Utilisation of Diffusion Tensor Imaging in Intracranial Radiotherapy and Radiosurgery Planning for White Matter Dose Optimization: A Systematic Review

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BACKGROUND: **Diffusion tensor imaging (DTI), which visualizes white matter tracts, can be integrated to optimize intracranial radiation therapy (RT) and radiosurgery (RS) treatment planning. This study aimed to systematically review the integration of DTI for dose optimization in terms of evidence of dose improvement, clinical parameter changes, and clinical outcome in RT/RS treatment planning.**

METHODS: **PubMed and Scopus electronic databases were searched based on the guidelines established by PRISMA to obtain studies investigating the integration of DTI in intracranial RT/RS treatment planning. References and citations from Google Scholar were also extracted. Eligible studies were extracted for information on changes in dose distribution, treatment parameters, and outcome after DTI integration.**

RESULTS: **Eighteen studies were selected for inclusion with 406 patients (median study size, 19; range: 2–144). Dose distribution, with or without DTI integration, described changes of treatment parameters, and the reported outcome of treatment were compared in 12, 7, and 10 studies, respectively. Dose distributions after DTI integration improved in all studies. Delivery time or monitor unit was higher after integration. In studies with long-term follow-up (median, >12 months), neurologic deficits were significantly fewer in patients with DTI integration.**

CONCLUSIONS: **Integrating DTI into RT/RS treatment planning improved dose distribution, with higher treatment delivery time or monitor unit as a potential drawback. Fewer neurologic deficits were found with DTI integration.**

INTRODUCTION

Radiation therapy, through either fractionated radiotherapy (RT) or radiosurgery (RS), is one of the primary treatment options for various types of neoplastic, vascular, and functional brain disorders.[1-3] Many ongoing studies have addressed improvements in radiation delivery precision as a result of the possibility of these treatments causing radiation-induced neuropathy.[3-6]

One of the most viable approaches to increase precision in this context is the integration of diffusion tensor imaging (DTI), which noninvasively traces neuronal tracts in the brain pathways, into treatment planning.[7-23] Brain lesions adjacent to the white matter can be delineated for treatment planning, and it has been used successfully in neurosurgical planning.[24,25] For RT/RS, the linkages and structures of white matter fibers may guide optimization of radiation beams to spare healthy and radiosensitive parts of the brain from high radiation doses.

The integration of DTI in RT/RS treatment planning is yet to be systematically reviewed in the literature to the best of our knowledge. This investigation is necessary to fully establish the benefits of the proposed DTI integration. In this study, we systematically and comprehensively examined studies integrating DTI with respect to the dosimetric outcome of the plans after integration. We also reviewed the changes in treatment parameters, including conformity and heterogeneity index, monitor units, and treatment delivery

Key words
- Diffusion tensor imaging
- Radiosurgery
- Radiotherapy
- Treatment planning

Abbreviations and Acronyms
CST: Corticospinal tract
DTI: Diffusion tensor imaging
fMRI: Functional magnetic resonance imaging
MEG: Magnetoencephalography
MRI: Magnetic resonance imaging
RS: Radiosurgery
RT: Radiotherapy

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time after DTI integration. The clinical outcomes of treatments were reviewed for studies that reported the integration of DTI in treated patients retrospectively or prospectively.

METHODS

Systematic Review Protocol

The systematic review protocol and methodology established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was used (Figure 1).[26-28]

Eligibility Criteria

Full-text original research articles (i.e., not systematic or narrative reviews), published, accepted for publication, or available online in a language we had the capability to review (English, Malay, or Chinese) were evaluated. For inclusion, study populations consisted of patients treated with or planned for cranial irradiation. Integration of DTI also needed to be related to the optimization of white matter dose. The study design could be methodological, including theoretic planning, observational, or clinical. Studies with extracranial target volume were excluded.

Search Strategy and Selection Process

Electronic databases (National Center for Biotechnology Information [PubMed] and Scopus) were searched to identify articles. Keywords and search strings used are detailed in the Supplementary Material. In the first phase, articles were reviewed in increasing specificity to remove articles not fulfilling the preset

