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Neurosurgical Applications of Magnetic Resonance Diffusion Tensor Imaging

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Abstract

Magnetic Resonance (MR) Diffusion Tensor Imaging (DTI) is a rapidly evolving technology that enables the visualization of neural fiber bundles, or white matter (WM) tracts. There are numerous neurosurgical applications for MR DTI including: (1) Tumor grading and staging; (2) Pre-surgical planning (determination of resectability, determination of surgical approach, identification of WM tracts at risk); (3) Intraoperative navigation (tumor resection that spares WM damage, epilepsy resection that spares WM damage, accurate location of deep brain stimulation structures); (4) Post-operative assessment and monitoring (identification of WM damage, identification of tumor recurrence). Limitations of MR DTI include difficulty tracking small and crossing WM tracts, lack of standardized data acquisition and post-processing techniques, and practical equipment, software, and timing considerations. Overall, MR DTI is a useful tool for planning, performing, and following neurosurgical procedures, and has the potential to significantly improve patient care. Technological improvements and increased familiarity with DTI among clinicians are next steps.

Introduction

Magnetic Resonance (MR) imaging uses magnetic fields to temporarily alter proton (hydrogen atom) orientation and then measures the energy emitted upon proton relaxation, enabling discrimination of tissues with different proton (water) compositions. Water molecules naturally diffuse in accordance with Brownian motion (imagine a drop of dye spreading out in a glass of water). A series of magnetic pulses can be applied to measure the inter-pulse magnitude and direction of proton diffusion. On a pixel-by-pixel basis, this diffusion is described by the Apparent Diffusion Coefficient (ADC), which can be determined in multiple axes. Mori et al[1] found that application of the diffusion pulse in a minimum of six directional axes is sufficient to resolve a diffusion vector in three dimensional space describing the overall diffusion for a given pixel, called a tensor (thus the name diffusion tensor imaging (DTI)). This approach has been particularly useful in identifying myelinated axons.The term anisotropy refers to the degree by which protons diffuse predominantly in a single direction. Myelinated fibers are relatively anisotropic with diffusion preferentially along the axis of the fiber. DTI data are depicted in parametric maps that assign colors to different directions (e.g., anterior, posterior, ventral, dorsal, right, left). Thus, MR DTI visually depicts the water molecules within myelinated neurons, crudely outlining WM tracts.

DTI has been validated by comparison with experimental histological specimens. Further proof of concept includes experiments where DTI-identified WM tracts were electrically stimulated and produced predicted physiologic responses. Traditionally, subcortical stimulation mapping has served as the gold standard for intraoperative neuronavigation, yet this technique does not visually delineate the intraparenchymal path of WM tracts. In contrast, DTI depicts WM tracts as they course through the central nervous system. Numerous innovative clinical applications of DTI have been described in the literature. Herein we thematically describe them and discuss limitations and future directions.

Tumor grading & staging

Tumor evaluation with DTI enables discrimination between different types of CNS lesions and visualization of WM tracts depicts WM-tumor interactions. Lazar et al[2] evaluated preoperative DTI images of 6 patients with brain lesions and observed various patterns of tumor-induced damage, which were categorized into deviation, deformation, infiltration, or apparent tract interruption. Preoperative knowledge of the WM-tumor interaction contributed to good clinical outcomes, as 4 patients with preoperative impaired motor functioning experienced complete symptom resolution postoperatively. Chen et al[3] applied this knowledge in a study of 10 patients with brainstem lesions. Prior to resection, some form of deviation, deformation, infiltration, or apparent tract interruption was diagnosed in each patient. Visualization of the tracts again after surgery ensured the tracts returned to their proper location.The authors concluded that WM tract imaging provided abundant risk stratification and prognosis information.

DTI can be used to evaluate specific tumor characteristics including extent of infiltration. One parameter called fractional anisotropy (FA) is a scalar value (ranging from 0-1) and is used to describe the degree of anisotropy of a diffusion process. Deng et al[4] found a negative correlation between the FA value and degree of tumor infiltration in twenty patients with gliomas, as lower FA values were observed in the areas of higher glioma infiltration. FA is a promising quantifiable marker of tumor infiltration (that cannot be otherwise determined from conventional MR images).

