity of the absorbed dose in the CTV and the structures at risk (SARs) to plausible variations in the gaze angle and linear displacement of the eye during treatment. Using Monte Carlo simulations of a 16 Gy three-field treatment, we calculated the absorbed dose in the CTV and the SARs while varying the gaze angles and displacement of the eye. For all types of setup error and intrafraction motion, we found that the prescribed dose in the CTV was stable and the SARs were adequately spared.

2. Materials and methods

2.1. Treatment technique

In the treatment position, the patient is seated in front of the stereotactic radiosurgery system (IRayTM, Oraya Therapeutics, Inc.), as shown in figure 1. The patient places his or her chin on the chinrest, and the headholder is lowered over the back of the patient's head to firmly hold the patient's forehead against a padded bar, lightly immobilizing the head. With the head stabilized, the lid is retracted using a customized lid retractor and the eye is gently immobilized using a suction-cup-like fixture (I-GuideTM, Oraya Therapeutics, Inc.), as shown in figure 2. The fixture consists of a suction-enabled contact lens attached to a center post that rotates via a ball joint in a horizontal stabilizer bar that is mounted to the headholder. After the lens is centered on the patient's limbus, suction is applied to affix the

fixture to the eye. This stabilizes the eye and causes the center post of the fixture to be coaxial with the geometric axis of the eye. The geometric axis of the eye defines the spherical treatment coordinate system, with the posterior pole defined as the intersection of the geometric axis (or 'z-axis') with the retina. The fovea is offset approximately 1.2 mm temporally and 0.5 mm inferiorly from the posterior pole. The radiosurgery system uses the positions of three retro-reflective fiducials mounted on the fixture to correctly position itself relative to the eye's geometric axis and deliver the treatment beams to the macula.

The radiosurgery system has a custom two-camera video imaging and tracking system that continuously monitors the positions of the fixture fiducials. For the initial alignment, the two fiducials on the stabilizer bar are used to bring the x-ray source into treatment position; the system has a mechanical targeting precision of approximately 200 μm . During treatment, the relative positions of all three fiducials are monitored in real time to calculate the gaze angle of the eye, the position of the eye relative to the starting position and the effective position of the treatment beam on the retina. Although the head and eye are immobilized, for patient comfort they are not rigidly fixed. However, computer software monitors the position of the beam on the retina and gates off the beam in the event of excess motion of the eye, for example if the patient's gaze drifts or head moves (see sections 2.4–2.6).

A prescribed absorbed dose of 16 Gy is delivered to a 4 mm diameter disc, which is the CTV, centered on the fovea. Three narrow beams overlap at the fovea to reduce the entrance dose in the pars plana, as shown in figure 3. The radiosurgery system is constrained to deliver beams along the surface of a cone with the vertex 150 mm from the anode (source-to-axis distance), regardless of the size of the patient's eye. The cone angle is variable, from 20° to 30°, and the fovea is positioned at the vertex of the cone. The beams are 4 mm in diameter (90% isodose) at the location of the fovea. Each beam enters the globe through three distinct positions on the pars plana, at azimuthal angles of 150°, 180° and 210°, and converges on the CTV. These field orientations were selected so that the beams would avoid the lens, cornea and optic nerve (Lee *et al* 2008) and the x-ray source could be positioned close to the eye while still providing adequate clearance with the patient's brow, cheek and eye lids. The radiosurgery system includes an x-ray tube (MXR160HP/11, Comet AG, Flamatt, Switzerland) operating at 100 kVp, 18 mA and 1.8 kW. The only patient-specific parameter of the treatment is the axial length of the eye. This affects targeting, as indicated by the distance that the radiosurgery system should be from the fixture fiducials, and treatment time (i.e. the length of tissue traversed by the beam is proportional to the axial length, so it directly affects the beam-on time). A 16 Gy treatment requires less than 5 min of irradiation time; the total treatment time, including setup, delivery and release of the patient, takes approximately 20 min.