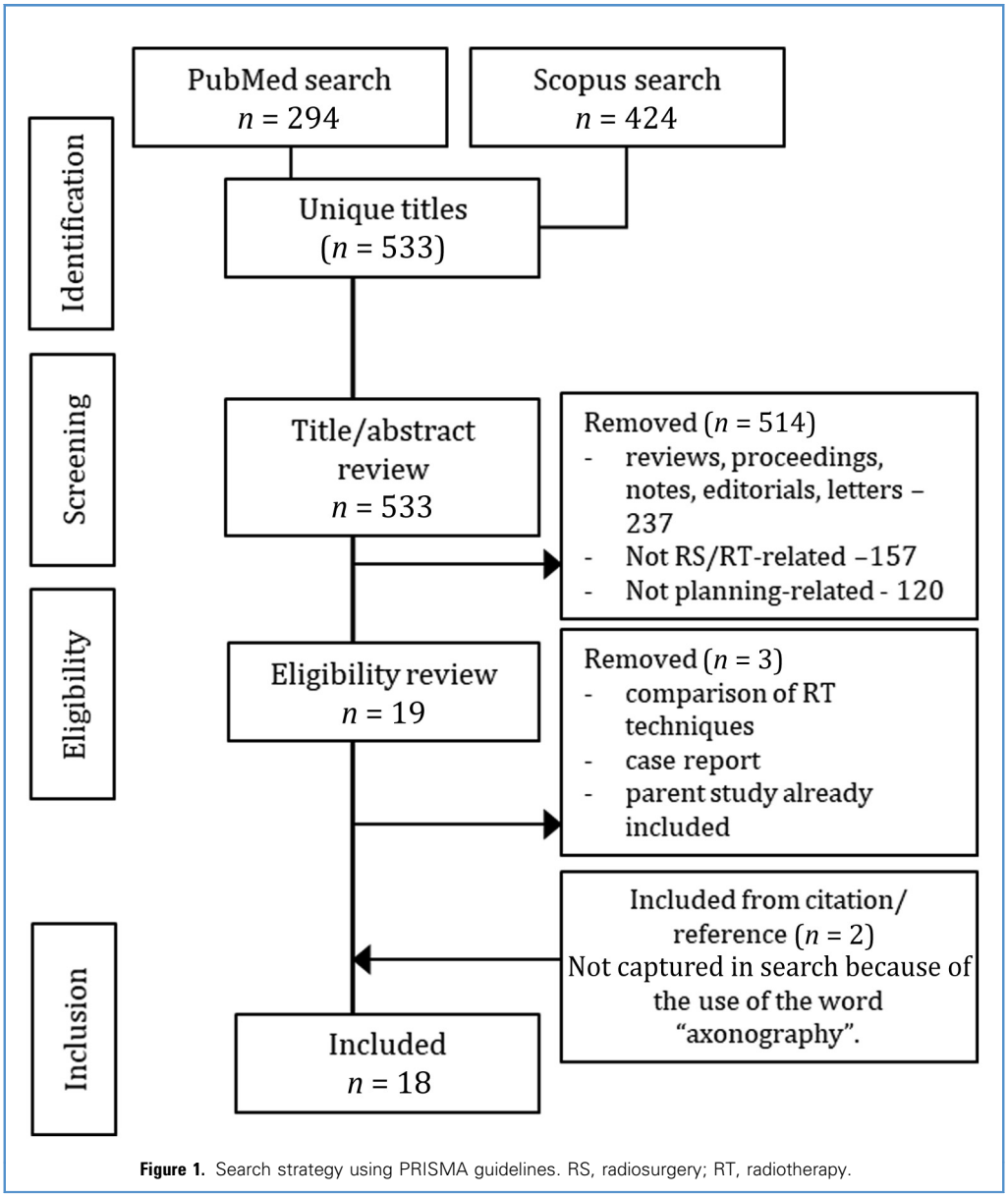

Figure 1. Search strategy using PRISMA guidelines. RS, radiosurgery; RT, radiotherapy.