FA values aid differentiation between tumor types. Byrnes et al[5] studied 28 patients with either glioblastoma or brain metastases using FA values. Mean FA was significantly lower in the edema surrounding metastatic tumors than surrounding glioblastomas. Imaging was able to accurately discriminate between tumor type for 87.5% (14 of 16) of glioblastomas and 83.3% (10 of 12) of metastases, as validated by histology. Similarly, Tropine et al[6] used various DTI metrics to distinguish between fibroblastic and benign meningiomas, concluding that FA values are the valuable predictors. After evaluating 30 patients with WHO grade 1 meningiomas, the authors reported that in comparison to benign subtypes, fibroblastic meningiomas present with higher FA values. Interestingly, the two categories demonstrate different tensor shapes; while tensors formed by benign meningiomas are predominantly spherically shaped (80%), a large amount of fibroblastic meningioma tensors are nonspherically shaped (43%). Jolapara et al[7] studied 21 tumor patients using DTI and found that atypical and fibroblastic meningiomas had higher mean FA value than benign meningiomas. The authors also evaluated Spherical Anisotropy, another measure of FA looking at the degree to which molecules are traveling in equal directions, and found higher Spherical Anisotropy values in benign meningiomas when compared to atypical and fibroblastic meningiomas. No reliable method of differentiating between atypical and fibroblastic meningiomas was found. Finally, Xu et al[8] determined that FA values are useful in differentiating between recurrent tumors and radiation-induced injury. Here, thirty-five glioma patients who had previously undergone radiation therapy underwent DTI. The average FA values were significantly higher in the group of recurrent tumors than that of the radiation-induced injury group. These studies demonstrate the diagnostic power of DTI.

