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Influence of eye size and beam entry angle on dose to non-targeted tissues of the eye during stereotactic x-ray radiosurgery of AMD

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Abstract

Age-related macular degeneration is a leading cause of vision loss for the elderly population of industrialized nations. The IRay® Radiotherapy System, developed by Ora Therapeutics, Inc., is a stereotactic low-voltage irradiation system designed to treat the wet form of the disease. The IRay System uses three robotically positioned 100 kVp collimated photon beams to deliver an absorbed dose of up to 24 Gy to the macula. The present study uses the Monte Carlo radiation transport code MCNPX to assess absorbed dose to six non-targeted tissues within the eye - total lens, radiosensitive tissues of the lens, optic nerve, distal tip of the central retinal artery, non-targeted portion of the retina, and the ciliary body – all as a function of eye size and beam entry angle. The ocular axial length was ranged from 20 to 28 mm in 2 mm increments, with the polar entry angle of the delivery system varied from 18 to 34 degrees in 2 degree increments. The resulting data showed insignificant variations in dose for all eye sizes. Slight variations in the dose to the optic nerve and the distal tip of the central retinal artery were noted as the polar beam angle changed. An increase in non-targeted retinal dose was noted as the entry angle increased, while the dose to the lens, sensitive volume of the lens, and ciliary body decreased as the treatment polar angle increased. Polar angles of 26 degrees or greater resulted in no portion of the sensitive volume of the lens receiving an absorbed dose of 0.5 Gy or greater. All doses to non-targeted structures reported in this study were less than accepted thresholds for post-procedure complications.

Keywords

Age-related macular degeneration (AMD); stereotactic radiosurgery (SRS); non-targeted tissue complication probability (NTCP); dose volume histogram (DVH)

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1. Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss for the elderly population of industrialized nations (Congdon et al., 2004). The current standard of care for the wet form of the disease is monthly injections of anti-VEGF drugs (Brown et al., 2006; Rosenfeld et al., 2005; Rosenfeld et al., 2006). Unfortunately, these treatments do not destroy the underlying choroidal neovascular membrane, and thus it is necessary to continue therapy indefinitely. While radiation has been shown to be successful at inducing involution of the choroidal neovascularization, it historically has resulted in unimpressive gains in visual acuity (Chakravarthy and MacKenzie, 2000; Finger et al., 2003; Sivagnanavel et al., 2004). However, recent improvements in radiation targeting have led to a significant improvement in dose conformity to the treatment site (Avila et al., 2009b; Gertner et al., 2010; Hanlon et al., 2009; Kishan et al., 2013; Lee et al., 2008). Use of radiation treatments in tandem with anti-VEGF therapies has been evaluated as a possible improvement upon anti-VEGF therapy alone (Avila et al., 2009a). Results show that epiretinal delivery of beta radiation is promising in terms of visual acuity, and suggest that 24 Gy to a small portion of the retina is very well tolerated (Avila et al., 2012).

Oraya Therapy™ Stereotactic Radiotherapy for wet AMD provides a noninvasive delivery of a one-time single fraction dose to the macula (Gertner et al., 2010; Moshfeghi et al., 2011). The goal of Oraya Therapy is to deliver a dose significant enough to arrest choroidal neovascularization without damaging other non-targeted tissues of the eye and head. The IRay System delivers up to 24 Gy over approximately five minutes using three narrow-field 100 kVp photon beams (Gertner et al., 2010; Hanlon et al., 2011; Taddei et al., 2010). The three beams enter through the inferior pars plana and overlap onto the macula. In a multi-center prospective, randomized, controlled clinical trial of 230 patients in Europe, Oraya Therapy was shown to significantly reduce the need for anti-VEGF injection. In the full cohort, anti-VEGF injections were reduced by 32%; in an analysis of best-responders, anti-VEGF injections were reduced by 54% and a mean vision gain of 6.8 ETDRS letters was achieved relative to the non-radiation control group (Jackson et al., 2013).