Table 1. Study Characteristics

	Reference	Year	Number of Patients	Diagnosis	Investigation	Type of Radiotherapy/ Radiosurgery	Other Imaging Techniques	Location/Tract/ Structure of Interest	Proximity of Lesions to Tracts	B_0; Vendor; Coil; Gradient (mT/m)	Diffusion Tensor Imaging Acquisition	Field of View; Matrix; Voxel Size (mm); Repetition Time/Echo Time (milliseconds); Acquisition Time (minutes:seconds)	Fiber Tracking Methods; Regions of Interest
Prospective clinical application													
1.	Aoyama et al.,[9]	2004	20 (6 with DTI)	AVM	Prospective clinical integration	6-MV linear accelerator-based stereotactic system	Magnetoencephalography	CST	Lesions located near or within the functional cortex or CST	1.5 T; Siemens; standard head coil; NR	Single-shot, spin echo, echo planar 1000 seconds/mm^2 3 directions	19 slice; 128 × 128; 1.8 mm axial; NR/87	Hyperintense area
2.	Foroni et al.,[11]	2010	15	AVM	Prospective clinical integration (4 cases)	Gamma Knife	—	CST	Lesions near the presumed course of the CST	3.0 T; Siemens; 4-channel coil	Single-shot spin echo, echo planar sequence 700 seconds/mm^2 12 directions	5 patients: 200; 128 × 128; 1.7 × 1.7 × 3; 7000/75; 9—12 10 patients: 270; 128 × 128; 2.1 × 2.1 × 2.0; 7000/75; 9—12	FA <0.15, angle <40°; ROI premotor, precentral, and postcentral gyri bilaterally, posterior limb of the internal capsule and cerebral peduncle bilaterally
3.	Gavin and Sabin,[12]	2016	20	Vestibular schwannoma (4 + 1 test), AVM (5), cerebral metastases (9), parasagittal meningioma (1)	Prospective clinical integration	Gamma Knife	—	Optic radiation, CST, AF, and PT	Lesions in the vicinity of tracts and/or the cortex	1.5 T; Philips; standard bird-cage head coil	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 32 directions	210; 512 × 345; 2 mm axial; 2700/160; 14—16	StealthViz, FA <0.20, angle <45°; ROI not detailed
4.	Koga et al.,[16]	February 2012	144 (71 with DTI)	AVM	Prospective clinical integration	Gamma Knife	—	PT, OR, and AF	Target lesion <1 cm apart from the fiber tracts	Not detailed. Authors referred to Refs.[18,19]			
5.	Koga et al.,[17]	May 2012	54 (28 with DTI)	AVM	Prospective clinical integration	Gamma Knife	—	CST	Located in AVM in the deep frontal lobe, deep parietal lobe, basal ganglia, and thalamus	Not detailed. Authors referred to Refs.[18,19]			
6.	Maruyama et al.,[18]	2005	7	AVM	Prospective clinical integration	Gamma Knife	—	CST	Lesion adjacent to CST	1.5 T; GE; standard head coil	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 13 directions	240 mm; 128 × 128; 5 mm axial; 6000/78; 5:36	In house, FA >0.18; ROI cerebral peduncle and primary motor cortex
7.	Sun et al.,[22]	2017	16	Meningioma (2), brain metastases (8), and AVM (6)	Theoretic planning and prospective integration	Cyberknife	fMRI	CST and sensory pathway	In critical areas	1.5 T; Siemens; NR	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 12 directions	251; 128 × 128; 1.9 ×1.9×3; 9400/147; NR	i-plan software; ROI not detailed
Retrospective integration													

8.	Conti et al.,[10]	2013	25 (13 with DTI)	AVMs (10), brain metastases (3)	Retrospective integration	Cyberknife	fMRI, transcranial magnetic stimulation	PT, AF	Lesions in critical areas	3.0 T; NR; 4-channel coil	Single-shot spin echo, echo planar sequence	NR; NR; 2.3×2.3×2.3; NR; NR	Diffusion Toolkit and TrackVis software; ROI not detailed
9.	Maruyama et al.,[19]	2007	10	AVM	Retrospective integration	Gamma Knife	—	OR	Lesion adjacent to OR	1.5 T; GE; standard head coil	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 13 directions	240; 128 × 128; 2.5 mm axial; 6000/78; 5:36	In house, FA >0.18; lateral geniculate nucleus and occipital pole
10.	Maruyama et al.,[20]	2009	12	AVM	Retrospective integration	Gamma Knife	—	AF	Lesion adjacent to the left AF especially patients who had aphasia after treatment	Same as Ref.[19]			
Theoretic planning studies													
11.	Altabella et al.,[7]	2018	19	High-grade glioma	Theoretic planning	Tomotherapy	—	CST and some subcortical intrahemispheric associative fascicles	Not mentioned	3.0 T (4 patients), 1.5 T (15 patients); Philips; standard head coil	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 32 directions (3 T) 15 directions (1.5 T)	For 3.0 T: 240; 96 × 96; 0.94 ×0.94×2.5; 8986/80; 10:46 For 1.5 T: 240; 96 × 96; 1.57×1.57×2.5; 3972/99; 12	Diffusion Toolkit software, FA <0.1, angle <55°
12.	Aoyama et al.,[8]	2003	2	AVM	Theoretic planning	6-MV linac-based stereotactic	Magnetoencephalography	CST	Lesions 4 and 0 mm to motor unit at the closest portion	Same as Ref.[9]			
13.	Gomes et al.,[13]	2016	20	Gamma Knife thalamotomy	Theoretic planning	Gamma Knife	—	In common regions in brainstem and posterior internal capsule limb	All in thalamus	1.5 T; GE; standard head coil	Dual spin echo, echo planar sequence 750 seconds/mm^2 33 directions	250 mm; 254 × 254; 1 mm axial; 11500/88.6-209; 8	Iplannet 3.0 stereotaxy software — FA thresholds between 0.2 and 0.35 ROI precentral gyrus, brainstem, and posterior internal capsule limb
14.	Igaki et al.,[14]	2014	2	High-grade glioma	Theoretic planning	Intensity-modulated radiotherapy	—	CST	Not mentioned	Referred to Ref.[18]			
15.	Kawasaki et al.,[15]	2017	23	Metastatic brain tumor (20), AVM (3)	Theoretic planning	Gamma Knife	—	PT	Lesions adjacent to PT	3 T; Siemens; 20-channel head and neck coil	Single-shot spin echo, echo planar sequence 1000 seconds/mm^2 20 directions	230 mm; 128 × 128; 2.5 mm axial; 10000/90; NR	ZIO Station, FA >0.2; ROI cerebral peduncle, posterior limb of the internal capsule, the primary motor cortex
16.	Koga et al.,[29]	2009	36 (18 with DTI)	Benign lesions (31), others (5)	Theoretic planning	Gamma Knife	Positron emission tomography	CST, OR	Not mentioned	Referred to Refs.[18,19]			

