Received:
13 February 2019

Revised:
26 April 2019

Accepted:
01 May 2019

<https://doi.org/10.1259/bjr.20190170>

Cite this article as:

Xiang M, Chan C, Wang L, Jani K, Holdsworth SJ, Iv M, et al. Physiological motion of the optic chiasm and its impact on stereotactic radiosurgery dose. *Br J Radiol* 2019; **92**: 20190170.

FULL PAPER

Physiological motion of the optic chiasm and its impact on stereotactic radiosurgery dose

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Objective: Avoidance of radiation-induced optic neuropathy (RION) from stereotactic radiosurgery (SRS) requires precise anatomical localization; however, no prior studies have characterized the physiologic motion of the optic chiasm. We measured the extent of chiasm motion and its impact on SRS dose.

Methods: In this cross-sectional study, serial MRI was performed in multiple planes in 11 human subjects without optic pathway abnormalities to determine chiasm motion across time. Subsequently, the measured displacement was applied to the hypothetical chiasm dose received in 11 patients treated with SRS to a perichiasmatic lesion.

Results: On sagittal images, the average anteroposterior chiasm displacement was 0.51 mm [95% confidence interval (CI) 0.27 – 0.75 mm], and the average superior-inferior displacement was 0.48 mm (95% CI 0.22 – 0.74 mm). On coronal images, the average

superior-inferior displacement was 0.42 mm (95% CI 0.13 – 0.71 mm), and the average lateral displacement was 0.75 mm (95% CI 0.42 – 1.08 mm). In 11 patients who underwent SRS to a perichiasmatic lesion, the average displacements increased the maximum chiasm dose (Dmax) by a mean of 14 % (range 6–23 %; $p < 0.001$).

Conclusion: Average motion of the optic chiasm was approximately 0.50–0.75 mm, which increased chiasm Dmax by a mean of 14%. In the occasional patient with higher-than-average chiasm motion in a region of steep dose gradient, the increase in chiasm Dmax and risk of RION could be even larger. Similarly, previously reported chiasm dose constraints may underestimate the true dose received during radiosurgery.

Advances in knowledge: To limit the risk of RION, clinicians may consider adding a 0.50–0.75 mm expansion to the chiasm avoidance structure.

INTRODUCTION

Stereotactic radiosurgery is a noninvasive means of treating intracranial lesions while minimizing effects on normal tissue. This is accomplished by precise delineation of critical structures, using highly conformal radiation plans with steep dose gradients, and ensuring accurate patient setup. One of the key critical structures in radiosurgical planning is the optic apparatus,¹ which spans the optic nerves, chiasm, and optic tracts.² Radiation-induced optic neuropathy (RION) can be manifested as decreased visual acuity, visual field deficits, or blindness.² While this feared complication is uncommon, occurring in 1–2% of patients in modern institutional series,^{2,3} prevention of RION nonetheless requires a high degree of confidence in localizing the components of the optic apparatus.

During radiosurgical treatment planning, the position of the optic chiasm has been regarded as static. As such, no

extra safety margin is added to the chiasm avoidance structure. Yet, the physiological motion of other critical neural structures has been well-documented, including movement of the optic nerves according to gaze changes⁴ and motion of the spinal cord due to cardiac pulsation and cerebrospinal fluid flow.^{5,6} By contrast, no prior studies have investigated the physiological motion of the optic chiasm. Some lesions, such as pituitary adenomas or meningiomas arising from the cavernous sinus or planum sphenoidale, may closely approach or abut the chiasm. Due to the sharp dose falloff required near critical structures, even small uncertainties in position could have a sizeable effect on radiation dose.

Therefore, an accurate understanding of the degree of physiological chiasm motion is fundamental to developing radiosurgical plans that minimize risk of RION. Here, we studied the extent of chiasm motion in 11 human subjects using serial MRI, from which we extrapolated the

hypothetical radiation dose to the chiasm in patients treated with radiosurgery to a perichiasmatic target.

