The Impact of Optic Nerve Movement on Intracranial Radiation Treatment

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Research Article

Abstract

Purpose: In radiotherapy, high radiation exposure to optic nerve (ON) can cause optic neuropathy or vision loss. In this study, we evaluated the pattern and extent of the ON movement using MRI, and investigated the potential dosimetric effect of this movement on radiotherapy.

Methods: Five volunteers were requested to gaze toward five directions during MRI acquisitions, including neutral (straight forward), left/right (horizontal movement), and up/down (vertical movement). The motion of the ON was analyzed quantitatively. To evaluate the potential dosimetric effect of this motion, the ON motion was hypothetically applied to three patients with perioptic tumors.

Results: The motion of ON followed a nearly conical shape among all five subjects. The anterior end of ONs moved with 10.4 ± 2.2 mm and 11.1 ± 1.4 mm horizontally for the left and right eyes, and 9.3 ± 0.8 mm vertically for the right eye. Posterior end of ON has negligible displacement. In the three clinical scenario, the hypothetical movement of ON in this measured range introduced non-negligible dosimetric effect.

Conclusion: The range of motion of the anterior portions of the optic nerves is on the order of centimeters, which may need to be considered with extra attention during radiation therapy workflow.

Introduction

Radiation-induced optic neuropathy (RION) is a severe potential ocular complication in patients treated with radiotherapy [1]. RION often presents as an acute, profound, and irreversible loss of vision about 10–20 months after radiation exposure [2]. It is believed that necrosis resulting from an overdose of radiation to the anterior visual pathway (AVP) is the primary cause of RION. Dosimetric studies have demonstrated that RION can occur when the cumulative dose to the AVP exceeds 50 Gy for conventional fractionation, or beyond 10Gy in a single fraction [2].

During radiation treatment, a planning margin, either a planning target volume (PTV) relative to clinical target volume (CTV) or planning risk volume (PRV) relative to organs at risk (OAR), is typically given to compensate for inter-/intrafractional motion and setup uncertainties. A 3–5 mm expansion is used for the optic apparatus in conventional radiation treatment, and a 0–1 mm expansion is used for single-/hypofractionated stereotactic radiosurgery (SRS). This concept is particularly crucial in SRS treatments, as the sharp dose falloff required near critical structures necessitates the reduction of small positional uncertainties that could have a sizable effect on radiation dose.

Compared to the optic chiasm [3], the range of movement for the optic nerve is higher. It has been documented that the optic nerve moves a mean distance of 11.8 mm during a 3-minute MRI scan[4]. Furthermore, instructing patients to fix their eyes on a single point for 5 minutes, or to close their eyes, did not significantly reduce movement [5]. These findings implied the occurence of non-negligible movement of the optic nerve, which may effect the dose exposure during radiotherapy. An accurate understanding of

the magnitude of optic nerve movement is fundamental to the development of intracranial radiation treatment plans that minimize the risk of RION. The purpose of this study is to investigate the pattern and extent of optic nerve motion using serial MRI scans, and evaluate the potential dosimetric influence of this motion in representative patients with perioptic tumors.

Results

Representative Images Showing Movement Pattern

A representative case showing optic nerve movement in the left-right (L-R, axial plane) and superior-inferior (S-I, sagittal plane) directions is displayed in Figs. 1 and 2. The middle images demonstrate the neutral position with the subject looking straight forward, while the lateral images demonstrate the subject gazing in different directions. It is evident that the optic nerves move in the opposite direction relative to the lens. When the subject's gaze was guided to the left, the optic nerves moved to the right, whereas when the subject was instructed to gaze upwards, the optic nerves moved downwards. Additionally, regardless of eye movement, the posterior end of the optic nerve, where it exits the optic canal, demonstrated minimal movement. As such, the anterior end had a larger magnitude of displacement relative to the posterior end.

Motion Assessment

Movement was assessed via both horizontal and vertical movement. As shown in Table 1, the anterior end (AE) moved in the range of centimeters horizontally, with an average of 10.4 ± 2.2 mm and 11.1 ± 1.4 mm for the left and right eyes, respectively. Conversely, the posterior end (PE) had minimal movement, being within 1 mm. The middle point (MP) movement is equivalent for both eyes and is about half of the AE movement, with 5.1 ± 1.3 mm both the left and right eyes. The same motion pattern was observed regarding vertical movement. The anterior end moved with an average distance of 9.3 ± 0.8 mm going up/down, and the posterior end connecting to the optic canal showed minimal motion. From these results, it can be postulated that the optic nerve rotates around the PE, where it exits the optic canal, and moves within a conical shape, as shown in Fig. 3.

Repeatability:

Horizontal movement was tested in the three younger subjects (S1-S3). The mean differences were 1.1 mm for left eye and 1.2 mm for the right eye while the maximal differences for the left and right eyes were 2.7 and 3.8 mm respectively.