DTI, diffusion tensor imaging; AVM, arteriovenous malformation; CST, corticospinal tract; NR, not reported; ROI, region of interest; AF, arcuate fasciculus; PT, pyramidal tract; OR, optic radiation; fMRI, functional MRI; MV, megavoltage; FA, fractional anisotropy; GE, General Electric.

Continues

Table 1. Continued

Reference	Year	Number of Patients	Diagnosis	Investigation	Type of Radiotherapy/ Radiosurgery	Other Imaging Techniques	Location/Tract/ Structure of Interest	Proximity of Lesions to Tracts	B_0; Vendor; Coil; Gradient (mT/m)	Diffusion Tensor Imaging Acquisition	Field of View; Matrix; Voxel Size (mm); Repetition Time/Echo Time (milliseconds); Acquisition Time (minutes:seconds)	Fiber Tracking Methods; Regions of Interest
17. Pantelis et al.,[21]	2010	4	AVM, astrocytoma, brain metastasis, and hemangioma	Theoretic planning	Cyberknife	fMRI	Patient-specific, fibers close to target volume only (optic pathway, PT)	Adjacent to visual pathway, motor cortex, or cerebral pons	3T; Siemens; standard head coil	Fat-saturated single-shot, spin echo, echo planar imaging with Stejskal-Tanner diffusion sensitization (GRAPPA factor = 2, repetition = 4) 1000 seconds/mm^2 18 directions	230 mm; 128 × 128; 1.7 × 1.7 ×3 mm axial; 6300/87; NR	FA >0.2, angle >30°, maximum number of tracts per voxel of 4; ROI not detailed
18. Wang et al.,[23]	2015	20	High-grade gliomas	Theoretic planning	Intensity-modulated radiotherapy	fMRI	CST	Adjacent to primary motor cortexes and CST	3 T; Siemens; 20-channel head and neck coil	Single-shot, spin echo, echo planar 1000 seconds/mm^2 25 directions	240; 128 × 128; 3 mm axial; 10000/98.8; 4:40	FA >0.2; angle <30°; ROI posterior limb of the internal capsule and pons

DTI, diffusion tensor imaging; AVM, arteriovenous malformation; CST, corticospinal tract; NR, not reported; ROI, region of interest; AF, arcuate fasciculus; PT, pyramidal tract; OR, optic radiation; fMRI, functional MRI; MV, megavoltage; FA, fractional anisotropy; GE, General Electric.

criteria via the title alone, abstract, then via full text by N.Y. and H.A.M. independently. In the second phase, bibliographic references and citations of the included articles were extracted from Google Scholar and reviewed for additional eligible studies. We have confidence in the robustness of this 2-step method to ensure no omission of relevant studies, taking advantage of the availability of a catchall and almost real-time database for citations, such as Google Scholar. No publication date or publication status restriction was imposed. Spreadsheet software was used to organize and assess the titles of included studies and identify duplicate entries, whereas the abstracts were viewed through word-processing software. Discrepancies in the results of the review were deliberated in team meetings. Study search and selection were completed on February 7, 2019.

Data Review and Extraction

On finalization of the selection process, data were extracted by both authors. Information was extracted into spreadsheets and included the following data: article title, authors, publication date, RT types, number of patients, diagnosis, type of study (prospective or retrospective clinical study, theoretic treatment planning), effects of integration, clinical outcome, and fiber tracts considered. The studies were clustered based on the type of study: 1) prospective clinical study, 2) retrospective replan with DTI integration, and 3) theoretic treatment planning with DTI integration.

