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Computational Assessment of Dose for Stereotactic Radiosurgery of Age-Related Macular Degeneration

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Purpose:

Age-related macular degeneration (AMD) is a leading cause of vision loss in the elderly population with limited treatment options. Radiation therapy options for the treatment of the wet form of the disease have been explored previously. Research for a treatment option involving kilovoltage stereotactic radiosurgery (SRS) is currently under development, specifically with the design of the IRay^{TM} device (Figure 1), which addresses many of the inherent limitations of other radiotherapy systems used previously to treat AMD.[1] The goal of this therapy is to destroy choroidal neovascularization beneath the pigment epithelium via delivery of three 100 kVp photon beams entering through the sclera and overlapping on the macula delivering up to 24 Gy of therapeutic dose over a span of approximately 5 minutes. The divergent x-ray beams targeting the fovea are robotically positioned and the eye is gently immobilized by a suction-enabled contact lens. Design of the IRay^{TM} device requires patient-specific assessment of radiation doses to non-targeted tissues.

Methods:

With Institutional Review Board approval (IRB #481-2007 University of Florida), 40 CT scans were obtained from Shands Hospital at the University of Florida for retrospective analysis. The gender distribution was 20 male and 20 female. The requirements for eligible CT sets included (1) maxillofacial axial scans, (2) 1 mm slice resolution, (3) soft tissue contrast settings, and (4) patient age over 18 years. The CT scans were analyzed using the image processing code *3D-DOCTOR^{TM}* and 16 were selected for three-dimensional reconstruction, accomplished by contouring anatomical structures of interest within the axial slices (Figure 2). The resulting polygon mesh files (Figure 3) were exported to *Rhinoceros 4.0^{TM}* to prepare each eye for Monte-Carlo based treatment simulation. This was accomplished by: (1) locating the center of the optic disc (approximated from the three-dimensionally reconstructed optic nerve), (2) determining the position of the posterior pole (3.3 mm lateral to optic disc center), (3) determining the position of the fovea (1.25 mm lateral and 0.5 mm inferior to the posterior pole), (4) locating the apex of the cornea from the three-dimensionally reconstructed globe, (5) aligning the treatment axis to intersect the fovea and to be parallel with the geometric axis, which is defined as the intersection of the posterior pole and the apex of cornea, (6) insertion of cylinder with 4 mm diameter and 0.5 mm thickness coincident with the fovea representing the macula tissue, and (7) tagging each structure with a tissue name for voxelization. The dimensions used for steps 2 and 3 (Figure 4) were derived from analysis of fundus images, from 100 healthy volunteers (Arnoldussen ME, et al. IOVS 2009; 50: ARVO E-Abstract 3789). Each model was voxelized to 0.5 mm x 0.5 mm x 0.5 mm resolution using an in-house *MATLAB^{TM}* code. MCNPX 2.5.0 (Los Alamos National Laboratory, Los Alamos, NM) Monte Carlo radiation transport code was used to simulate stereotactic radiosurgery. A total of 10^7 x-ray photon histories were completed for each simulation, and the resulting statistical errors for tissue-averaged dose tallies were found to be less than 1% for whole tissues and ranged from 0.6% to 2% for each macula voxel. The output data was scaled to report doses to non-target tissues for a 3 beam x 8 Gy (cumulative 24 Gy) treatment dose to the macula tissue.

Figure 1: IRay^{TM}
(Oraya Therapeutics, Inc., Newark, CA)

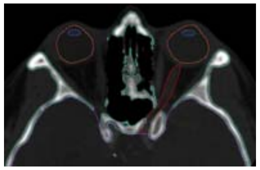

Figure 2: CT image with the following organs segmented: lens, globe of the eye, optic nerve, brain, bone, and skin
(skin contour not shown here)

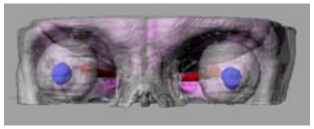

Figure 3: Three-dimensionally reconstructed polygon mesh model

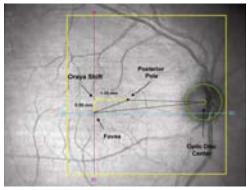

Figure 4: Foveal shift

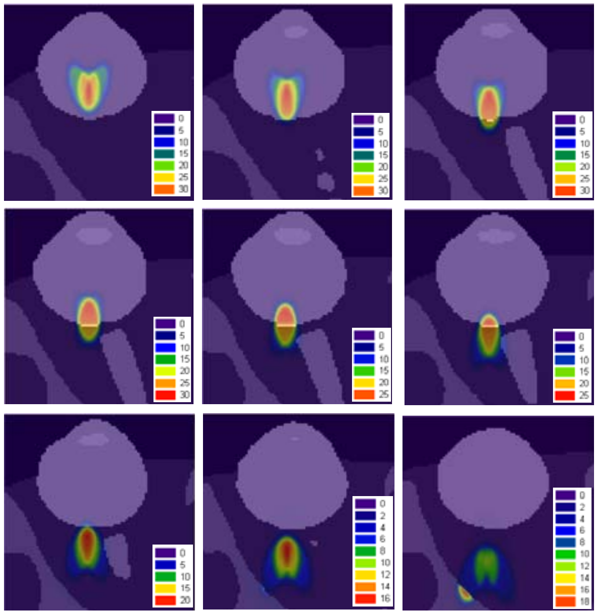

Figure 5: Dose contour maps for patient model *mer*. Image progression is from inferior (Top left) to superior (Bottom right) in 1 mm intervals, with the (Center) median slice intersecting the middle of the macula target. Legend units are in Gy.