Each beam of the IRay System is robotically positioned such that the macula is 150 mm from the x-ray source regardless of eye size. The eye of the patient is gently immobilized by a suction enabled lens (I-Guide™ Eye Stabilization Device) (Gertner et al., 2010). Concurrently, the IRay System uses an active tracking system during the procedure. If the position of the eye deviates beyond preset threshold limits, a gating event is registered which halts beam delivery to ensure patient safety.

The peak energy used during Oraya Therapy is 100 kV, less than the peak energy used during a standard chest radiograph. Typical external beam radiation therapy (EBRT) involves peak energies of several MV, greater than the IRay System by more than a factor of ten. The lower energy of the IRay System results in significantly less scatter than would be the case for other EBRT treatments, thus resulting in lower doses to non-targeted tissues.

In a previous study by Hanlon et al (Hanlon et al., 2011), treatment simulations were performed with patient-specific voxel models to explore dose to non-targeted tissues as a result of varying gaze angle, ocular anatomy, and cranial anatomy. In the present study, dose assessment has been expanded to include tissues that could not be evaluated using the voxel models as their resolution was too coarse to accurately define many of the smaller structures in ocular anatomy. To overcome this issue, a library of stylized models was created for this work which included the following target tissues: the total lens, radiosensitive volume of the lens, optic nerve, distal tip of the central retinal artery, non-targeted portion of the retina, and the ciliary body. The dose dependence of these non-targeted tissues was examined as a

function of both eye size (axial length ranging from 20 mm to 28 mm in 2 mm increments) and treatment beam polar angle (ranging from 18 degrees to 34 degrees in 2 degree increments) for a total of 45 different treatment combinations, all of which included 3 beams with nominal azimuthal entry angles.

2. Materials and methods

A series of five stylized eye models was constructed with axial lengths ranging from 20 to 28 mm in increments of 2 mm with the axial length being defined as the distance from the front of the cornea to the front of the retina (see Figure 1A). The eye models were based upon those developed originally by Lee et al (2008), but with a more sophisticated design for the optic nerve based upon data accumulated in Hanlon et al (2009). The optic nerve was modeled as a right truncated cone that decreases in radius as it leaves the eye, as opposed to the fixed diameter cylinder model used previously. Each model was scaled according to the change in axial length. While some structures such as the lens were scaled in all three dimensions, other structures such as the retina were scaled two dimensionally while maintaining a constant tissue thickness. Volumes of the tissues as a function of eye size are given in Table 1. Unlike the other tissues considered, the size of the CRA is the same for each eye model. Further, in each model, the macula target was offset from the geometric axis of the eye by 1.26 mm laterally and 0.56 mm inferiorly. In the ophthalmology community, the fovea is known to be offset from the posterior pole of the eye, and this offset was quantified with an in-house study of 55 healthy volunteers (Arnoldussen et al., 2009). Finally, a ciliary body structure was added to each model. The ciliary body was modeled as a band of muscle surrounding the edge of the lens which connects to the sclera of the eye. All material compositions and densities were derived from reference values given in ICRU Report 46 (1992). Table 2 shows the materials assigned to the various tissues of the eye model.

The Monte Carlo N-Particle eXtended (MCNPX) is a general purpose radiation transport code used to model the interactions of radiation over a broad range of energies, developed at the Los Alamos National Laboratory (Los Alamos, NM) (Pelowitz, 2008). The features of MCNPX presented an efficient method to construct a set of eye models and simulate ocular radiotherapy for AMD. All simulations of ocular radiotherapy were conducted with MCNPX version 2.6.0 with 50 million sampling histories. Mesh tally calculations were used to create DVHs for six non-targeted structures within the eye: lens, sensitive volume (SV) of the lens, optic nerve, distal tip of the central retinal artery (CRA), non-targeted portion of the retina (retina), and the ciliary body (see Figure 1A). The non-targeted portion of the retina was defined as the entire retina less the macula target. MCNPX has three different geometrical mesh tally shapes (cuboidal, cylindrical, and spherical), all of which were used to overlay the critical structures of interest. Track-averaged mesh tallies were applied using the pedep keyword in MCNPX. Post-processing of the data was necessary to select the appropriate voxels for each mesh tally and to scale the delivered dose according to the macula target treatment. The SV of the lens, based on a model developed by Behrens et al (2009), was not defined explicitly in the MCNPX geometry, but was included through the post-processing code. In addition, dose to the macula was scored for scaling purposes.