RESULTS

Study Selection and Characteristics

The database queries produced 294 and 424 records from PubMed and Scopus, respectively. After duplicate removal, the articles were reviewed for inclusion in increasing details (title, abstract, and full text) in the first step, and 16 met the inclusion criteria. In the second phase, in which references and citations of the previously selected articles were reviewed using Google Scholar (which updates citations in real time, including gray literature), 2 additional studies were included. The 2 articles were missed from the original search potentially because of the use of the term "axonography" instead of more typical words, such as "tractography" and "diffusion tensor imaging." A flowchart detailing the article selection process based on PRISMA guidelines is shown in **Figure 1**.

Table 1 summarizes the characteristics of the selected studies. The publication dates ranged from 2003 to 2018. The studies included 449 patients planned for/treated with RT/RS to the brain, of whom 324 had integration of DTI in their treatment plans. The patient sample size ranged between 2 and 144 (median, 19). Most of these studies (15) included patients treated with stereotactic RS, including 10, 3, and 2 studies using Gamma Knife (Elekta, Stockholm, Sweden), CyberKnife (Accuray, Sunnyvale, California, USA), and conventional linac-based RS, respectively. The remaining 3 studies used DTI for patients planned for or treated with other methods, including tomotherapy (1 study) and intensity-modulated RT (2 studies). Indications for RT/RS were diverse, with arteriovenous malformation being the most common (266 patients). Eight studies used DTI in theoretic planning studies, whereas the remaining studies were clinical studies prospectively integrating DTI in treatment planning or retrospectively to determine dose received by the

Table 2. Dose Changes to White Matter Tracts After Diffusion Tensor Imaging Integration in Radiotherapy/Radiosurgery Treatment Planning

Reference	Changes to Tracks of Interest After Integration	Magnitude of Change (If Significant)
Mean dose		
Altabella et al., 2018[7]	Mostly significant decrease	Contralateral: average reduction between 25.6% and 39.5%. Ipsilateral: average reduction between 7.02% and 8.57%
Conti et al., 2013[10]	Decrease	
Igaki et al., 2014[14]	Decrease	
Sun et al., 2017[22]	Significant decrease	In 1 and 3 fractions plans. Average reduction 22.71%
Wang et al., 2015[23]	Significant decrease	Average reduction between 20.2% and 37.6%
Maximum dose		
Altabella et al., 2018[7]	Mostly not significant	
Aoyama et al., 2004[9]	Not significant	
Kawasaki et al., 2017[15]	Significant decrease	Average reduction 11.4%
Koga et al., 2009[29]	Significant decrease	Average reduction 29.2% (5.6 Gy) (CST) and 15.3% (1.9 Gy) (optic radiation)
Pantelis et al., 2010[21]	Decrease	
Sun et al., 2017[22]	Significant decrease	In 3 fractions plans. Average reduction 16.86%
Wang et al., 2015[23]	Significant decrease	Average reduction between 23.1% and 33.4%
Minimum dose		
Altabella et al., 2018[7]	Mostly significant decrease	Shown graphically
Sun et al., 2017[22]	Not significant	
Dose-volume		
Altabella et al., 2018[7]	Mostly significant decrease (V10—V50)	Shown graphically
Aoyama et al., 2003[8]	Decrease (V10—V15)	
Aoyama et al., 2004[9]	Not significant (V10)	
Aoyama et al., 2004[9]	Significant decrease (V15)	From 1.8 cm^3 to 0.5 cm^3
Igaki et al., 2014[14]	Decrease (V30—V50)	
Igaki et al., 2014[14]	Decrease (D98)	
Dose constraints		
Gavin and Sabin, 2016[12]	Constraints met	Within previously published tract tolerances based on Refs.[18-20,30]
Gomes et al., 2016[13]	Constraints met in 65% of cases	Internal capsule constraint of <15 Gy in 65% of cases

Significance was set at $P < 0.05$. Statistical analyses were not performed in some studies.
Vx, relative volume of tissues receiving x dose.

white matter or a mix of theoretic and clinical integration. In addition to DTI, 2 studies integrated magnetoencephalography,[8,9] 3 studies integrated functional magnetic resonance imaging (fMRI),[21-23] and 1 study integrated both fMRI and transcranial magnetic stimulation.[10] Various fiber tracts were investigated, including the fascicles,[7,10,12,15,17,20,21] pyramidal tracts,[10,12,15,17,21] optic radiation,[12,17,19,21,29] and the corticospinal tracts (CST), which are the most common.[7-9,11,12,14,16,18,22,23,29] Most studies selected only patients with lesions close to the white matter fiber tracts, except for the studies by Altabella et al.[7] and Gavin and Sabin.,[12] in which patients had lesions in diverse sites regardless of relative distance to the fiber tracts.