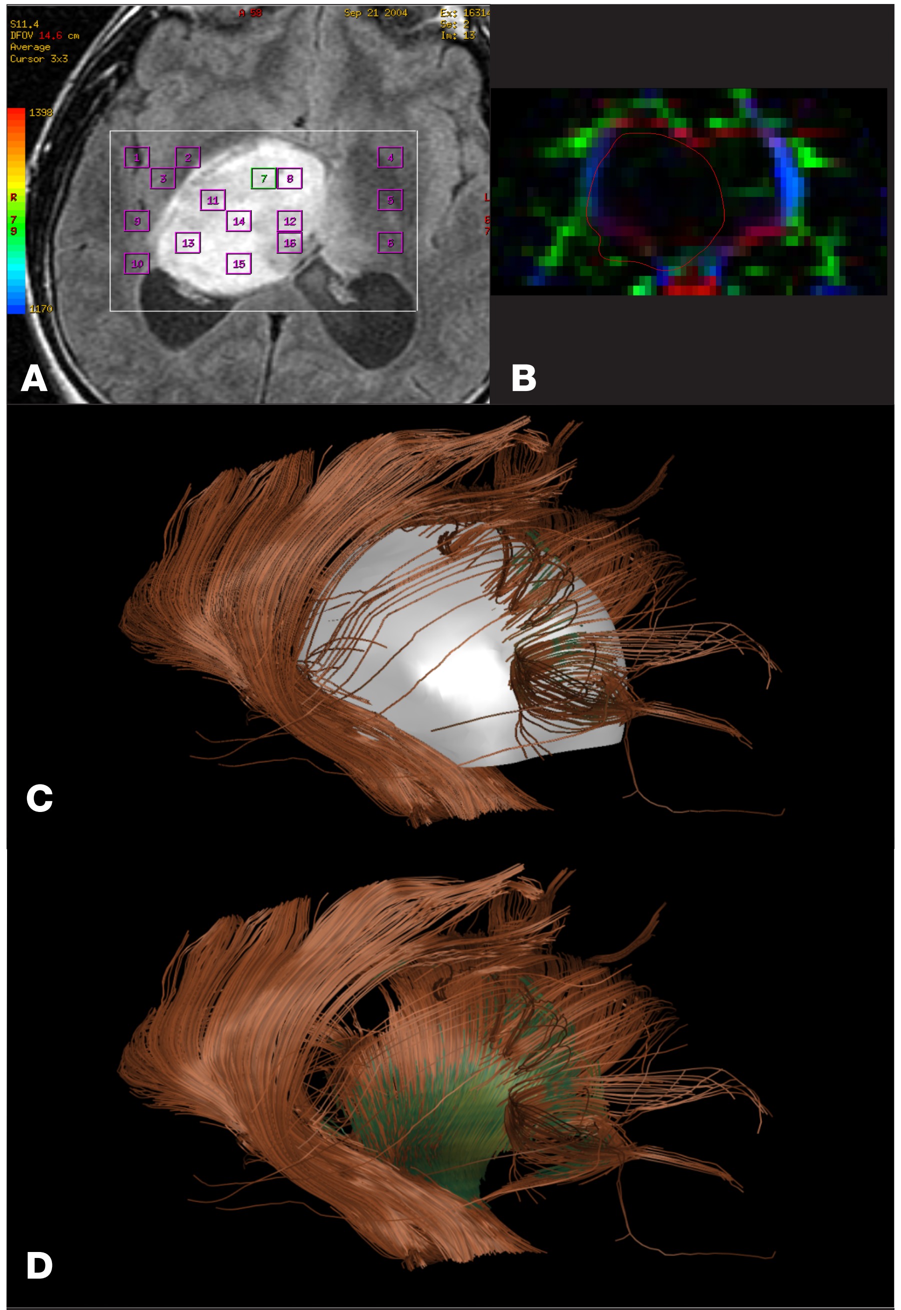

Figure 1

(A) T1 gadolinium-enhanced axial view of right-sided cranial tumor; (B) Axial color-coded DTI image of with tumor circumscribed in red; (C) 3D rendering of tumor/fiber relationship with tumor and fibers as opaque objects; (D) Translucent tumor with cutaway view.

Presurgical planning

Before a patient's operation begins, DTI information can assist surgical planning in several ways. It may be used to evaluate tumor respectability and determine surgical feasibility. Setzer et al[9] studied 14 patients with intramedullary spinal cord tumors and categorized them according to the interaction between the lesion and the surrounding WMtracts. Lesions were considered resectable (Type 1) when no fibers entered the lesion. Type 2 consisted of lesions that contained only the minority of fibers from a given tract, and was considered resectable only if less than 50% of the tumor, by volume, contained fibers. Lesions were deemed non-resectable (Type 3) when the majority of the lesion contained fibers or the tumor had already demonstrated destruction of fibers. These classifications were clinically translatable: all 5 Type 1 lesions were fully resected, the Type 2 case deemed resectable was fully resected, while 1 of 2 unresectable Type 2 tumors was unresectable, and 5 of 6 Type 3 lesions were unresectable, as evidenced at time of biopsy.

Surgical planning is enhanced by preoperative visualization of WM tract location and orientation. Yu et al[10] studied 16 brain tumor patients using DTI to reconstruct lesion location and relationship to the surrounding WM, which informed surgical planning that preserved vital tracts and maximized tumor resection. The study group demonstrated a significantly higher extent of tumor removal and postoperative improvement in locomotor function when compared to a control group whose preoperative planning included only conventional MRI methods. Qiu et al[11] enrolled 45 patients with suspected gliomas and used DTI to acquire a better understanding of the anatomical relationship between the tumor and pyramidal tract, including the direction of the pyramidal tract to the tumor, how the lesion invaded the pyramidal tract, and the distance between them. The authors noted that because this information was available to them in the planning stage, a surgical approach that was unambiguous and