Simulations were run for cases in which mesh tallies only scored photon energy deposition and in which mesh tallies scored energy deposition from both photons and secondary electrons. For the transport of photons, MCNPX default settings were used as the accuracy of these settings has been demonstrated in a previous study (Lee et al. 2008). However, electron transport was performed using both the default MCNPX settings and ITS indexing. In addition, the number of electron energy substeps (estep) was varied across an order of magnitude with little difference seen in the outputs. It was found that the inclusion of

secondary electron transport and scoring did not significantly alter the values of the doses to the non-targeted tissues of the eye, in agreement with the results from Lee et al (2008). As a result, secondary electron transport was not performed for the majority of the treatment scenarios for computation efficiency.

An in-house MATLABTM code was written for the purpose of constructing DVHs from the mesh tally data. Since the dose to the macula is known (8 Gy for each beam), dose scored to the macula tally was used to find an appropriate scaling factor which was then applied to all other tissues. The code used the geometry of the problem to appropriately select voxels from each mesh tally. Only voxels that were completely within the true geometry of the desired structure were selected. For spherical and cylindrical tallies, it was also necessary to create a weighting system for the voxels as not every voxel has the same volume. Appropriately scaled voxels (scaled for dose and, if necessary, volume) were then used to construct data for each of the non-targeted tissues. The same mesh tally was used to construct the DVHs of the lens and the SV of the lens, using different geometrical parameters. It should be noted that the geometry of the lens is the entire lens, including the SV of the lens.

The source definition consisted of three beams at the five, six, and seven o'clock positions (azimuthal angles of 150, 180, and 210 degrees, respectively) with polar angles 18, 20, 22, 24, 26, 28, 30, 32, and 34 degrees relative to the geometric axis of the eye (see Figure 1B). The spectrum used was generated with the Institute of Physics and Engineering in Medicine computer software described in Report No. 78 (Cranley et al., 1997). The x-ray emission spectrum was characterized using a tungsten anode tube operated at 100 kVp, anode angle of 12 degrees, and total filtration of 0.75 mm aluminum and 0.8 mm beryllium. The beam source was an area of 1 mm × 1 mm, representing a 1 mm² focal spot. The divergent beam was collimated with a tungsten aperture such that the beam diameter was 4 mm at the macula target, with a source-to-target distance of 150 mm in all cases. These spectrum characterization parameters were determined in the previous study by Lee et al (2008) in which the x-ray source term and photon interactions were experimentally verified via depth dose measurement in solid water. Output from each treatment simulation was compared to see if there were any significant differences in dose to the six non-targeted tissues as either eye size or polar beam angle were changed.

3. Results

Graphical representations of dose to non-targeted tissues as a function of eye size for the standard 26 degree polar treatment angle are shown in Figures 2A to 2F. Study results indicate that as the size of the patient's eye increases, there is an insignificant increase in dose by percent volume for both the optic nerve and CRA. This pattern is due to corresponding increases in x-ray scatter of the primary beam. An eye with a longer axial length also has a longer tissue path length, which results in more scattered radiation. In addition, the distance between the macula target and both the CRA and optic nerve does not change across the different eye models.

The dose by percent volume with the total lens, SV of the lens, and ciliary body generally decrease as the eye size increases. For these tissues, the increase in scatter does not have as large of an effect as the increase in tissue volume. Most of the difference in scatter due to tissue path length for different sized eyes occurs downstream of the lens and ciliary body. Furthermore, for larger eyes, the three beams intersect the ciliary body further from the macula target and thus overlap less onto that ocular structure.