Dosimetric Impact

Three clinical cases were selected to evaluate the dosimetric impact of possible optic nerve motion. Two cases (Patients #1 and 2) had optic nerves in close proximity to the target volumes, while a third case (Patient #3) had an optic nerve sheath meningioma where the nerve was part of the target volume itself.

A conical shape with fixed PE and a 5 mm expansion for the AE was used to create a motion-inclusive planning optic nerve margin for all cases to evaluate the dosimetric impact further.

Patient #1, as shown in Fig. 4, was diagnosed with a meningioma that treated with two partial arcs to a total dose of 6600 cGy in 33 fractions. In the original treatment plan, a conventional 3 mm expansion was used to create the optic nerve PRV. According to the latest QUANTEC recommendation for conventional fractionation [6], the estimated risk of toxicity for the optic apparatus is < 3% when the maximum point dose, D_{max} is less than 55Gy, 3%-7% if D_{max} is within 55-60Gy, and 7−20% when D_{max} is larger than 60Gy. In the patient's original plan the D_{max} of the optic nerve is approximately 52 Gy (Table 2), which is within the tolerance limit; however, with the consideration of possible optic nerve movement, the D_{max} could have increased to 56 Gy, falling into the range of increased risk (3−7%) for developing optic neuropathy (RION).

Patient #2, as shown in Fig. 5, was diagnosed with a perioptic pituitary adenoma treated with hypofractionated SRS to a total dose of 2500 cGy in 5 fractions. When utilizing the motion-inclusive margin, the maximum dose $D_{0.035\,cc}$ (the dose covering the 0.035cc volume receiving highest dose), as shown in Table 2, increased from 24.4 Gy (clinically acceptable) to 25.2 Gy, which is above the dose constraint of 25 Gy, in accordance with AAPM TG-101 [7]. The $D_{0.2cc}$ (the dose covering the 0.2cc volume receiving highest dose) increased from 22.9 Gy to 23.4 Gy, which also exceeded the recommended dose constraints (≤23Gy) as per protocol [7].

Patient #3, as shown in Fig. 6, was diagnosed with an optic nerve sheath meningioma with a large portion of the optic nerve itself being targeted with proton beam therapy to a total relative biologically effective (RBE) dose of 5220cGy in 29 fractions. The PTV percent volume that received at least 95% of the prescription dose (D_{95}, yellow) with conventional 3mm expansion from the GTV was 95% of the prescription dose in the treated plan; however if the motion-inclusive expansion PTV (purple) was utilized, the D_{95} target coverage actually dropped to 92%, as shown in Fig. 6a. The minimum dose, D_{min}, to the gross tumor volume (GTV) also dropped from 95% of the prescription dose in the treated plan to 90% with the motion-inclusive expansion as shown in Fig. 6b.

Discussion

The purpose of this study was to identify the extent of optic nerve motion using MRI and to further evaluate the dosimetric impact on perioptic lesions that have undergone radiation treatment. Optic nerve motion was found to be in the opposite direction of globe motion and followed a nearly conical shape. The displacement of the PEs of the optic nerves, where they adjoin the optic canal, was minimal (within 1 mm) in all subjects, yet the displacement of the AEs of the nerves, where they connect to the globes, could be over 10 mm. A simple rigid motion model was applied to three clinical scenarios to evaluate the dosimetric effects of optic nerve movement based on the finding of this study. In these three cases, non-negligible dosimetric changes were observed.

A few studies have investigated optic nerve motion previously. Clarke et al. [8] demonstrated that by having patients look at different sides the optic nerves could move up to 6 mm as compared to the neutral position, based on CBCT images of four patients. In a study investigating optimal MRI sequence design for optic nerve disease by Moodley et al. [4], it was found that the mean total distance that the optic nerves travel during eye movement was 11.8 mm; however, none of these prior studies systematically evaluated the movement patterns for the optic nerves in multiple directions, nor did they further assess the dosimetric impact of these movements.