Table 1. Categorized Clinical Applications of MR DTI

Application	Author	No. of Patients	Patient Type
Tumor Staging			
Identification of WM Pathology	Chen et al.[3]	10	Brainstem Lesions
Glioblastoma/Metastases Differentiation	Deng et al.[4]	20	Glioma
Glioblastoma/Metastases Differentiation	Byrnes et al.[5]	28	Glioblastoma
Fibroblastic/Benign Meningioma	Tropine et al.[6]	30	Meningioma
Atypical or Fibroblastic/Benign Meningioma Differentiation	Jolapara et al.[7]	21	Meningioma
Recurrent Tumor/Radiation-Induced Injury Differentiation	Xu et al.[8]	35	Glioma
Presurgical Planning			
Determination of Resectability	Setzer et al.[9]	14	Intramedullary Spinal Cord Tumor
	Yu et al.[10]	16	Various Tumors Types
	Qiu et al.[11]	45	Suspected Gliomas
Determination of Surgical Approach	Chen et al.[12]	1	Brainstem Cavernous Angioma
	Moshel et al.[13]	6	Juvenile Pilocytic Astrocytoma
	Golby et al.[14]	5	Various Tumors Types
	Cao et al.[15]	9	Brainstem Lesions
Identification of WM Tracts at Risk	Clark et al.[18]	4	Various Tumors Types
Intraoperative Navigation			
Tumor Resection Sparing WM Damage	Mamata et al.[20]	3	Various Tumors Types
	Wu et al.[21]	118	Pyramidal Tract Lesion
	Nimsky et al.[23]	38	Pyramidal Tract or Optic Radiation Lesion
	Nimsky et al.[24]	19	Metastatic Melanoma
	Nimsky et al.[25]	16	Temporal Lobe Epilepsy
	Hlatky et al.[22]	1	Metastatic Melanoma
Postoperative Assessment			
Identification of WM Damage	Chen et al.[33]	48	Temporal Lobe Epilepsy
	Yogajarah et al[34]	21	Temporal Lobe Epilepsy
	Winston et al.[35]	10	Medial Refractory Epilepsy
Identification of Tumor Recurrence	Price et al.[36]	25	Varying WHO Grade Tumors

Table 2. Neural Pathways Already Tracked Using MR DTI

Pathways Tracked
Pyramidal Tract
Corpus Callosum
Optic Radiation
Corticospinal Tract
Medial Lemniscus
Internal Capsule
Superior Longitudinal Fasciculus
Prefronto-caudo-thalmic Pathway
Anterior Thalmic Radiation
Dentatorubrothalmic Tract
Meyer's Loop
Uncinate Fasciculus
Geniculo-Calcarine Tract
Inferior Frontooccipital Fasciculus
Inferior Longitudinal Fasciculus
Periaqueductal/Periventricular
Pain Pathways
Sub-callosal Fasciculus
Cingulum
Anterior Commisure
Carona Radiata
Medial Longitudinal Fasciculus
Gracile Fasciculus
Cuneate Fasciculus

precise was designed. Without having to worry about disrupting the pyramidal tract, a high degree of gross total resection was possible (73.3%), with subtotal resection occurring in 13.3%. Postoperative clinical outcomes were encouraging, as 85% of the 40 patients who participated in a follow-up visit 6 months later had high Karnofsky Performance Status scores (80-100).

Chen et al[12] navigated the corticospinal tract and medial lemniscus using DTI in preparation for treatment of a brainstem cavernous angioma. Based on the orientation of the lesion to these critical WM structures, they concluded that a subtemporal presigmoid approach would provide a "safe corridor" where the lesion could be accessed. The lesion was subsequently removed while the CST and medial lemniscus remained fully intact. Likewise, Moshel et alreported their experience utilizing DTI in the pre-operative treatment planning of 6 juvenile pilocytic astrocytoma cases. In order to select the appropriate surgical approach, the fibers of the posterior limb of the internal capsule (PLIC) must first be accounted for, a task for which DTI is appropriately suited. This method was especially useful in one case where DTI identified that PLIC fibers deviated abnormally, and a more lateral approach was therefore utilized. In all 6 cases, however, gross total resection of all cystic and solid tumor was possible.