2.2. Monte Carlo model

Monte Carlo simulations were performed using the Monte Carlo N-Particle eXtended (MCNPX) code, version 2.6b (Pelowitz 2008). The MCNPX and MCNP codes are commonly used in medical applications, including ocular radiotherapy using low-energy x-ray fields (Rivard *et al* 2006, Lee *et al* 2008, Hanlon *et al* 2009, Rivard 2009) and proton beams (Herault *et al* 2005, Koch and Newhauser 2005, 2010, Mourtada *et al* 2005, Newhauser *et al* 2007, Koch *et al* 2008). The geometric model (figure 4) comprised an x-ray source, a collimator assembly and an anthropomorphic eye protruding from a water tank. The 100 kVp x-ray tube was simulated with the following components: a parallel beam of 100 keV electrons originating from a $1 \times 1 \text{ mm}^2$ rectangular source; a tungsten wedge angled at 11°; a 0.8 mm thick beryllium window and a 19 mm thick brass housing, the interior of which was evacuated. X-rays were produced by bombarding electrons on the tungsten target. After exiting the beryllium window, the x-rays traveled through a collimator assembly. Components of the collimator assembly in the field, from the farthest upstream

component to farthest downstream component, included a tungsten collimator, an aluminum filter, a thin glass mirror (for a coaxial targeting laser) and a second tungsten collimator that defined the field size. The thickness of the aluminum filter was 0.75 mm, the glass mirror had a thickness of 0.15 mm and was at an angle of 45° (resulting in a thickness of 0.21 mm along the beam axis), and the downstream collimator had an aperture with a 2.5 mm diameter. The geometric model of the eye was created in the MCNPX code to replicate that of Dobler and Bendl (2002) and was adapted from a model that was used in previous investigations (Koch and Newhauser 2005, 2010, Koch *et al* 2008). For simplicity, the material composition of the eye was liquid water. The axial length of the eye was 24 mm; the center of the CTV was placed at the therapeutic target, which is 1.16 mm to the patient's right and 0.53 mm to the patient's inferior from the intersection of the geometric axis of the eye and the retina, commonly referred to as the posterior pole. The center of the eye was shifted 7 mm from the edge of the water tank (i.e. the anterior surface of the eye extruded 5 mm out of the anterior surface of the water tank). The optic nerve was represented by a 3 mm diameter cylinder that extended 17.2 mm from the optic disc and was rotated 18.4° to the patient's left, with respect to the center of the eye. Thus, the eye model corresponded to a patient's right eye.

Although the MCNPX code has been extensively used for low-energy photon simulations, single-field simulations were also performed to verify the accuracy of the Monte Carlo calculations against the measured data. In these simulations, the eye model and water tank were replaced by a solid water phantom to be consistent with the apparatus used for the measurements. The absorbed dose was calculated as a function of depth in adjacent, cylindrical subvolumes along the central-beam axis (CMESH3 mesh tally in the MCNPX code). The tally subvolumes were only within the phantom and were each 2 mm in height and 2.5 mm in diameter. To characterize the field at the depth of the CTV, lateral dose distributions were calculated in a two-dimensional matrix of $2 \times 0.5 \times 0.5 \text{ mm}^3$ voxels, with the 2 mm dimension along the central-beam axis, centered at a depth of 21.8 mm and extending from -10 to 10 mm in both lateral directions (RMESH3 mesh tally in the MCNPX code). Additionally, beam hardening was observed by calculating the photon spectral fluence (f4 discrete tally in the MCNPX code) immediately outside the x-ray tube, immediately distal to the collimator assembly and in the water phantom at the depth of the CTV (21.8 mm).

Corresponding measurements were also performed following the guidelines of the American Association of Physicists in Medicine (AAPM) Task Group 61 on kilovoltage dosimetry (Ma *et al* 2001). Measurements of the absolute absorbed dose in water were made using a parallel-plate ionization chamber (type N34013, PTW, Freiburg, Germany) together with an electrometer (Unidos E, PTW, Freiburg, Germany). Measurements of the relative absorbed dose in water were made using radiochromic film (Gafchromic® EBT Dosimetry Film, International Specialty Products, Wayne, NJ) in a certified, therapy-grade solid water phantom (457-CTG, Gammex-RMI, Middleton, Wisconsin), resulting in profiles of the dose versus depth as well as the dose versus lateral position.