Dose Distribution in RT/RS Plans with the Use of DTI

Twelve studies reported the dose distribution in the RS/RT plans after the integration of DTI (Table 2). Where comparisons were made, all studies showed a reduction in mean dose to the tracts of interest after DTI integration. The magnitude of change ranges approximately from 7% to 40%. For maximum and minimum doses, the observations were less consistent across studies, with some studies showing no significant difference after DTI integration. The mean of the maximum dose for studies that found a significant difference was approximately between 11% and 33%. Other dose indices derived from dose—volume histograms were similarly decreased after integration. The magnitude of change depended on the types and laterality of tracts studied. Altabella et al. observed that 1) dose reduction in contralateral tracts were more prominent with percentage differences between 25.6% and 39.5%, depending on the specific tracts, and 2) for ipsilateral tracts, the changes were mostly significant but less prominent (i.e., between 7.02% and 8.57%).[7] In contrast, Wang et al. observed fewer laterality effects with reductions highly significant in both the ipsilateral and contralateral tracts.[23] Aoyama et al.[9] and Gomes et al.[13] both observed that modifications were possible for 71% and 65% of the plans, respectively, and maintained the therapeutic dose to target volumes.

Changes in Treatment Parameter

Seven studies reported the change in treatment parameters after the introduction of DTI in the treatment planning process (Table 3). Conti et al.,[10] Gomes et al.,[13] Kawasaki et al.,[15] Pantelis et al.,[21] and Sun et al.[22] observed increased monitor units or

Table 3. Changes of Treatment Parameters Following Diffusion Tensor Imaging Integration in Radiotherapy/Radiosurgery Treatment Planning

Reference	Changes After Integration
MUs and delivery times	
Conti et al., 2013[10]	MU controlled
Gomes et al., 2016[13]	Delivery time significantly longer, approximately double
Kawasaki et al., 2017[15]	Delivery time significantly longer, 3.5 minutes average
Pantelis et al., 2010[21]	MU higher
Sun et al., 2017[22]	MU significantly higher in 3-fraction plans, 17% increase
Conformity index	
Conti et al., 2013[10]	Conformity index controlled
Pantelis et al., 2010[21]	Decrease
Sun et al., 2017[22]	Not significant
New conformity index	
Koga et al., 2009[29]	Significantly lower, 0.06 difference
Pantelis et al., 2010[21]	Lower
Sun et al., 2017[22]	Not significant
Homogeneity index	
Pantelis et al., 2010[21]	Same
Sun et al., 2017[22]	Significantly higher in 3-fraction plans, 0.1 difference
Wang et al., 2015[23]	Not significant
Collimators and beams	
Pantelis et al., 2010[21]	Smaller/more types of collimator and more beams
Sun et al., 2017[22]	Not significant

New conformity index = (tumor volume (TV) × prescription isodose volume (PIV))/target volume covered by prescription isodose volume (TV_{PIV}).[2,31] Significance was set at $P < 0.05$. Statistical analyses were not performed in some studies.
MU, monitor unit.

delivery time in DTI-integrated plans. No obvious patterns were observed for conformity index and new conformity index, heterogeneity index, types and size of collimators, and number of beams across studies.

Clinical Outcomes

Few studies with short-term follow-up availability (median, <12 months) did not observe any neurologic deficits or injury after irradiation[10-12,22] (Table 4). In studies comparing patients who were planned with and without DTI integration,[9,16,17] the outcome favored plans with DTI integration, which was statistically significant in the study by Koga et al.[16] Two studies that reported prospective or retrospective DTI integration speculated the dose-effect relationships.[18,19] A significant dose-effect relationship was observed with optic radiation, whereby receiving >8 Gy was more likely to cause neurologic changes, including visual disturbances and headache.[19] The volume of CST receiving ≥25 Gy and the maximum dose to the CST significantly and independently correlated with motor complications ($P < 0.05$).[18] Maruyama et al. in 2009[20] suggested the potential differences in tolerance of the tracts with no dysfunction observed after a maximum radiation dose of 10.0–16.8 Gy and 3.6–5.2 Gy to the frontal and temporal tracts, respectively.

DISCUSSION

We conducted the first systematic review to methodically accumulate evidence on the use of DTI in RT and RS treatment planning. The primary results showed that the integration of DTI information can improve sparing of important white matter tracts without affecting target dose and coverage. Second, the delivery time or monitor unit of the treatment plans after DTI integration was significantly higher compared with those without integration potentially as a result of more complex dose distribution in treatment plans with DTI. Other treatment parameter changes caused by DTI integration were found to be inconsistent across studies, suggesting the impact of preference or skills of planners. Despite the fact that only a few studies have assessed the clinical outcome, these studies have shown a consistently positive impact of DTI integration with significantly fewer neurologic deficits in patients treated with DTI-integrated treatment plans.