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Table 3. DTI Applications for Different Diseases

Disease	Use
Cancer	Evaluate WM Damage
	Quantify Tumor Infiltration
	Evaluate Tumor Resectability
	Surgical Design
	Identify WM Tracts at Risk
	Ensure Maximal Resection
	Prevent Over-resection
	Account for Intraoperative Brainshift
Epilepsy	Surgical Design
	Protect Optic Tract
Parkinson's	Locate Deep Brain Stimulation Targets
Myclonus Dystonia	Locate Deep Brain Stimulation Targets
Pain Management	Visualize Pain Pathway Connections

DTI software applications enable operators to closely interrogate structures of interest. WM tract location and relationship to brain regions can be visualized. Golby et aldemonstrated that operators may choose to depict WM tracts within given distances from structures of interest, such as tumors. By manipulating this distance, the anatomical context of tumor location and WM tract involvement can be discerned. One group developed individually-tailored procedures, based on patient anatomy, and found that the usefulness of DTI was most appreciated in the preparation of brainstem resections, where numerous nuclei are present and WM tracts are vulnerable to injury if not accounted for. While treating 9 patients with brainstem lesions, they noted DTI was essential in one particular case where the lesion compressed the CST and medial lemniscus posteriorly. In this instance, the standard suboccipital approach would have likely destroyed parts of the WM tracts, so the surgeons instead opted for a retromastoidal approach. Indeed, surgical approach should incorporate not just the location of the lesion, but also its relation to various WM tracts.

Rasmussen Jr. et al[16] showed that DTI could be seamlessly incorporated with functional (f) MRI and structural MRI into an ultrasound based neuronavigation system to develop tailor-made presurgical planning as well as navigation based on updated multimodal information during surgery. Here, 24 patients with primary gliomas underwent DTI and fMRI to determine the location and orientation of WM in relation to brain lesions. Patient outcomes were divided into 3 categories: Gross Total Resection (3 patients), >90% Resection[12], and Subtotal Resection[9]. No surgically induced deficits occurred in the first two groups, whereas one Subtotal Resection case resulted in expressive aphasia and hemiplegia. The authors concluded that the tandem use of DTI and fMRI provides a far superior mode of identifying functional systems to be avoided during surgery than relying only on fMRI. In a study by Berntsen et al[17], fMRI and DTI were both utilized in the treatment of 51 patients with lesions close to eloquent WM structures. The protocol proved to be critical, and led to the alteration of the clinical course in 4 patients (8%).

Prevention of damage to WM tracts is critical. By imaging 4 tumor patients, Clark et al[18] were able to identify the relative danger to the corpus callosum, CST, and superior longitudinal fasciculus as the space occupying lesions were causing significant displacement of the tracts. No longer coursing through their expected locations, these tracts would have otherwise been vulnerable to injury during surgery if not previously identified. Encouraging results have been reported by Kamali et al[19], showing that DTI is useful in even determining the placement of smaller tracts. Despite the fiber bundles being considerably thin, the prefronto-caudo-thalmic pathway and anterior thalamic radiation were reliably delineated in 5 healthy controls.

Intraoperative navigation

DTI may be utilized for intraoperative neuronavigation that facilitates tumor resection while minimizing WM tract damage.Mamata et al[20] have been attributed with first reporting on the feasibility of incorporating DTI into surgical procedures. They describe the protocol with which DT images were taken during the neurosurgical procedures of three patients, creating additional benefits to the preoperative DTI advantages previously discussed. Specifically, intraoperative changes in fiber orientation due to surgically induced brain deformation were detected, and intraoperative mapping of WM anatomy may help to avoid injury to critical WM tracts.

A study by Wu et al[21] reflects the enormous impact that intraoperative DTI may have on patient outcome. Here, 238 patients with gliomas in the vicinity of the pyramidal tract were randomized into two groups: 118 patients had DTI of the pyramidal tract incorporated into their neuronavigation for their procedures while the 120 patients in the control group used only anatomic MRI in conjunction with neuronavigation. The study group presented with a significantly better postoperative outcome based on a number of different elements, including higher occurrence of gross total resection (72.0% to 51.7%), greater incidence of improvement of motor function (18.6% to 5.9%), lower incidence of deterioration of motor function (15.3% to 32.8%), higher KPS scores at 6 month follow ups (86 ±20 to 74±28), and a longer survival time (21.2 months to 14.0). Further, a hazard ratio reported a 43.0% reduction in the risk of death when using DTI.