METHODS

Magnetic resonance protocol and image acquisition
This retrospective, cross-sectional study was approved by the institutional review board. Our IRB did not require consent for retrospective collection and analysis of imaging data that were obtained as part of routine care. MRI data from 11 subjects at our institution, who were scanned for various clinical reasons (including evaluation of movement disorder, seizures, and vestibular schwannoma but without any orbital or optic apparatus abnormality), were collected from June 2017 to October 2018. MRI was performed on multiple 3 Tesla scanners (MR750 or 750W; GE Healthcare, Milwaukee, WI), equipped with an 8-channel head coil. Imaging of the optic apparatus was performed with balanced steady-state free precession imaging (bSSFP) [Fast Imaging Employing Steady-State Acquisition (FIESTA)] acquired during active eye movement. Parameters for the bSSFP sequence were as follows: repetition time/echo time (TR/TE): 5.7 ms/2.5 ms; flip angle 40°; slice thickness/gap: 2.1 mm/0 mm; matrix: 224 × 224; field of view: 160 mm; and 50 time frames. Three different sections of the chiasm were acquired in both the sagittal and coronal planes, resulting in a temporal resolution of 3.8 s for each slice, and scan time of 3:12 min for each plane. Cumulatively, each of the respective planar series had three image sets, each containing 50 images. Additionally, three sections of the optic nerves were acquired during eye movement in the axial plane to ensure that gross movement could be detected using this protocol.

Semi-automated chiasm delineation

Due to the submillimeter motion of the chiasm, a consistent method of delineating the chiasm contour was critical. This was accomplished by using a semi-automated segmentation procedure in MATLAB (R2018b, Natick, MA). First, an averaged (composite) image for each set of 50 images was produced, on which a rectangular region of interest (ROI) and a representative model chiasm contour were manually delineated. A custom MATLAB script then processed each image within the image set to automatically segment the chiasm based on the model contour. The ROI for each image was converted from grayscale to binary using varying thresholds based on Otsu's method.⁷ Next, object boundaries were detected using intrinsic functions from the MATLAB Image Processing Toolbox. Finally, the script selected the auto-contour maximizing edge strength (magnitude of the image gradient) along the boundary of the auto-contour, and similarity of shape and area of the auto-contour compared to the model contour. All auto-contours were visually inspected to ensure they were satisfactory.

Determination and quantification of chiasm displacement

To further safeguard against noise associated with the boundary of the chiasm auto-contours, chiasm displacement was measured according to movement of the auto-contour centroid (and not movement of the auto-contour boundary). In each image frame, the centroid of the auto-contour was determined using intrinsic

MATLAB functions. The maximal displacement of the centroid along each spatial axis (anteroposterior and superior-inferior for sagittal images; lateral and superior-inferior for coronal images) was calculated across the 50 images in each image set. As noted above, most subjects had three evaluable image sets in each of the respective planar series, only slightly offset from one another. Thus, in effect, each patient had three technical replicates. The median displacement measured among the three image sets was used.

Dosimetric and statistical analyses

Eleven patients treated at our institution from 2008 to 2017 with stereotactic radiosurgery to a lesion within 3–5 mm of the optic chiasm were identified by retrospective chart review. The radiation planning CT scan, radiation dose grid, and chiasm contour were transferred from the CyberKnife MultiPlan platform (Accuray Inc., Sunnyvale, CA) to MIM (MIM Software Inc., Cleveland, OH). The CT was resampled at a voxel size of 0.25 mm. Since the risk of chiasm injury is related to the highest doses it receives, we simulated the effect of chiasm movement by creating a new contour that was an expansion of the original contour, effectively generating a motion-inclusive planning organ at risk volume (PRV). The expansion in each direction corresponded to the displacement measured along that axis.

The dose to the highest 0.03 cc of chiasm (D0.03cc) and the maximum chiasm dose (Dmax) for the original chiasm (assuming static position) and the motion-inclusive PRV were obtained from the dose volume histogram. All doses were converted to 3-fraction equivalent doses using the linear quadratic formula with $\alpha/\beta = 2$ Gy for normal tissue tolerance. The two-sample t-test was used to compare the magnitude of the displacements in different spatial directions. The paired t-test was used to compare the D0.03cc and Dmax of the original chiasm and the chiasm PRV. MATLAB was used for statistical calculations, and all tests were two-sided. Results were considered significant at $p < 0.05$.