Doses to the non-targeted retina show a decreasing trend as the axial length increases. Though there is enhanced scatter from a longer tissue path length, there is also a larger distance between the beam path and the peripheral portions of the increasingly larger retina

volume. However, larger point doses are seen in the retina as the axial length increases, though the affected volumes are very small (less than 1%). This pattern is primarily due to areas of the retina immediately adjacent to the macula target.

Dose tally errors varied for the different non-targeted ocular structures. For the optic nerve, standard errors were as large as 3%, but were typically less than 1%. Errors for the lens and SV of the lens were as large as 4%, but were usually less than 3%. For the retina, errors rose as large as 10%, but were typically at 4% or less. Errors for ciliary body values rose as large as 9%, with values typically at 5% or less. Errors for the CRA were the largest ranging between 8% and 10%. While these errors are larger, the volume of the voxels was extremely small for the CRA which resulted in consistently larger statistical errors.

Graphical representations of the doses to non-targeted tissues as a function of beam polar angle for the 22 mm axial length eye are shown in Figure 3. Only the results for the 22 mm eye are shown, but the results of the other eye sizes are very similar. Doses to the lens, SV of the lens, and ciliary body decrease as the beam polar angle increases. Doses to the non-targeted retina increase as the beam polar angle increases for two reasons. First, the overlapping beam spot is more ellipsoidal at the back of the eye for larger polar angles, and so some voxels of the mesh tally defining the non-targeted portion of the retina that are closest to the macula receive a larger dose. Second, some voxels defining the anterior portion of the retina score a larger dose because they are in the path of the entering beams. Dose variations for the CRA and the optic nerve were smaller than the associated errors, indicating that they do not significantly change for different beam entry polar angles.

4. Discussion

For the different sized eye models, small fluctuations can be seen in the doses to non-targeted tissues. It can also be seen that not all tissues have the same trend, as some increase in dose while other tissues decrease in dose with increasingly larger axial lengths of the treated eye. Overall, the fluctuation in dose is not large enough to have a significant influence on treatment planning for this therapy.

The sensitivity of the optic nerve to radiation has been previously studied for cases in which the optic nerve was unavoidably or accidentally exposed (Girkin et al., 1997). From these cases, it was suggested that optic nerve doses of 8 Gy may create problems in the optic nerve. Of the forty-five eye size/polar entry angle combinations explored in this study, each of which included 3 beams with the nominal azimuthal entry angles, none resulted in any portion of the optic nerve receiving a dose exceeding 1 Gy.

None of the treatment scenarios resulted in any portion of the CRA receiving 1 Gy or more. The ICRP has cited animal studies in which no retinal vascular changes were seen in rats irradiated with an 8 Gy proton beam (ICRP, 2012). Therefore, it seems unlikely that there would be any radiation-induced complications to the CRA for patients treated with the IRay System.

For some of the larger polar beam angles, portions of the non-macular retina receive a dose approaching the macular target dose. However, the percent volume receiving this larger dose is very small. Less than one-third of all eye size/polar entry angle combinations resulted in doses 1 Gy or greater to more than 1% of the retinal volume. Furthermore, only two of the combinations (34 degree polar angle for the 20 and 22 mm eye) showed more than 1% of the retinal volume receiving 10 Gy or more. Given that the majority of the retina receives a very small dose and the absence of complication in other EBRT and brachytherapy studies (Evans et al., 2010; Finger et al., 1996; Finger et al., 1999; Finger et al., 2003; Finger and Kurli, 2005; Jaakkola et al., 1998; Jaakkola et al., 2001; Jaakkola et al., 2005; Zambarkji et

al., 2006), it seems unlikely that any radiation-induced sight-limiting complications would be expected in patients treated with the IRay System. Indeed, in a three-year follow-up of 34 patients receiving 24 Gy from intravitreal brachytherapy, only one patient showed any microvascular changes associated with radiation; furthermore, their visual acuity was unaffected (Avila et al., 2012).