Three-field Monte Carlo simulations were performed for the sensitivity tests (see sections 2.4–2.6). For the three-field simulations with the eye model depicted in figure 3(a), the x-ray tube and collimator assembly were first rotated 28° inferiorly. Next, the x-ray tube and collimator assembly were rotated 30°, 0° and -30° to simulate the 5-o'clock, 6-o'clock and 7-o'clock beam orientations, respectively. Each rotation of the x-ray tube and collimator assembly was about the center of the CTV. Thus, the three fields entered through the pars plana at azimuthal angles of 150°, 180° and 210°. Discrete tallies volumes to calculate the absorbed dose in the CTV and the SARs were placed in subvolumes located in strategic locations within these structures, as explained in section 2.4.

The results of the Monte Carlo simulations were normalized as follows. In all simulations, the output of the Monte Carlo code was reported in terms of the absorbed dose or spectral fluence per source particle (i.e. source electron). In the single-field simulations, we calculated the number of source electrons required to deliver a mean dose of 5.33 Gy to the CTV as the inverse of the absorbed dose per source electron (direct output of the Monte Carlo code). Likewise, in the three-field simulations, we separately calculated the number of source electrons required to deliver a mean dose of 5.33 Gy to the CTV for each of the three fields. Thus, we normalized the single-field results to 5.33 Gy in the CTV and the results of each of the three-field simulations to 5.33 Gy in the CTV for each field. The total absorbed dose in the CTV for the three-field treatment was 16 Gy.

2.3. Variance reduction

Two techniques were used to reduce the Monte Carlo simulation time and, thus, reduce uncertainty. First, for each of the four field orientations (three fields for the treatment setup and one field for the calibration setup), a phase space file of photons was created at the upstream face of the beryllium filter within the x-ray machine. That is, the trajectories and energies of all the photons that crossed the upstream face of the beryllium filter were recorded in a data file for use in subsequent simulations. For the simulation in which the single calibration field was simulated to create a phase space, 1.5×10^{11} electrons and their secondary photons were tracked (MODE P E in the MCNPX code); for each of the treatment field simulations, to create phase spaces, 1.5×10^{10} electrons and their secondary photons were tracked (MODE P E in the MCNPX code). These phase space files were recycled for subsequent Monte Carlo simulations, increasing the computational efficiency of the Monte Carlo modeling. Second, geometry splitting was implemented in the Monte Carlo code on several surfaces throughout the model, including the upstream face of the beryllium filter. Implementing the geometry splitting reduced the variance by more than a factor of 2. All of the subsequent simulations tracked each photon (MODE P in the MCNPX code), beginning at the upstream face of the beryllium filter, until the energy of the photon fell below 1 keV (the default cutoff for photons in MCNPX). The uncertainties in the values of the absorbed dose and spectral fluence were estimated considering only statistical uncertainties and with the assumption that component uncertainties were uncorrelated. Statistical uncertainties in the absorbed dose and spectral fluence values were based on the coefficients of variation reported by the Monte Carlo code and are reported at the 68% confidence interval.

2.4. Sensitivity to gaze angle

In the treatment position, the eye position is fixed so that the patient looks straight ahead and the beams converge at the fovea. Because of the possibility of the patient's gaze drifting during treatment, we tested the sensitivity of the absorbed dose in the CTV and the SARs to the variation in gaze angle in the polar (i.e. vertical) and azimuthal (i.e. horizontal) directions. During treatment, although the eye is stabilized by the fixture (see section 2.1), eye and head motion are still possible. Because of this, a gating system is in place to track the position of the eye and gate off the beam if the eye moves excessively. The gating algorithm is a function that is linear in time and quadratic in displacement in order to allow brief excursions that are not dosimetrically significant (e.g. spasm caused by blink response) while shutting off the beam when actual drift occurs. In practice, a maximum of a 5° error in gaze angle is expected (based on a small set of patient data). The software algorithm that governs the gating system treats targeting as a two-dimensional problem. Therefore, to conservatively investigate the impact that this deviation in gaze angle has on dosimetric coverage of the CTV and sparing of the SARs, we calculated the absorbed dose in the CTV and the SARs for the nominal case (i.e. deviating 0° polar and 0° azimuthal) and for cases where the gaze angle deviated by $\pm 5^\circ$ in the polar and azimuthal directions. In the Monte Carlo code, the absorbed dose was calculated in sub-millimeter-diameter spherical