Some issues of study methodology should be discussed. First, the studies included in the current systematic review generally have a smaller sample size, with a median of 19 patients. This situation may be a result of the low prevalence of neoplastic, vascular, and functional disorder of the brain compared with other organs requiring radiation treatment and low rate of MRI use in non-RS treatment planning.[32] A longer time frame of study similar to that by Koga et al.[17] had been proved to be more beneficial in terms of the total number of patients accrued. Second, many of the studies were not prospective clinical studies with outcome assessment. Because the theoretic planning and retrospective replanning studies have less clinical impact, the discretion of the final plans in terms of clinical feasibility and impact is often not at an equivalent level of a prospective study.

The results across studies consistently showed that delineation of fiber tracts was beneficial to guide planners to further spare healthy tissues from the high radiation dose, which consequently reduces the risk of radiation-induced complications. This dose reduction was achieved without disturbing the dose necessary for target volume, which can be attributed to the highest hierarchal priority given to target coverage during plan optimization. However, we found studies reporting up to double delivery time for Gamma Knife–based treatment and significantly increased monitor unit for linac-based treatment. This situation may be associated with more complex treatment to achieve more sparing and maintain the target dose distribution. The integral dose increases as exposure time increases.[33]

In most studies, DTI was integrated into cases only where the white matter fiber tracts were close to the lesions. However, improvement in terms of dose distribution was also found in 1 study with lesions in diverse locations.[7] No study specifically quantified the maximum distance between lesions and tracts that can benefit from DTI integration in treatment planning.

Table 4. Outcome of Studies with Clinical Integration of Diffusion Tensor Imaging in Treatment Planning

Reference	Follow-Up Period	Prospective Integration of DTI?	Toxicity Scoring	Outcome (Including Dose and DTI Integration Effects)	n/N (%) of Toxicities
Follow-up period median/mean <12 months					
Conti et al., 2013[10]	10 patients with arteriovenous malformations had a mean follow-up of 17 months, 12 patients with malignant brain tumors (9 months) and 3 patients with meningiomas (8 months)	No	Clinical	No neurologic deficit caused by radiation was recorded	0/25 (0)
Foroni et al., 2010	6 months for 2 patients	Yes	Clinical and imaging	No new neurologic deficits or postradiosurgical imaging changes	0/2 (0)
Gavin and Sabin, 2016[12]	6—12 months	Yes	Clinical	No new neurologic deficits	0/5 (0), only arteriovenous malformation cases explicitly reported
Sun et al., 2017[22]	Not mentioned	Yes	Clinical	No neurologic complication caused by radiation damage was observed in the follow-up period	0/16 (0)
Follow-up period median/mean ≥12 months					
Aoyama et al., 2004[9]	3—35 months (mean, 12 months)	Yes	Clinical	1) Intracranial bleeding, death 2) Imaging changes, no neurologic symptoms 1) Minor motor deficit	4/20 (20)
Koga et al., 2012[16]	3—72 months (median, 23 months)	Yes	Clinical	1) Permanent worsening dysesthesia 1) Mild transient hemiparesis 2) Transient speech disturbance before starting integration of the arcuate fasciculus tractography, but no patient thereafter. 3) Increased preexisting epileptic attacks 1) Convulsive seizure 2) Hemorrhage Nidus obliteration, 29%	10/142 (7)
Koga et al., 2012[17]	Median 62 months (range, 36—113 months) for patients before integration and median 48 months (range, 36—80 months) for patients after integration	Yes	Clinical and modified Rankin Scale	Neurologic events, 6 patients without DTI integration (21.4%) and 3 patients with DTI integration (12.5%) ($P = 0.18$). Deterioration of modified Rankin Scale, 3/6 patients without DTI integration and 1/3 patients with DTI integration Motor complications, 5 patients without DTI integration (17.9%) and 1 patient with DTI integration (4.2%) ($P = 0.021$) Obliteration rates were not significantly different	9/52 (17.3), neurologic events 6/52 (11.5), motor complications
Maruyama et al., 2005[18]	19—32 months (median, 22 months)	Yes	Clinical	2 transient and 1 permanent motor complications Significantly and independently correlated with the volume of the corticospinal tract that received ≥25 Gy and with a maximum dose to the corticospinal tract ($P < 0.05$).	3/7(42.8)
Maruyama et al., 2007[19]	14—85 months (mean, 38 months)	No	Clinical	1 quadrantanopia 1 resolution of migraine 1 resolution of epilepsy 1 development of migraine 1 development of visual hallucination optic radiation D_{max} ≥8 Gy significantly related to neurologic change ($P < 0.05$).	5/10 (50)

DTI, diffusion tensor imaging; D_{max}, maximum dose.