For most scenarios, no portion of the ciliary body received more than 35 Gy, with the largest doses seen in the 20 mm eye due to overlap of the dose profiles of the beams. Maximum doses trended down through the 24 mm eye, but increased in the 26 and 28 mm eyes. The decrease is caused by less overlap of the beam dose profiles, with the increase coming as a result of larger surface doses needed for a single beam entry. This dose is larger because the increased tissue path length to the macula target requires a longer treatment time and the anterior portion of the larger eyes is closer to the source. For shallow polar angles, portions of the ciliary body in the 20 mm eye received doses approaching 45 Gy, though the volumes receiving these larger doses are less than 0.5% of the total volume. In all cases, less than 25% of the volume of the ciliary body received 1 Gy or greater. The ICRP recommends a dose limit of 55 Gy to muscle tissue based upon evidence from 2 Gy fraction schemes (ICRP, 2012). While the IRay System is a single fraction treatment, the ciliary body is a parallel structured tissue and large point doses should not affect the entire ciliary body systematically. This conclusion is supported by the results of the INTREPID trial, in which no adverse radiation related events were seen (Jackson et al., 2013).

A potentially significant dose to the lens was measured in treatment simulations of small polar beam angles that are outside the current range of clinical use for the IRay System. While the volumes receiving large doses were generally small, there is still a possibility of causing opacities that could eventually lead to cataracts if smaller polar beam angles were allowed. There has been an increased focus upon dose received by the lens, as the ICRP has recently lowered their recommended threshold for radiation-induced cataracts down to 0.5 Gy for both acute and fractionated exposures (ICRP, 2012). The results of this study show that, for beam polar angles of 26 degrees or greater, no portion of the sensitive volume of the lens would receive a dose of 0.5 Gy or greater. A proprietary beam algorithm to check beam clearance is employed by the IRay System which prevents treatment at shallow polar beam angles that could potentially cause these complications.

5. Conclusions

Given the small influence of eye size on ocular tissue doses, the natural variation in the eye size within the typical patient population will have minimal impact on the treatment planning for this AMD therapy. While beam polar angle can have a significant effect on tissue dose, steps have already been taken to ensure that only beam polar angles resulting in a dose of less than 0.5 Gy to the sensitive volume of the lens are used clinically. Therefore, proper selection of beam polar angle within the typical patient population will reduce concern for dose to non-targeted tissues with Oraya Therapy.

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Figure 1. Schematic of eye and treatment geometry. Top: Geometric description of the stylized MCNPX eye model employed in this study. Bottom Left: Sagittal view with the 6 o'clock beam in isolation. Bottom Right: Frontal view with all three treatment beams.

Figure 2.

Absorbed dose to non-targeted tissues as a function of eye size; beam polar angle fixed at 26 degrees. A: Ciliary Body. B: Lens. C: Sensitive Volume of the Lens. D: Retina. E: Optic Nerve. F: Central Retinal Artery.

Figure 3.

Absorbed dose to non-targeted tissues as a function of beam polar angle in the 22 mm eye. A: Ciliary Body. B: Lens. C: Sensitive Volume of the Lens. D: Retina. E: Optic Nerve. F: Central Retinal Artery.

Table 1

Volume of eye tissues as a function of axial length (all units in cm^3)

Axial Length	Ciliary Body	Lens	SV of Lens	Retina	Optic Nerve	CRA
20 mm	0.150	0.129	0.015	0.159	0.215	0.0000302
22 mm	0.181	0.174	0.021	0.211	0.261	0.0000302
24 mm	0.228	0.221	0.024	0.253	0.310	0.0000302
26 mm	0.271	0.293	0.039	0.323	0.364	0.0000302
23 mm	0.295	0.356	0.045	0.395	0.422	0.0000302

Table 2

Materials assigned to the tissues of the eye model from ICRU Report No. 46

Eye Lens	Water	Brain	Soft Tissue (male)
Lens	Vitreous Fluid	Optic Nerve	Cornea
SV of Lens		Optic Nerve Sheath	Iris Ciliary Body Retina Sclera CRA