Hlatky et al[22] were the first to report the use of DTI-guided intraoperative neuronavigation to resect a deeply situated metastatis. Tractography of a patient with malignant melanoma aided the surgery for a single metastasis within the paraventricular WM of the CST. Postoperatively, the patient showed no intracranial recurrence and intact neurological function, suggesting that both the CST and pyramidal tracts were undamaged. Nimsky et al[23] applied intraopertive DTI during resections of 38 patients with various brain abnormalities and found intraoperative imaging to be a useful marker that surgical objectives were achieved. Intraoperative views allowed visualizations showing when an acceptable amount of resection had occurred and that MW tracts had returned to their natural positions. A second study by Nimsky et al[24] implemented intraoperative imaging during resections of 19 patients with lesions located near the pyramidal tract. Image data was used for an immediate visualization of the shifted pyramidal tract in relation to the resection cavity or any remaining tumor so that the neurosurgeon could decide whether to continue the resection or not. This proved to be a significant tool, as 6 patients (31.6%) resulted in an extended resection due to the availability of updated anatomical image data. The authors highlight the importance of having a precise layout of the fiber tracts throughout the procedure, describing how it allows the surgeon to be more aggressive in his approach without the fear of disrupting eloquent WM tracts. Nimsky et al[25] used intraoperative imaging to protect the patient on the other end of the spectrum as well. When operating on 16 patients with lesions near the pyramidal tract or optic radiation, intraoperative DTI was used to have continually updated information on the location of WM tracts. Here, the authors comment on its ability to prevent too extensive resections and possibly damage the WM, which could result in postoperative neurological deficits.

Epilepsy treatment resections have greatly benefited from DTI, sparing WM damage through intraoperative navigation. Postoperative visual field deficits are common in this treatment, as Meyer's loop courses through the often-resected temporal area. Through the use of DTI, Taoka et al[26] furthered our understanding of the challenges involved in epilepsy treatment by reviewing the images of 14 patients who underwent temporal resections in treatment of temporal lobe epilepsy. A major issue identified by the authors was the anatomic variability in the distance between Meyer's loop and the temporal tip. This range, which was found to lie between 30.0 – 43.2 mm, made it difficult to predict the location – and therefore avoid – Meyer's loop during the resection. This study directly highlights the importance of imaging the optic tracts prior to epilepsy resections to preserve the visual field. This is precisely what Thudium et al[27] did in preparation for selective amygdalohippocampectomies (SelAH) on 12 patients with mesial temporal lobe epilepsy. Despite reports[28,29] – of 37% and 53% of SelAHs resulting in major visual field deficits, the authors reported fewer postoperative visual field deficits when implementing DTI to first visualize the location of Meyer's loop prior to resection. The visual tracts were clearly delineated in each case, resulting in 9 patients (75%) recovering with no visual field deficits, while 3 patients (25%) recovered with only peripheral incomplete quadrantanopia.

Benefits have also been seen in the area of Deep Brain Stimulation (DBS), where DTI has been used to navigate to target sites of therapy. The first instance of DTI-based fiber tract targeting in DBS surgery was done by Coenen et al[30], who treated a patient with longstanding pure head tremor from myoclonus dystonia. DTI was used to visualize the dentatorubrothalmic tract, which had been previously identified as a target for movement disorders. Electrodes were successfully implanted and the tremor was alleviated. The authors note that this technique depends on a high degree of mapping accuracy, which is achieved through DTI. In a similar report by Coenen et al[31], DTI targeted the dentatorubrothalmic tract as it passed through the thalamus in the treatment of an individual suffering from tremor-dominant Parkinson's disease. Similar to the previous case, the tremor symptoms were alleviated postoperatively. The authors found this form of scanning provides a superior atlas for stereotactic surgical strategies. Owen et al[31] showed that DTI can help further our understanding of specific pathways using a patient who underwent a leg amputation 25 years prior and had since been experiencing extreme hypersensitivity and excruciating pain. By mapping out the fiber tracts that were connected to DBS electrodes implanted in the patient's periaqueductal/periventricular grey areas, the authors developed an enhanced understanding of pain pathways and were subsequently able to alleviate the patient's pain.