Although the absolute risks of RION remain relatively low in most patients, the risk for toxicity increases exponentially as therapeutic dose increases. This is especially true in patients with perioptic lesions such as meningiomas, pituitary adenomas etc.,, where hypofractionated SRS can be the definitive treatment. Due to sharp dose falloff required near critical structures with SRS, even small uncertainties in position could have a sizeable effect on the radiation dose delivered. The risk of RION can be further increased in patients who have undergone prior radiation treatments to the same area, where avoiding excessive dose to the optic nerve is crucial. For SRS, most clinical sites use either no margin or 1 mm margins for the optic nerve contours/PRV. For conventional external beam treatment, a 3 to 5 mm margin is generally used, pending image guidance and treatment technique. The results obtained from this study demonstrated that the displacement of the optic nerves as patients change the direction of their gaze can exceed these defined margins, and this may lead to insufficient dosing to the target volume if the tumor is of the optic nerve (i.e., optic sheath meningiom), or excessive dosage to the organs at risk (i.e., optic nerve itself) if the PTV is adjacent to the nerve. It should be noted that the three clinical scenarios were evaluated assuming patients kept staring at sideways throughout the treatment. For conventionally fractionated external beam radiation therapy, treatment is divided into multiple fractions over a longer course of. The eyeball movement will most likely be averaged out in all directions. This differs with SRS, where optic nerve motion could result in a higher impact, especially for patients treated with high-dose-rate beams (e.g. 1400MU/min for 6FFF beam). Additionally, a majority of patients treated in radiation oncology are simulated with CT images, which only take a few to tens of seconds. If the patient is simulated with optic neves at non-neutral positions the dosimetric estimation regarding the nerves itself could be inaccurate since the treatment plan was purely generated based on that image set. A possible solution to this could be that patients may need to be counseled to look straight ahead (or in a pre-determined direction based on target location) or to utilize eye-tracking if deemed necessary [9, 10]. Furthermore, during treatment, it may be benifical to guide the patient to look towards the desired optimal side/direction, in order to minimize the radiation dose to the optic nerve. Nevertheless, data on how far and frequently the patients move their eyes during the entire course of radiation treatment and how stable the optic nerve can stay at neutral position with/without couching, although beyond the scope of the current study, warrants larger-scale clinical investigations.

This study has a few limitations. First, to shorten the imaging acquisition time for improved patient comfort, two-dimensional imaging sequences with relatively thick slices (3mm) were used. Even though the in-plane resolution is relatively high (0.7 mm), the thicker slices could still lead to uncertainty in the measured range of movement. Given the imaging parameters, this uncertainty should not exceed 1−2

mm, in order to avoid affecting the conclusion of this study. In addition, a rigid movement model was assumed throughout the course of the study. The optic nerve, being an organ consisting of soft tissue, deforms with motion. Based on imaging results, the anterior portion of the optic nerves, which are close to the posterior walls of the globes, followed the rotation of the globes and bent towards their posterior aspects. This slightly reduces the actual movement of the optic nerves following the motion of the globes. The rigid movement model used in this study serves as a conservative estimate for the range of motion. It also shows that optic nerves maintain linear shapes following movement. This is consistent with the findings that displacement of the middle points of the optic nerves is always close to half of the displacement values measured for the anterior portions. Therefore, a rigid movement model, which may overestimate the movement slightly, should still provide a very reasonable and relatively accurate estimation of the range of motion. Finally, the clinical impact of the dosimetric changes found based on the motion-inclusive model is difficult to assess and a prospective study would better eludicate the overall impact on reducing the incidence of RION or improving tumor control.

Conclusion

In this exploratory study that included five healthy volunteers, the optic nerves were found to follow a nearly conical shape relatively to the motion of the eyes. The range of motion of the anterior portions of the optic nerves was on the order of centimeters, which exceeds the current considerations in the field of clinical radiation oncology. Special attention may be needed for radiation simulation, treatment planning, and treatment monitoring to avoid excessive dosage to the optic nerves, or to ensure sufficient coverage of the target on the optic nerves, depending on varying clinical scenarios.

Methods

Volunteers and Image Acquisition

The MRI study was approved by the Institutional Review Board at University of Virginia, and all experiments were performed in accordance with guidelines and regulations relevant to this study. Five healthy volunteers without any orbital or optic apparatus abnormalities were recruited with informed consent obtained, including three young subjects (ages 24, 30, and 35 yrs, all males) and two older subjects (a 65-year-old female and a 67-year-old male). MRIs were performed on a 3T MR scanner (Siemens Magnetom Prisma, Erlangen, Germany) with a 64-channel head/neck coil. Images were taken with T2-weighted FLAIR-HASTE acquisition (duration: 50–74 seconds, resolution: 0.7 x 0.7 x 3.0 mm^3, slice number 8–12 slices, TE/TR = 90/3060ms, GRAPPA factor = 4). All subjects were scanned in the supine position and were instructed to gaze in five different directions during MRI acquisitions: neutral (straight forward), left/right (horizontal movement), and up/down (vertical movement). Axial plane images were acquired for both eyes to assess horizontal motion and sagittal plane images of the right eyes were obtained to evaluate vertical motion. To be able to reproduce eye motion, extra scans

assessing horizontal movement were taken on two different days within a 14-day window for the three younger subjects.

Motion Assessment

On day 1, a baseline was established using the acquired MRI with the eyes in the neutral position. All other scans captured at different eye positions or on different days were rigidly aligned to the baseline using Velocity (Varian Medical Systems, Palo Alto, CA). Three measurement points were created, an anterior end connecting to the globe, a posterior end connecting to the optic canal along each optic nerve, and a middle point with equal distance between the optic nerve and the anterior/posterior ends. The L-R displacement was calculated along the axial plane to represent the horizontal movement of the eyes, while the S-I motion was assessed along the sagittal plane to represent vertical movement. The reproducibility of these points was also evaluated by comparing the repeated results to the initial ones. Furthermore, a new motion-inclusive model was constructed based on the pattern of physiological movement of the optic nerve established from this study using Solidworks (Dassault Systèmes, Velizy-Villacoublay). Finally, the extent of movement was determined from the average displacement of the optic nerve as measured in the five volunteers.