subvolumes (f6 discrete tallies in the MCNPX code) in several locations—in the centers of the CTV, lens and cornea, and in the regions nearest to the treatment field in the optic disc, sclera, lens and cornea. The mean absorbed dose in the entire optic nerve was also calculated.

2.5. Sensitivity to linear displacement

Because of the possibility of setup error or intrafraction motion of the patient's eye, we tested the sensitivity of the absorbed dose in the CTV and the SARs for plausible excursions from the nominal setup position caused by patient motion during irradiation. The built-in gating system attempts to keep the average position of the beam on the retina within 400 μm of the setup position. Therefore, as a conservative test, we calculated the absorbed dose in the CTV and the SARs for orthogonal linear displacements of ± 1 mm separately in each orthogonal direction—right and left, inferior and superior, and posterior and anterior. The same tally volumes that were used in the gaze angle sensitivity test were used in this displacement sensitivity test. In addition to simple targeting error, this tests the effects of displacement on non-convergence of beams; that is, the radiosurgery system treatment vertex stays stationary while the patient moves under it. Excessive anterior or posterior motion could put the fovea in a region where overlap of the beams is incomplete.

2.6. Sensitivity of the three-field junction to the anterior–posterior position

Because of the variation of the position of the eye along the anterior–posterior axis, which is defined as the geometric axis of the eye, we tested the sensitivity of the union or the separation of the three fields to the anterior–posterior position of the eye. In particular, we quantified the convergence of the three beams along the posterior wall of concentric spherical shells with diameters from 20 to 28 mm, which in clinical practice conservatively encompasses all plausible variations in the anterior–posterior position of the eye. Dose tally volumes in the form of segments along concentric spherical shells ($2^\circ \times 2^\circ$ segments, diameters = 20 mm, 22 mm, 24 mm, 26 mm, 28 mm) were implemented in the Monte Carlo model such that for the nominal eye size, with a 24 mm diameter, the shell crossed through the CTV, sclera and optic disc. A limitation of this technique is that the human eye is elliptical and not spherical. However, this limitation was of little consequence in this sensitivity test because the region of interest, i.e. the macular region, including the CTV and optic disc, is nearly spherical.

3. Results

3.1. Verification of the Monte Carlo dose predictions and characterization of the field at the depth of the CTV

The relative absorbed dose along the central-beam axis versus depth in a solid water phantom is shown in figure 5 from the single-field Monte Carlo simulation and measurement. The excellent agreement between the Monte Carlo predictions and the measured data verified the accuracy of the relative dose calculations from the Monte Carlo code. The brain tissue begins at a depth of approximately 40 mm. The relative dose calculated by Monte Carlo at depths of 21.8 mm (i.e. at the CTV) and 40 mm (i.e. at the brain) were 32% and 14% (not shown), respectively. Thus, for a field that deposits 5.33 Gy at the CTV, the maximum dose in the portion of brain tissue nearest to the eye is no more than 2.4 Gy (assuming no type B uncertainties). This is a conservative estimate because bone separates the brain from the eye, and more attenuation would occur in bone than in water. Figure 6 shows the lateral dose profiles in both the horizontal and vertical directions at the depth of the CTV for the Monte Carlo simulations and the film measurements. These dose profiles verified that the field widths in the horizontal and vertical directions were about 4 mm for the simulated and the measured data. The penumbrae were similar for the

simulated and measured data, with the measured data having a slightly sharper penumbra. The penumbra from the measured data was slightly sharper because the actual focal spot was smaller in diameter (0.85 mm) than the nominal value in the technical specifications (1 mm), on which the electron source in the Monte Carlo simulations was based.