Postoperative assessment

DTI has shown the ability to accurately assess WM tract damage and predict postoperative outcomes. Chen et al[33] used DTI-based fiber tracking in 48 patients undergoing anterior temporal lobectomies for temporal lobe epilepsy to evaluate how Meyer's loop was oriented in respect to where resection would occur. In addition to reliably depicting the optic tract within each patient, a strong correlation was found between visual field deficits and injury to the optic radiation. The authors attributed the accuracy with which they could predict postoperative deficits to DTI's ability to demonstrate the change of the actual size of Meyer's loop – a far more accurate assessment than predicting the deficits based on the resection size from conventional MRI images. Similarly, Yogarajah et alused DTI-based fiber tracking in 21 patients with temporal lobe epilepsy, where accurate predictions of postoperative deficits were made based on the interaction between Meyer's loop and resection size. Using this information, quantifiable statistics could be gathered that allowed patients to be assigned to high risk or low risk categories for expected deficits.

The significance of having this valuable information prior to surgery is highlighted by a study by Winston et al.[35] While treating 10 patients with medial refractory epilepsy, DTI scans clearly delineated the optic radiation in relation to the lesioned areas, allowing the patients to have a greater understanding and appreciation of the risks involved and the likelihood of postoperative visual field deficits to occur. This directly impacted clinical decision-making, as two patients declined to have surgery after being informed of the risks, and two other patients decided to first pursue alternative medications before attempting surgery.

The ability to monitor tumor recurrence is yet another capacity of DTI. Price et al[36] evaluated the images of 25 patients of varying WHO grade tumors and were able to categorize various patterns of WM tract abnormalities. Based on patterns of tumor infiltration or occult tumor not readily seen on conventional MRI, they were able to predict the event of tumor recurrence and design an individualized treatment regiment accordingly.

Discussion

Diffusion Tensor Imaging (DTI) has become a powerful neurosurgical tool, but faces several challenges. DTI is currently unable to differentiate between WM tracts that cross one another, because mathematical algorithms combine several different eigenvectors to form one large, averaged tensor that signifies the primary directionality of that tract[37].Thus, when two different fiber tracts cross one another – for example, motor tracts coming in contact with the Superior Longitudinal Fasciculus – postprocessing software applications generate images based on the largest eigenvector, reducing both tracts into a single fiber bundle.Although this is more a deficiency in the software than DTI per se, it is a present limitation of this modality nonetheless. Further, while DTI readily depicts large fiber tracts, such as the CST, smaller tracts are far more difficult to identify, and require great knowledge of WM anatomy to visualize.[39]

Secondly, preoperative DTI images may not correlate to intraoperative brain position. Maesawa et al[41] found that 89.2% of patients demonstrated significant shifting of WM tracts during their surgical resections, rendering the preoperative imaging no longer reliable. This is not a specific deficiency of DTI, however, and is an expected problem whenever the skull is opened. Nimsky et al[41] found a similar occurrence of 'brainshift' during their study (92%) and reported that the marked displacement of WM ranged from -8 to +15mm. Based on these results and others where brainshift was a concern,[11,17,33] one can appreciate the hesitation of solely relying on preoperative images for the entirety of a surgical procedure. While intraoperative imaging is therefore recommended, it poses its own set of limitations. In addition to the technical challenges, numerous studies have documented the additional time required to successfully generate intraoperative images, which can be upwards of 20 minutes.[24,39]

There are some inherent limitations to DTI.The tractography generated by DTI will vary according to FA, angular threshold, vector stop length, and size and location of regions of interest.[18] Further, the interpretation of images is directly related to the user's anatomical knowledge of WM tracts.[14] In other words, the user must actively interrogate the DTI dataset for specific WM tracts as these tracts may not be inherently or intuitively visible.

The future of DTI is promising. Researchers are currently addressing many of the existing challenges to ensure greater accuracy and precision. Encouraging results have already been reported in terms of differentiating fiber bundles, as Smits et al[43] have reportedly been able to distinguish hand, foot, and lip fibers within the CST.Progress is also being made in identifying smaller fiber tracts. Similarly, researchers have recently begun to establish a protocol and determine optimal conditions through which intraoperative images may be taken.[39,44]

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