Dosimetric Impact

To evaluate the potential dosimetric effect of optic nerve movement, three patients with perioptic tumors (defined as a lesion within 3–5 mm of the optic nerve) were identified: Patient #1 was diagnosed with a meningioma that was treated with external beam radiation utilizing two partial arcs to a total dose of 6600 cGy in 33 fractions on a Truebeam (Varian Medical Systems, Palo Alto, CA); Patient #2, was diagnosed with a pituitary adenoma that was treated with hypofractionated stereotactic radiosurgery to a total dose of 2500 cGy in 5 fractions using the Gamma Knife Icon™ (Elekta, Stockholm, Sweden); and Patient #3, who was diagnosed with an optic nerve sheath meningioma treated with proton beam therapy to a total dose of 5220cGy RBE in 29 fractions with the Mevion S250 Proton Therapy System (Mevion Medical Systems, Littleton, MA).

The planning images (CT or MRI), plan dose, and contours were transferred to Eclipse (Varian Medical Systems, Palo Alto, CA) for direct comparison. We then further simulated the effect of optic nerve movement by creating a new estimated contour that was conically expanded from the original contour, effectively generating a motion-inclusive margin. The maximum point dose (D_{max} or $D_{0.035cc}$) and $D_{0.2cc}$ to the optic nerve on both the conventional and motion-inclusive margin models were obtained, while the D_{min} to the GTV and D_{95} for the PTV were reported in the worst-case scenarios and then compared with the actual/original values.

Declarations

AUTHOR CONTRIBUTION:

K. Q. set up the MR protocols, analyzed the data and wrote the manuscript

K.N. and A.C. designed the study, provided patient data, evaluated treatment plan, and revised the manuscript

J. S. evaluated the MR protocols, supervised the MR studies

J.W. provided patient data and evaluated the treatment plan

B.L. prepared Figure 2, 4, 5, and 6, assisted K.Q. to analyze the data, and revised the manuscript

X.F. scanned the healthy volunteers on MR scanner and assisted K.Q. to collect imaging data

T.C., Y.Z., J.Z., and X. W. provided patient data and helped K. Q. to generate comparison treatment plan

Q.C. analyzed the MRI data and assisted in manuscript writing

S.P. assisted in manuscript writing and data analysis

S. K. provided patient data and evaluated treatment plan

All authors reviewed the manuscript.

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Tables

Table 1. Horizontal movement of the optic nerves

	Horizontal Movement						Vertical Movement		
	Right Eye			Left Eye			Right Eye		
	L*->C*	C->R*	L->R	L->C	C->R	L->R	U*->C	C->D	U->D
Anterior(mm)	4.9±0.8	6.2±1.3	11.1±1.4	5.9±0.7	4.6±1.3	10.4±2.2	5.3±1.7	4.2±2.1	9.3±0.8
Middle(mm)	2.6±0.5	3.0±0.6	5.2±0.6	3.2±0.3	2.1±0.8	5.1±1.3	3.1±0.9	2.1±1.1	5.1±0.8
Posterior(mm)	0.7±0.3	0.5±0.2	0.8±0.3	0.3±0.4	0.3±0.2	0.4±0.2	0.4±0.3	0.4±0.3	0.5±0.3

*denotes five directions: L – Left, C-Center, R-Right, U-Upwards, D-Downwards

Table 2. Changes of maximal doses due to potential movement of optic nerves.

	D_{max} (Gy)	$D_{0.035cc}$(Gy)	$D_{0.2cc}$(Gy)	$D_{0.5cc}$(Gy)
Patient #1	52.0→55.7	50.0→51.6	47.1→49.4	42.9→45.3
Patient #2	26.9→31.6	25.6→26.3	22.9→23.4	13.4→12.8*