Photon spectral fluences calculated by the Monte Carlo simulations are shown in figure 7 at three locations along the central-beam axis. The plot at the machine exit represents the 100 kVp photon spectral fluence that results from a 100 keV electron source impinging on the tungsten wedge, followed by the photons traveling through the exit window of the x-ray tube. At this location, the lowest energy bremsstrahlung photons have been largely removed by the beryllium filter in the exit window and the slightly hardened characteristic x-ray peak remained at 9.5 keV. After traveling through the two aluminum filters, a quartz-glass mirror and two tungsten collimators, the characteristic x-ray peak was removed, and the photons below about 30 keV were preferentially attenuated. Finally, at the fovea, after traveling through 21.8 mm of water, the photons with energies below approximately 40 keV were preferentially attenuated and photons with energies below 15 keV were completely removed. The average energy of the hardened x-ray spectrum at the fovea was 48.8 keV.

3.2. Sensitivity to gaze angle

Fluctuations in the absorbed dose in the CTV and the SARs versus plausible gaze angles are shown in figure 8. The values of the mean and the maximum absorbed dose in the CTV and the SARs for the nominal gaze angle are plotted along with those for polar and azimuthal deviations. For all plausible angular deviations in the gaze of the eye during treatment, the dose in the CTV was within 5% of that in the nominal case, the maximum dose in the sclera was 19 Gy, the maximum dose in the optic disc was 0.6 Gy, the maximum dose in the lens was 0.3 Gy, and the mean dose in other SARs was less than 0.3 Gy. Therefore, the deviation in the gaze angle during treatment is of minimal dosimetric consequence and presents very low radiological danger to the optic disc and optic nerve.

3.3. Sensitivity to linear displacement

Fluctuations in the absorbed dose in the CTV and the SARs for plausible linear displacements of the eye along with the nominal case are shown in figure 9. The values of the mean and the maximum absorbed dose in the CTV and the SARs for the nominal placement of the eye are plotted along with those for 1 mm displacements in the right, left, inferior, superior, posterior and anterior directions. For plausible displacements in orthogonal directions (± 1 mm), the dose in the CTV was within 6% of that in the nominal case, the maximum dose in the sclera was 19 Gy, the maximum dose in the optic disc was 0.6 Gy, the maximum dose in the lens was 0.3 Gy and the mean dose in other SARs was less than 0.3 Gy. Therefore, the motion of the patient along the geometric axes of the eye is of minimal dosimetric consequence and presents very low radiological danger to the optic disc and optic nerve within the variations stated herein.

3.4. Sensitivity of the convergence of the three fields to the anterior–posterior position

Figure 10 shows the plane projections of the spherical tally results, representing the union of the three beams at several anterior–posterior positions. Conservatively, the uncertainty of the position of the eye in the anterior–posterior direction is less than 1 mm. Therefore, spherical shells with diameters of 22 mm, 24 mm and 26 mm (figures 10(c)–(e)) represent plausible, realistic cases and spherical shells with diameters of 20 mm and 28 mm represent unrealistic cases. In the realistic cases, the union of the three fields was preserved, adequate coverage of 16 Gy to the CTV was observed and the optic disc and optic nerve were adequately spared. The spreading of the three beams at the largest concentric sphere, 28 mm diameter, (figure 10(f)) provides strong evidence that the fields completely separate before reaching the brain.

These results indicate that the coverage of the prescribed dose in the CTV and the sparing of normal structures are not sensitive to plausible variations in the anterior–posterior position of the eye.

3.5. Statistics and computing

The statistical uncertainties in the single-beam benchmarking results were less than 1%, and the statistical uncertainties in the three-beam sensitivity testing results were less than 5%. According to AAPM Task Group 61, ‘the final uncertainty in the absorbed dose...should be better than $\pm 5\%$ ’ (Ma *et al* 2001). The uncertainties in the absorbed dose values in this study were within that of the AAPM protocol, and they were sufficient for demonstrating that no significant difference was observed in the dose in the CTV for all types of setup error and intrafraction motion.