RESULTS

Physiological extent of chiasm motion

In total, serial MR images were acquired from 11 subjects without optic pathway abnormalities to measure chiasm motion over time. Axial series at the level of the mid-orbit served as a positive control for detecting motion using our MRI protocol, which was accomplished by observing gross movement of the optic nerves on lateral gaze ([Supplementary Figure 1](#)).

In the sagittal and coronal series, the chiasm was delineated in a semi-automated fashion to ensure consistency of contours as described in the methods. [Figure 1](#) depicts examples of chiasm auto-contours. [Supplementary Figure 2](#) is an animated graphics interchange format file that compiles the 50 imaging frames and auto-contours for one of the subjects' coronal image sets. Chiasm movement was determined from the auto-contour centroids (not the auto-contour boundaries) to minimize the impact of small frame-to-frame variations and noise that may exist at the boundaries.

Figure 1. Representative examples of chiasm auto-contours in the (A) sagittal and (B) coronal planes (subject 10). Insets in the upper left corner of each panel correspond to the region of interest containing the chiasm, magnified 5-fold (sagittal) or 3-fold (coronal). The centroid of the auto-contour is indicated by a red dot.

On the sagittal images, the maximal displacement of the chiasm, averaged across the 11 subjects, was 0.51 mm [95% confidence interval (CI) 0.27–0.75 mm] in the anteroposterior axis, and 0.48 mm (95% CI 0.22–0.74 mm) in the superior-inferior axis. On the coronal images, the maximal displacement in the superior-inferior axis averaged 0.42 mm (95% CI 0.13–0.71 mm), which closely agreed with the result of 0.48 mm from the sagittal images and was not statistically different ($p = 0.37$). Lastly, the maximal lateral displacement from the coronal images averaged 0.75 mm (95% CI 0.42–1.08 mm), which was significantly higher than the anteroposterior and superior-inferior displacements ($p = 0.002$ and $p < 0.001$, respectively). These results are summarized in Table 1.

Implications of chiasm motion to radiosurgery dose
To see how these displacements might affect the radiation dose received by the chiasm in real-life clinical scenarios, we identified 11 patients who underwent stereotactic radiosurgery to a perichiasmatic target (nine meningioma, two pituitary adenoma). An example radiosurgical treatment for one of the patients is shown (Figure 2). All treatments were hypofractionated given the proximity to the optic apparatus: 24 Gy in 3 fractions in nine cases, 25 Gy in 5 fractions in one case, and 30 Gy in 5 fractions in one case. The two cases treated with five fractions were converted to 3-fraction equivalent doses using $\alpha/\beta = 2$ Gy. Treatments were prescribed to the 72–81% isodose line (mean: 77.4%).

The effect of chiasm movement on radiation dose was simulated by expanding the original chiasm contour by 0.50 mm

anterior-posteriorly, 0.50 mm superior-inferiorly, and 0.75 mm laterally to generate a motion-inclusive chiasm planning organ at risk volume (PRV). For each patient, the dose to the highest 0.03 cc of chiasm (D0.03cc) and the maximum chiasm dose (Dmax) were calculated for the original chiasm contour, and then compared to the D0.03cc and Dmax for the chiasm PRV (Figure 3).

Across the 11 patients, the average D0.03cc for the original chiasm (assuming static position) was 15.1 Gy [standard deviation (SD) 3.1 Gy; range, 9.7–19.8 Gy], and the average Dmax was 20 Gy (SD 2 Gy; range, 17.3–22.5 Gy). For the chiasm PRVs accounting for motion, the average D0.03cc was 18.2 Gy (SD 2.4 Gy; range, 14.8–21.8 Gy), and the average Dmax was 22.7 Gy (SD 1.9 Gy; range, 19.3–25.1 Gy). The mean relative increase in D0.03cc was 22% (SD 12%; range, 8–53%), and the mean relative increase in Dmax was 14% (SD 6%; range, 6–23%). Both dose increases were statistically significant ($p < 0.0001$).

DISCUSSION

To our knowledge, this is the first study to investigate the physiological motion of the optic chiasm and its implications for radiosurgical treatment planning. By obtaining serial MRI of the chiasm in multiple planes in 11 human subjects with semi-automated contour delineation, we found that the average movement in chiasm position was approximately 0.50 mm in the anteroposterior and superior-inferior axes and 0.75 mm laterally. Since these values were the average displacements, some patients may

Table 1. Maximal chiasm displacement, averaged across 11 subjects (with 95% confidence interval), in each spatial axis as calculated from the sagittal and coronal planar images.