Values before and after symbol → are original doses and doses after potential movement of optic nerve. * decrease of D0.5cc is because the total volume of the optic nerve is 0.7cc. Even though the maximal dose increases, the minimal dose covering the 0.5cc volume decreases.
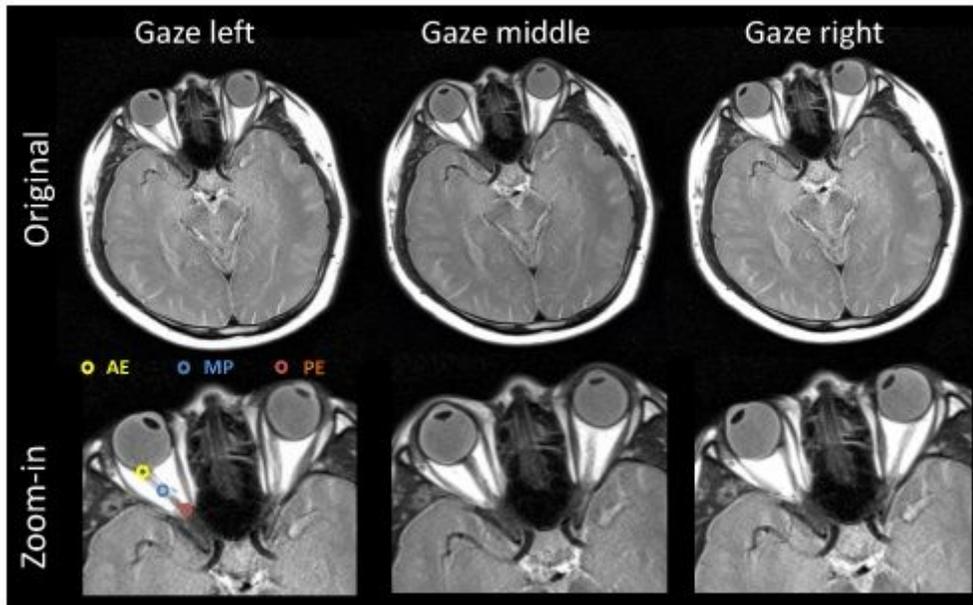
Figures

Figure 1

Representative images obtained from subject S1 (29-year-old male) for horizontal motion of the eyes. Optic nerve structure and measurement points are shown as: the anterior end (AE) of the optic nerve connects to the globe, the posterior end (PE) connects to the optic canal, and the middle point (MP) is the midpoint of the optic nerve. It is quite evident that the anterior ends of both optic nerves move quite substantially in the opposite direction of the motion of the eyes (lens), as compared to their locations when the subject is looking straight forward (gaze middle).
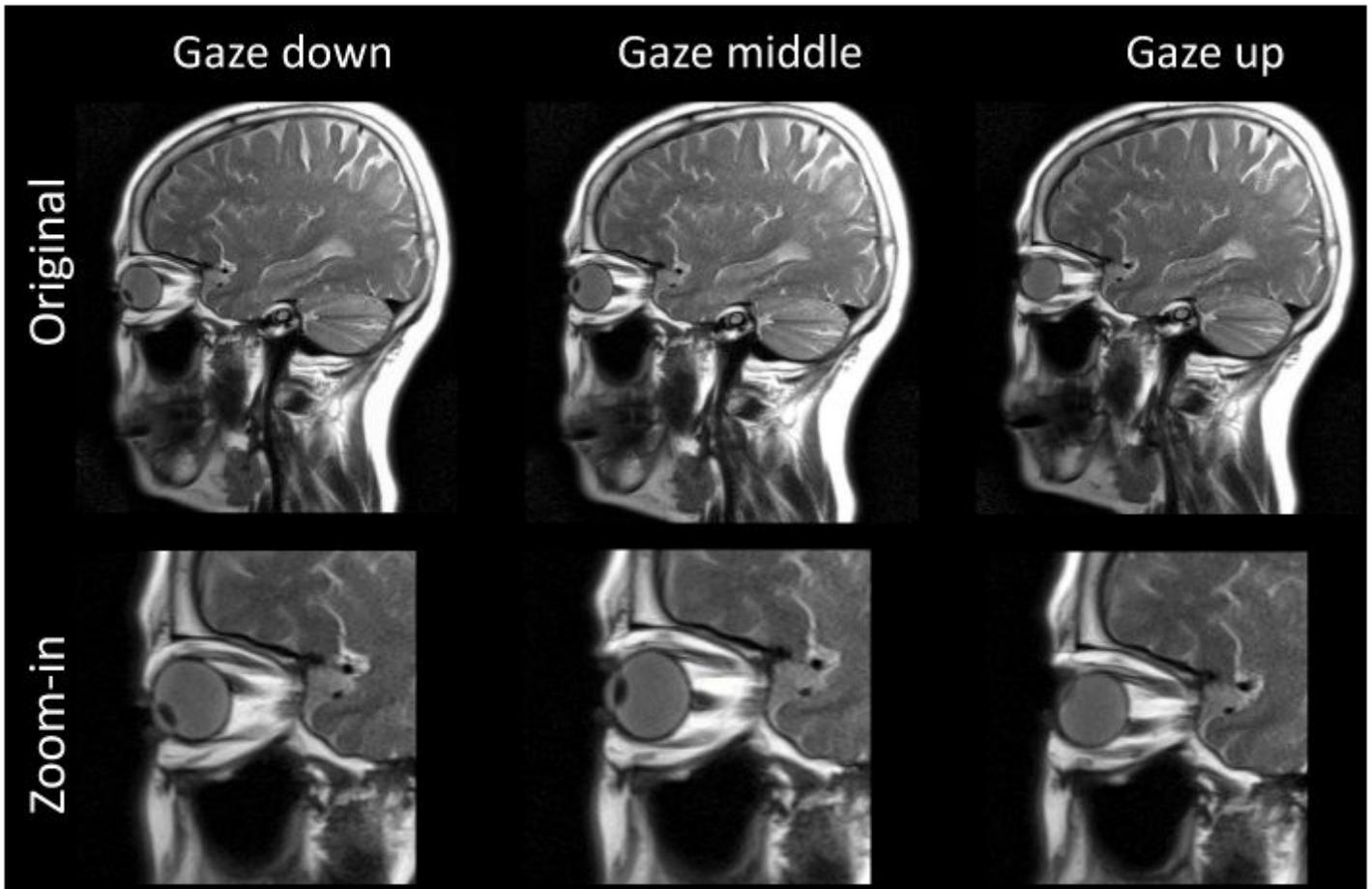
Figure 2