Results:

Table 1: The highest tissue-averaged doses received from the set of 32 eyes undergoing treatment simulation and the associated eye model.

Tissue	Beam I		Beam II		Beam III		Total	
	mGy		mGy		mGy		mGy	
macula	8000		8000		8000		24000	
lens	72	(mar)	56	(fjl)	64	(fal)	175	(fal)
optic nerve	1275	(fkl)	447	(mol)	1017	(fmr)	1651	(fkl)

Table 2: The gaze angles, voxelized optic nerve volume, and percentage of that volume receiving more than the absorbed dose listed, representing the dose distribution, for a cumulative 24 Gy treatment dose to the macula. Computational error for dose has been incorporated.

Model	Vertical Gaze Angle	Horizontal Gaze Angle	Optic Nerve Voxel Volume	0.5 Gy	1 Gy	5 Gy	12 Gy
	degrees	degrees	mm³	%	%	%	%
Both vertical and horizontal gaze are clinically realistic							
fkr	9.0	-3.2	556.8	6.5	2.2	0.4	0
fml	9.5	2.2	664	10.4	4.4	1.8	0.5
mel	-0.5	-1.0	632.5	12.8	6.4	3.2	0.5
mer	-1.0	-0.3	621.9	5.3	1.7	0.4	0
mkl	5.2	-2.9	599.4	14.7	6.9	3.3	1.0
mkr	8.7	1.2	702.8	8.1	3.1	1.2	0.2
mll	7.2	-4.4	523.8	16.9	8.8	3.5	0.4
Either vertical or horizontal gaze is clinically realistic							
mlr	4.5	-6.0	640.3	13.4	7.4	3.0	0.2
fkl	8.7	-16.4	521.6	35.7	23.7	11.9	1.1
mml	-1.6	-16.7	590.6	24.0	14.2	7.0	0.8
fnr	12.6	-18.1	704.9	33.7	26.0	3.6	0
far	-3.6	3.3	551.3	7.9	2.9	0.8	0
mar	-6.0	-1.5	566.8	6.9	2.2	0.7	0
ffl	-10.9	-3.3	287.8	12.0	3.2	0.8	0
for	-17.7	-0.5	460.5	4.5	0.9	0	0
fol	-20.2	-2.6	547.1	5.1	1.8	0.7	0.1
Neither vertical or horizontal gaze is clinically realistic							
fcr	-2.4	-6.0	410.3	9.0	3.4	0.5	0
mgr	-3.3	-19.0	909.1	10.4	6.8	3.5	0.5
mal	-3.4	-3.9	431	15.1	7.6	4.0	1.2
mgl	-4.4	8.6	686.1	11.5	6.1	3.1	0.9
mor	22.1	-14.5	445	10.0	4.7	0.8	0.1
fal	-4.8	-6.1	482.4	17.9	9.6	4.3	0.7
mfr	-7.4	-18.9	621.9	9.8	4.9	2.3	0.3
ffr	-7.5	-8.5	356.5	6.9	1.4	0.2	0
mmr	-7.9	-17.5	640.1	16.1	11.1	4.2	0
fcl	-8.5	-8.1	588.8	14.9	7.0	2.9	0.4
mfl	-8.6	-5.4	776.4	13.2	7.4	4.1	1.2
mol	30.1	-29.8	480	34.9	21.4	8.5	0.9
fdr	-34.4	-8.7	207.9	6.0	0.9	0	0
fdl	-34.6	7.2	259.1	7.3	1.2	0.2	0
fjr	-41.4	19.8	395.0	3.7	0.5	0.1	0
fjl	-46.5	-28.0	728.6	8.8	3.7	2.1	1.0

Discussion:

A recent study suggests that the optic apparatus may be able to receive up to 14 Gy without risk of developing RON.[2] Despite the variability of the location of the optic nerve observed in this study, the highest cumulative tissue-averaged dose received was 1.65 Gy by model *fkl* (Table 1). This patient demonstrated a lateral horizontal gaze of roughly 16°, outside the range of clinically relevant horizontal gaze angles. Ultimately, the risk of developing RON is negligible for all simulated patient models in this study given the dose volume data presented in Table 2.

The tissue-averaged dose threshold for radiation cataractogenesis is 700 mGy.[3] The highest tissue-averaged dose observed in the present study was 175 mGy (Table 1).

The threshold for development of necrosis in brain tissue due to radiological toxicity is 12 Gy for volumes 5 cm^3 and larger.[4] No brain voxels received a dose greater than this threshold in this computational study.

Conclusions:

The computational assessment performed indicates that a previously established therapeutic dose can be delivered effectively to the macula with the scheme described without the potential for complications to non-targeted radiosensitive tissues.

Key References:

[1] Gertner M, Chell E, Pan KH, Hansen S, Kaiser PK, Moshfeghi DM. Stereotactic targeting and dose verification for age-related macular degeneration. Med Phys 2010;37(2):600-606.

[2] Hasegawa T, Kobayashi T, Kida Y. Tolerance of the optic apparatus in single-fraction irradiation using stereotactic radiosurgery: evaluation in 100 patients with craniopharyngioma. Neurosurgery 2010;66(4):688-694.

[3] Worgul BV, Kundiyev YI, Sergiyenko NM, et al. Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exporsures. Radiat Res 2007;167(2):233-243.

[4] Lawrence YR, Li XA, el Naga I, et al. Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S20-S27.

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