The simulations that resulted in phase spaces required a total of 6.5 days of computing time with parallel processing on 500 2.6 GHz, 64-bit microprocessors (Opteron; Advanced Micro Devices, Inc., Sunnyvale, CA); the final simulations that were based on the phase spaces required a total of 2.2 days of computing time on a single 2.4 GHz microprocessor. For the nominal single-field case, the number of source electrons required to deliver 5.33 Gy to the CTV was 6.12×10^{18} . For the nominal three-field simulations, the numbers of source electrons required to deliver 5.33 Gy to the CTV were 6.7×10^{18} , 7.0×10^{18} and 6.6×10^{18} , for the 5-o’clock, 6-o’clock and 7-o’clock beam orientations, respectively.

4. Discussion

The objective of this study was to test the sensitivity of a three-field stereotactic external beam radiosurgery treatment for AMD to plausible variations in the gaze angle and position of the eye caused by setup errors or motion during treatment. Specifically, using Monte Carlo calculations, we quantified the dosimetric impact in the CTV and the SARs for plausible variations in gaze angles and linear displacements. The results of this study revealed that for all setup error and intrafraction motion of the eye the average absorbed dose in the CTV remained stable (i.e. within 6% of the nominal dose) and covered the CTV and the absorbed doses in the SARs (i.e. sclera, optic disc, optic nerve, lens, cornea, and brain) were kept below acceptable limits. The Monte Carlo model and its predictions were validated in terms of the relative dose against measurements.

The treatment system includes a safety gating algorithm that terminates the beam in the event that the calculated beam position on the retina deviates moderately from the nominal position. However, the tolerance defining ‘moderate’ positional deviation was previously somewhat simplistic, i.e. it ignored the effects caused by the separation of the fields in three-dimensional space that may occur. This work has shown that the dosimetric effects of the spreading of the fields are negligible in the CTV and that adequate treatment is maintained for plausible variations in eye position examined.

The clinical implication of this study is that the dosimetric coverage provided by this treatment technique is insensitive to the setup error and the intrafraction motion that is typical for this treatment. This study supports the feasibility of escalating the dose in the CTV, e.g. through hypofractionation, while sparing normal structures near and within the eye. Although the dose in the sclera was up to 19 Gy, the sclera is radioresistant, and a dose of less than 20 Gy does not result in any significant morbidity. Indeed, experience with ocular melanomas has shown the absence of clinical effects at doses into the hundreds of Gy (Missotten *et al* 1998, Hermann *et al* 2002, van Ginderdeuren *et al* 2005). We also found that for realistic motion in the anterior–posterior direction, the displacement of the fovea would have minimal impact on the overlap of the beam and would not pose a threat to the

optic disc. Furthermore, because of the geometric orientation of the fields, the beams begin to separate soon after the fovea and divide completely before encountering any critical structures, e.g., the brain. A primary intention of using three fields rather than one was to reduce the maximum doses to the brain and the sclera. The predicted brain dose in a single-field simulation was less than 2.4 Gy (conservatively), and the findings of a previous study that demonstrated that the mean dose in the brain was kept below 10 mGy for a 16 Gy treatment (Hanlon *et al* 2009) provide strong evidence that hot spots greater than 3 Gy will not occur in the brain. Together, these findings further support the use of this technique in a clinical setting.

Previous attempts to use external photon radiotherapy for AMD have predominantly involved MV beams with much larger fields ($\gg 1 \text{ cm}^2$) to assure adequate targeting. As such, they have tended to include the entire optic nerve of the ipsilateral eye and, occasionally, even the contralateral eye (Marcus *et al* 2001). In addition, the dose falloff in tissue was gradual because of the high energy of the photons, resulting in higher doses in the distal tissues than those of lower energy beams. Thus, the low energy of this radiosurgery system is advantageous both because the beams attenuate rapidly before reaching the brain and because secondary charged particles of lower energy beams travel a much shorter distance than those of higher energy beams.

In conclusion, our study supports the feasibility of applying this adjuvant low-energy external beam radiosurgical technique to patients with early- and late-stage AMD. For all plausible setup errors and intrafraction motions of the eye, the delivered and prescribed doses in the CTV agreed within 6% while keeping the dose in normal structures far below tolerance dose levels. A European clinical trial is in progress, and a US pivotal trial is foreseen.