Representative images obtained from subject S4 (65-year-old female) for vertical movement of the eyes. Similarly, the anterior ends of both optic nerves move in the opposite direction of the vertical motion of the eyes (lens).
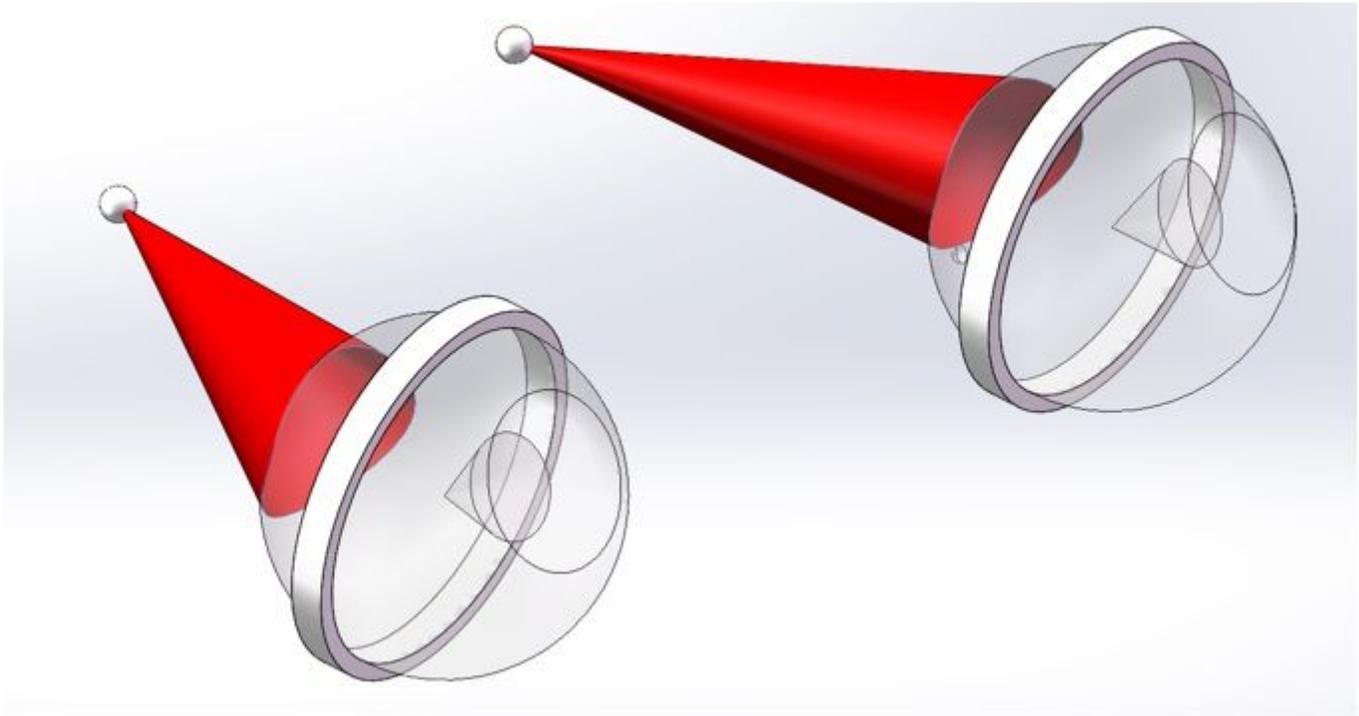
Figure 3