	Average maximal displacement (95% confidence interval)		
	Anteroposterior	Superior-inferior	Lateral
Sagittal series	0.51 (0.27–0.75) mm	0.48 (0.22–0.74) mm	N/A
Coronal series	N/A	0.42 (0.13–0.71) mm	0.75 (0.42–1.08) mm

Figure 2. Representative example of radiosurgical treatment of a patient with a perichiasmatic target that received 24 Gy in three fractions. Representative slices are shown in the (A) axial, (B) sagittal, and (C) coronal planes. Isodose lines are 4 Gy (purple), 8 Gy (cyan), 12 Gy (green), 16 Gy (yellow), 20 Gy (orange), 24 Gy (red). The chiasm is contoured in dark blue.

have higher-than-average chiasm motion; for example, the upper 95% estimate for the lateral displacement was 1.08 mm.

Our measured displacements for the chiasm were similar in magnitude to prior studies of spinal cord displacement resulting from cardiac pulsation and flow of cerebrospinal fluid. In one study, anteroposterior movement of the spinal cord averaged 0.60 mm across nine subjects⁶; another study found that both anteroposterior and lateral motion were typically within 0.50 mm.⁵ The superior–inferior displacement measured from the sagittal images closely matched the displacement measured from the coronal images, serving as a validation of those results. Interestingly, the lateral displacement of the chiasm was significantly higher than the anteroposterior or superior–inferior displacements by 1.5-fold. We speculate this may be due to torque applied to the chiasm by the movement of the optic nerves on right-left gaze. We are not able to confirm this hypothesis in the current study because our axial images were intended to capture the optic nerves and not the chiasm. Axial imaging of the chiasm was not performed because it was consistently obscured by artifact on balanced steady-state free precession imaging.

Additionally, we extrapolated the potential radiation dose received by the chiasm in patients treated with radiosurgery to a perichiasmatic target based on a motion-inclusive planning organ at risk volume (PRV). On average, the Dmax increased by 14%, with a maximum increase of 23% in our 11-patient sample,

relative to the dose received by the original chiasm (assuming static position). Most prior series of RION have reported on the point Dmax^{2,3} received by the optic apparatus. However, a volumetric-based constraint (such as D0.03cc) may be more consistent and robust against the effects of a discrete radiation calculation grid and imaging voxel size.² This approach has been used in a national clinical trial of spine radiosurgery (RTOG 0631)⁸ and in the report on stereotactic body radiotherapy from the American Association of Physicists in Medicine Task Group 101 (AAPM TG101).⁹ Therefore, we calculated the D0.03cc to the chiasm and found it also increased significantly, by an average of 22%.

In some clinical scenarios, these dose increases may be clinically relevant. For single-fraction radiosurgery, RION has been reported with Dmax to the optic apparatus as low as 7.4 Gy and as high as 14.8 Gy.³ Reflecting these uncertainties, maximum single-dose constraints ranging from 8 to 12 Gy have been proposed.³ Such discrepancies in RION risk may be partly due to idiosyncratic patient factors (such as underlying small-vessel disease or genetic susceptibility), but may also be partly due to previously unappreciated physiological motion of the chiasm near high dose-gradient regions. Given that the average increase in Dmax was 14% with SD of 6%, approximately 1 in 50 patients could have a true Dmax that is 2 SDs, *i.e.* 26% higher than the supposed Dmax. In fact, one patient in our 11-patient sample had a 23% increase in Dmax. The increase would be even larger

Figure 3. Radiation dose to the original chiasm contour and chiasm PRVs (planning organ at risk volumes) across the 11 patients treated with radiosurgery to a perichiasmatic target. (A) D0.03cc ($p < 0.0001$) and (B) Dmax ($p < 0.0001$). Red bars indicate means.

in a patient with higher-than-average chiasm motion, since our dose extrapolation assumed average chiasm displacement.