Continues

Table 4. Continued

Reference	Follow-Up Period	Prospective Integration of DTI?	Toxicity Scoring	Outcome (Including Dose and DTI Integration Effects)	n/N (%) of Toxicities
Maruyama et al., 2009[20]	17—52 months (median 29 months)	No	Clinical	1 conduction aphasia 1 motor aphasia Speech dysfunction was not observed after a maximum radiation dose of 10.0—16.8 Gy was delivered to the frontal fibers and 3.6—5.2 Gy to the temporal fibers	2/12 (16.7)

DTI, diffusion tensor imaging; D_{max}, maximum dose.

However, Koga et al.[17] suggested 1 cm as a cut point distance of the lesions to the pyramidal tract, optic radiation, or arcuate fasciculus for integration. In another study, Koga et al.[16] included only lesions located in the deep frontal lobe, deep parietal lobe, basal ganglia, and thalamus for CST DTI integration.

Clinically, we found that integrating DTI in treatment planning is beneficial in preventing neurologic changes. This finding is in line with a multitude of studies observing clinical changes after radiation treatment.[5,34-39] Ascertaining the dose constraint of white matter tracts results in a more evidence-based optimization of the dose. At this stage, as noted in the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) report, the toxicity risk for large fraction sizes and single fraction treatment is unpredictable.[40] In particular, identifying the constraints is difficult because a substantial variation was shown among the outcomes of different centers.[40] This factor is similarly noted in the current systematic review, with most studies reporting nonstandardized outcomes. Specific to the optimization of white matter tract using DTI, the results from several studies by Maruyama et al.[18-20,30] have been widely used as guides. However, these suggestions are limited by a small number of studies, which are further limited by the myriads of indications, involved tracts, and risk of adverse events investigated.

The risk of bias is potentially high for all studies reporting the clinical outcome. It is understandable that randomizing patients into treatments with and without DTI integration, in light of significant improvements of dose distribution in plans with DTI integration shown in numerous theoretic planning studies, may pose doubt over its clinical equipoise.[41,42] Retrospective integration, as exemplified by 2 studies included in the present study, has the potential to enable dose-effect relationships and dose constraints to be established without randomization.[19,20] The group integrated optic radiation and arcuate fasciculus DTI into simulated treatment planning for RS and delivered doses. Subsequently, the distances between treated lesions and tracts were correlated to posttreatment changes.[19,20] Although both studies suggested dose constraints, the sample size in these studies was small (10 each), which requires validation in other cohorts potentially through retrospective integration to include patients with a long-term follow-up after treatment.

The conception of multimodal imaging has been adopted to enable better RT/RS planning and outcome because no single imaging technique is able to map all important areas. Another type of MRI-based imaging, fMRI, used in several RT/RS treatment planning studies, was included in the present review.[10,21-23] fMRI detects a change in signal intensity caused by increased blood flow to the functionally eloquent cortices during specific tasks, including physical movement and memory tasks.[43,44] A combination of DTI and fMRI may allow a synergistic approach to improve treatment outcome in terms of critical structure preservation. Although the same improvement may be achieved using transcranial magnetic stimulation and magnetoencephalography, as shown by some studies,[8-10,45-47] the use of fMRI to localize eloquent cortices has a major advantage in terms of accessibility and ease of integration. This advantage is especially true for stereotactic RS, which has already used MRI in treatment planning, unlike RT, which only recently transitioned into using MRI more extensively.[48,49]

This study aimed to answer a specific question on the use of DTI in RT/RS treatment planning to optimize white matter dose, focusing on 3 main aspects: dose distribution changes, parameter changes, and the outcome of treatment using DTI. The use of DTI to determine white matter infiltration for planning,[50-52] prediction of tumor recurrence,[53,54] and progression pattern[55,56] was not within the scope of this study and merits dedicated systematic reviews.

CONCLUSIONS

This systematic review suggests that integrating DTI images into treatment plans is beneficial in clinical practice. The only potential minor drawback is that higher treatment delivery time or monitor unit is needed to achieve DTI-optimized treatment plans. Evidence of the clinical outcome is sparse. A retrospective integration approach may be used to determine the clinical effects and potentially establish dose-effect relationships for white matter tracts because of the ethical issues related to randomizing patients to treatment plans without DTI integration.

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