Images generated by Solidworks (Dassault Systèmes, Velizy-Villacoublay,), showing the range of motion (red) for the optic nerves based on measurement of anatomy gathered from MRI of subject S1.
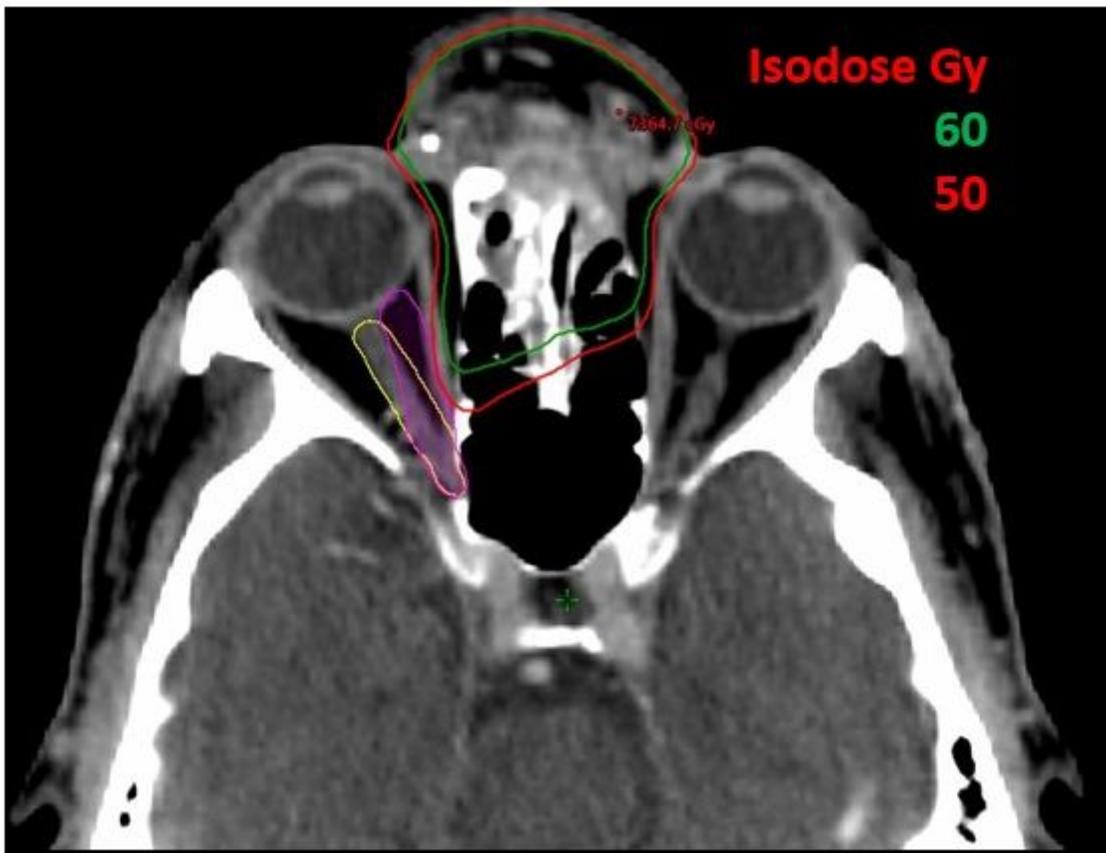
Figure 4

A 61-year-old male patient with skin cancer who was previously treated on Truebeam (Varian Medical Systems, Palo Alto, CA) for 66 Gy in 33 fractions. Original contour for optic nerve is shown in yellow and optic nerve with motion in worst scenario is shown in purple contour.
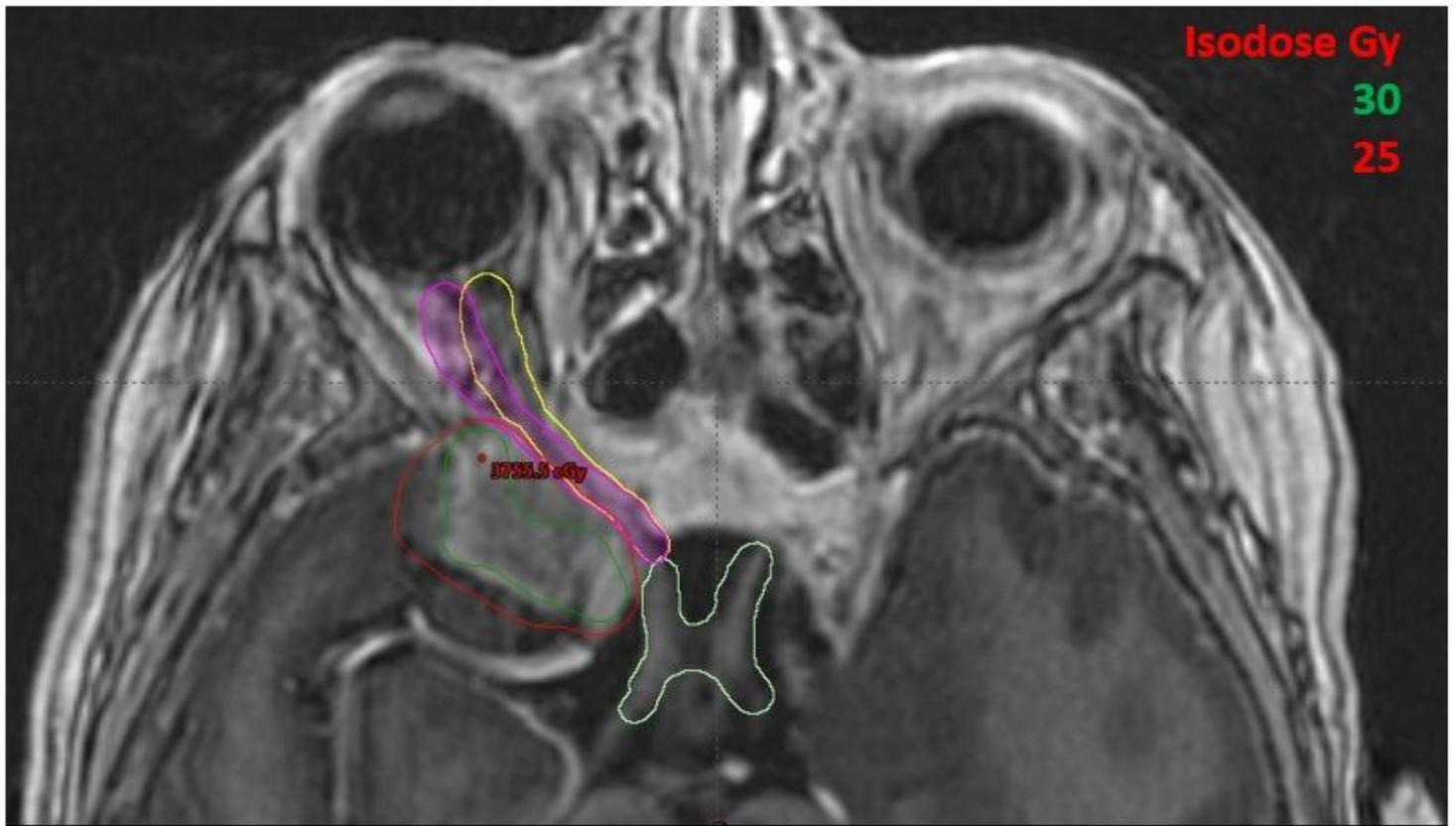