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Figure 1. Robotic stereotactic radiosurgery system. A test subject is shown with his head in the treatment position within the immobilization system.

Figure 2.

(a) Eye stabilization and imaging fixture, (b) placed on a test subject's eye. The suction-enabled contact lens is centered on the patient's limbus, which establishes the geometric axis of the eye as the treatment coordinate system. Three retro-reflective fiducials that are used to determine the position and gaze angle of the eye in real time are shown; the central post is free to rotate within the horizontal stabilizer bar that extends to the left-hand side in the figure. The test subject's lower eyelid is pulled completely out of the path of the fields using a customized lid retractor.

Figure 3.

(a) Orientation of the three-field external beam treatment as the fields enter the eye proximally through the pars plana and converge distally on the macula. (b) Fundus image of a patient's retina, with vasculature extending out of the optic disc and converging on the macula (CTV), beneath a theoretical but typical dose wash showing a sharp penumbra of the small, low-energy field. Black circles mark the optic disc and CTV, and the 90% and 10% isodose lines are shown.

Figure 4.

Each component of the geometric model in the Monte Carlo simulations, including the x-ray tube, collimator assembly and the eye in the mid-eye horizontal plane crossing through the macula (CTV). Labeled in the diagram are the electron source, tungsten (W) wedge, beryllium (Be) filter, water phantom, first tungsten collimator, aluminum (Al) filter, mirror, aluminum holder, brass housing and second tungsten collimator. The subvolumes within the eye are contoured in the zoomed-in diagram of the eye. In the eye, the shading represents the energy deposited in angular segments in concentric spheres for the nominal 6-o'clock field (log-scale, arbitrary units). The orientation of the x-ray tube/collimator assembly to the eye and water phantom has been rotated out of the treatment position and into the X-Z plane for this figure. The number scale on the left side of the figure represents distances from the focal point in millimeters.

Figure 5. Percent depth dose in solid water along the central-beam axis for the single-field Monte Carlo simulation (solid line) versus measurements (solid circles) made with film. Error bars are contained within the line thickness and symbols, respectively.

Figure 6.

Absorbed dose profiles through the isocenter (i.e. at the depth of the fovea) for the single-field Monte Carlo simulation (solid line) versus measurements (solid circles) made with film. The dose in voxels along the horizontal and vertical axes is shown in (a) and (b), respectively. The data are normalized to deliver a mean of 5.33 Gy to the CTV. Error bars are contained within the line thicknesses and symbols, respectively.

Figure 7.

Photon spectral fluences for a single beam at three locations: at the exit of the x-ray tube, after the filtration and collimation, and at the fovea, which is the center of the CTV. The curves were first normalized to the delivery of 5.33 Gy to the CTV, and then the curves other than the fovea curve were scaled for comparison, as shown in the legend. For clarity, error bars are not shown; they are within three line widths in magnitude.

Figure 8.

Fluctuations in the absorbed dose in the CTV and the SARs with respect to plausible maxima in eye gaze angles during treatment. Angular values are shown for the eye gaze deviating a combination of (polar, azimuthal) degrees. Values of the mean absorbed dose in the structure are plotted, except where noted as the maximum absorbed dose in the structure.

Figure 9.

Fluctuations of the absorbed dose in the CTV and the SARs with respect to plausible linear displacement of the eye during treatment by ± 1 mm in all orthogonal directions. The nominal case, in which there was no displacement, is labeled as 'none.' Values of the mean absorbed dose in the structure are plotted, except where noted as the maximum absorbed dose in the structure.

Figure 10.

Absorbed dose distributions in segments along the back of the eye for spheres with diameter between 20 and 28 mm. The arrow represents the size and direction of the 6-o'clock field, and the Z direction points from anterior to posterior, with the eye facing to the left of the page. The diameters of the spherical-shell tally volumes are labeled along with the approximate locations of the CTV and optic disc. The 24 mm diameter sphere (d) represents the nominal case. The gray dot in each figure marks the location of the posterior pole of the spherical tally.