Hiniker et al modeled normal tissue complication probability curves using an institutional series of 262 patients with 2 cases of RION.³ A $\leq 1\%$ risk of RION is typically considered acceptable.³ The estimated Dmax corresponding to 1% risk of RION was 12.7 Gy for single-fraction treatment and 20.9 Gy for 3-fraction treatment. If the true Dmax were 14% higher (at 14.5 Gy in 1 fraction and 23.8 Gy in three fractions), then the estimated risk of RION would be doubled to 2%. If the true Dmax were 26% higher (16 Gy in 1 fraction and 26.3 Gy in three fractions), then the estimated risk of RION would be 3%. Recently, Milano et al published a comprehensive systematic review of RION series since 1997 comprising 1224 patients with nine cases of RION.² The estimated Dmax for 1% risk of RION was 12.1 Gy for single-fraction treatment and 20.0 Gy for 3-fraction treatment. Similar to the results from Hiniker et al, a 14% increase in the Dmax would result in 2% risk of RION, and a 26% increase in the Dmax would result in approximately 3% risk of RION.

These are large increases in relative risk, although the absolute risks of RION remain fairly low in the average patient. Also, these normal tissue complication probability curves were derived assuming a static chiasm; by acknowledging chiasm movement, the doses previously associated with RION may be underestimates of the true dose, which may indicate that the chiasm dose tolerance is higher than appreciated. However, the risk for toxicity increases exponentially as the dose increases further. In the occasional patient with higher-than-average chiasm motion undergoing radiosurgery to a perichiasmatic target where there is a steep dose gradient, the true Dmax to the chiasm may be significantly higher than expected, potentially leading to a 5–10% or even greater risk of RION. This level of risk would be unacceptable without patient foreknowledge and consenting. The risk is further exacerbated in patients with prior radiation to the same area, in whom the risk of RION may be magnified 10-fold.²

We contend that the variability in chiasm position warrants consideration along with other factors, such as vascular supply to the chiasm, intrafraction motion management, and overall machine accuracy, in patients at high risk for RION. One solution is to use a lower Dmax constraint. For example, while a point Dmax of 12 Gy in a single fraction (as per QUANTEC)^{1,3} likely has $<1\%$ risk of RION per Hiniker et al and Milano et al, many

practitioners commonly use a more conservative Dmax of 10 Gy (as per the AAPM TG101 report),⁹ in which case even if the true Dmax were 26% higher (*i.e.*, 12.6 Gy), the estimated risk of RION per Hiniker et al and Milano et al still lies around 1%. The other solution is to add an additional margin around the chiasm delineated on the simulation scan to account for geometric uncertainties, generating a planning organ at risk volume (PRV) that is subject to dosimetric constraints during plan optimization. For example, some practitioners add a 0.5–2 mm PRV margin to the spinal cord for spine radiosurgery,^{10,11} although substantial variation exists across clinical practice. Additional factors that may impact the chiasm dose are the immobilization method, errors in image fusion, and the heterogeneity algorithm used in planning. A PRV expansion may also help to account for these other sources of uncertainty.

A strength of our study is that this is the first report to analyze and quantify the extent of physiological chiasm motion, as well as its potential effect on dose received by the chiasm in real-life clinical scenarios. Another strength was the use of semi-auto-mated chiasm delineation (with human verification to ensure all auto-contours could have been plausibly delineated manually) to ensure consistent contouring. Limitations may arise from MRI resolution/voxel size and imaging artifact, which could impact auto-contour accuracy. However, our use of the centroid rather than the boundary to measure motion is less sensitive to noise associated with uncertainties in the contour boundary. Also, patients had three technical replicates per plane of imaging (of which the median displacement was used), helping to reduce variability.

CONCLUSION

In summary, we measured the physiological motion of the chiasm to be approximately 0.50 mm in the anteroposterior and superior–inferior axes, and 0.75 mm laterally. When these displacements were applied to actual radiosurgical treatment plans targeting a perichiasmatic lesion, the average increase in the chiasm Dmax was 14%. However, in the occasional patient with higher-than-average chiasm motion in a region of steep dose gradient, the increase in chiasm Dmax and risk of RION could be substantially larger. Based on our findings, we suggest consideration of applying a 0.50–0.75 mm planning organ at risk volume (PRV) expansion to the chiasm to constrain the risk of RION.

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