Figure 5

A female patient with a perioptic pituitary adenoma treated with hypofractionated SRS for 2500 cGy in 5 fractions. Original contour for optic nerve is shown in yellow and optic nerve with motion in worst scenario is shown in purple contour.
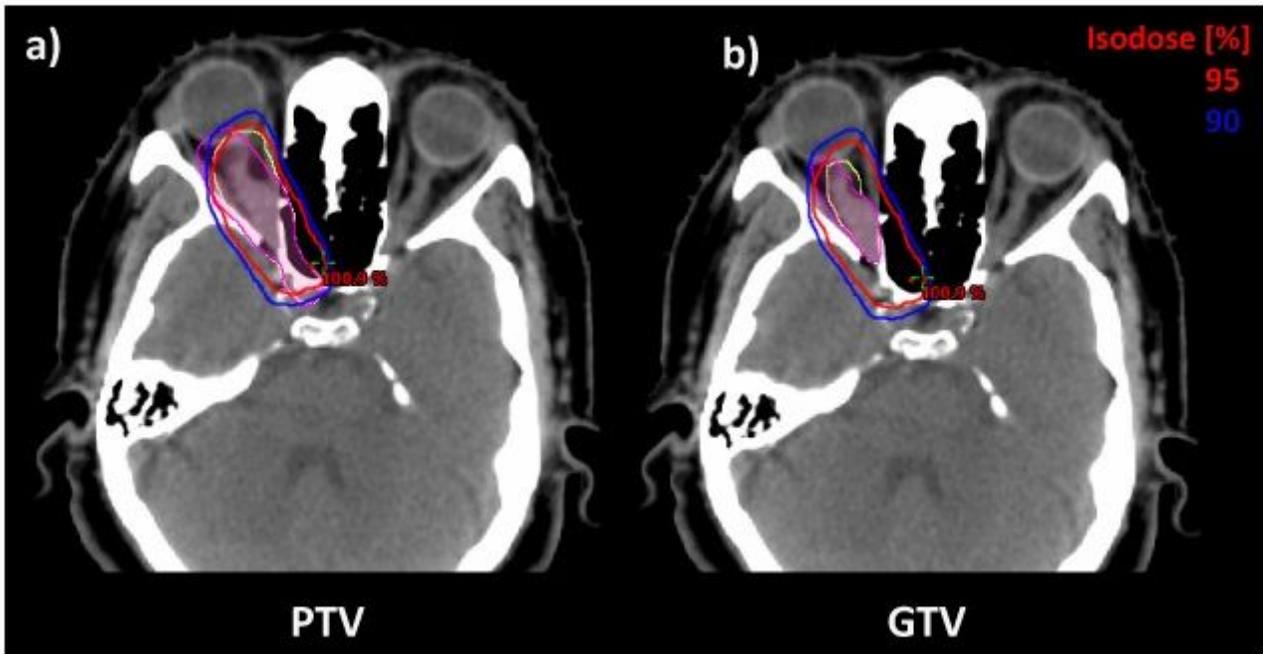
Figure 6

A 51-year-old female with a benign meningioma treated on the Mevion S250 Proton Therapy System (Mevion Medical Systems, Littleton, MA) for 52.2 Gy in 29 fractions. Original contours for GTV and PTV are shown in yellow and GTV and PTV moving with optic nerve in worst scenario are shown in purple contours.