Chapter 9

The role of diffusion tensor imaging in brain tumor surgery: a review of the literature

A.R.E. Potgieser¹
M. Wagemakers¹
A.L.J. van Hulzen¹
B.M. de Jong²
E.W. Hoving¹
R.J.M. Groen¹

¹Department of Neurosurgery
²Department of Neurology
University Medical Center Groningen, University of Groningen, the Netherlands

Clinical Neurology and Neurosurgery 2014;124:51-58
ABSTRACT
Diffusion tensor imaging (DTI) is a recent technique that utilizes diffusion of water molecules to make assumptions about white matter tract architecture of the brain. Early on, neurosurgeons recognized its potential value in neurosurgical planning, as it is the only technique that offers the possibility for in vivo visualization of white matter tracts. In this review we give an overview of the current advances made with this technique in neurosurgical practice. The effect of brain shift and the limitations of the technique are highlighted, followed by a comprehensive discussion on its objective value. Although there are many limitations and pitfalls associated with this technique, DTI can provide valuable additional diagnostic information to the neurosurgeon. We conclude that current evidence supports a role for DTI in the multimodal navigation during tumor surgery.
The role of diffusion tensor imaging in brain tumor surgery

INTRODUCTION

The consequence of the extent of glioma resection regarding life expectancy is still debated due to lack of class I evidence, although current results seem to favor a more radical resection for both low grade and high grade gliomas [1]. The ultimate goal and major challenge in glioma surgery is to obtain maximal resection while minimizing loss of neurological function. Diffusion tensor imaging (DTI) is a tool that contributes to achieve this goal by visualizing white matter tracts. From the early introduction of the fiber tracking technique neurosurgeons saw potential for non-invasive mapping of white matter tracts, especially in planning the optimal approach to a lesion. The first practical implementation was the integration of the pyramidal tracts, estimated with diffusion weighted imaging, in a neuronavigation system [2]. Meanwhile, a large number of studies investigated the value of diffusion tensor tractography for neurosurgical planning, focusing mainly on the major white matter tracts as they are most easily visualized. Most studies involved benign or malignant lesions involving the corticospinal tract [3–35], optic tract [3,17,19,23,29,36–43], superior longitudinal fasciculus [5,26,27,44] and arcuate fasciculus [3,19,29,45,46]. Nearly all authors report a positive experience with this relatively new technique. However, the beneficial effect is hard to quantify. Many authors describe the use of tractography as ‘helpful’, ‘of great help’ or ‘beneficial’, without exactly determining what the value was. It may have influenced the choice of approach and intraoperative decision making, but whether it has affected the quality and quantity of the resection remains difficult to ascertain. Few authors described in detail how tractography changed their surgical strategy, e.g. Chen et al. or Nimsky et al. [22,34]. Until now, there are no controlled studies that relate clinical outcome to the integration of DTI in a neuronavigation system.

Following a general introduction to the method, we want to outline the pitfalls and potential benefits of DTI as a tool for pre- and intraoperative neurosurgical planning in tumor resection in this review.

Principles of DTI

In vivo quantification of diffusion of water molecules using magnetic resonance imaging (MRI) was first described in 1986 [47]. Diffusion can be described as random thermic motion, or Brownian motion [48]. The technique utilizes the fact that in tissue diffusion is not necessarily random due to barriers that limit diffusion in one or more directions (see Le Bihan and Johansen-Berg for an excellent introduction) [49]. Unhindered diffusion of water molecules is referred to as isotropic diffusion. Restriction of movement along only one axis is called anisotropic diffusion. Among others, the measured diffusion process depends on the applied magnetic gradients and the axis of myelinated white matter tracts [50–53]. The mechanism of this anisotropy along white matter tracts is not exactly known. From studies in developing brains it has become clear that the degree of myelinisation has a role, with more myelinisation causing more anisotropy [54–57]. However, this is only a partial explanation, because anisotropy is also apparent before the white matter is myelinated [58]. With DTI it is possible to use anisotropy to analyze axonal organization of brain. This is based on the concept of a diffusion tensor, which is a mathematical model that describes the three-dimensional process of diffusion in different axes [59]. In theory, it is already possible to get an impression of the diffusion process if scanning is performed in six directions [60,61], but generally many more directions are scanned to obtain a better recording. There are various ways to perform tractography based on the diffusion tensor. Fiber assignment by a continuous tracking (FACT) algorithm is frequently used [62]. This is a deterministic approach that uses
the average axonal orientation within a voxel to estimate axonal projections, based on user-defined variables such as the fractional anisotropy (FA) and the maximum tract angle. Later on, a probabilistic approach was introduced to be able to trace tracts up to and within the gray matter without relying on the arbitrary anisotropy threshold [63]. This method is also more resistant to noise, because it is less vulnerable to halts in the tractography due to individual voxels with an ambiguous fiber direction.

Several research groups used DTI to create white matter tracts atlases [64–68]. These atlases show good correspondence with atlases created with real-tissue dissections.

**Technical limitations of the technique**

Numerous technical considerations should be addressed in order to create a realistic concept of DTI when using this technique for neurosurgical planning. Current DTI techniques fall short on spatial resolution, signal to noise ratio (SNR) and susceptibility to a heterogenic magnetic field [69]. A first remark should be made about the resolution of diffusion-weighted imaging, which is in the range of millimeters. The diffusion process that is the source for computational modeling of white matter tracts takes place at molecular level [49]. Thus, DTI does not depict the actual diffusion process and derived actual tracts. For the intraoperative tractography the air-tissue boundary introduces additional susceptibility artifacts. Another issue is the user-dependedness of the technique, which starts at the acquisition of the data. Differences may be introduced in for example the amount of scanning directions, diffusion-weighting [70] and in magnetic field strength. It has been shown that the SNR increases when using a higher field strength [71–74]. This leads to enhanced visualization of fiber tracts. The SNR is a quantitative measure to compare the strength of the MRI signal with the noise. There are many different methods to calculate the SNR [75]. For example, the easiest method to get an impression of the SNR is to define the signal (S) as the mean signal intensity in a 2D region of interest of ten by ten voxels with maximum uniform signal intensity in every slice of the DTI scan. The noise (σ) is the standard deviation of the signal intensity in this region of interest. SNR is then calculated according to the following formula [75]: $\text{SNR} = S/\sigma$.

Recently it has been stated that for analysis of major white matter tracts (such as the corpus callosum with an FA of 0.8) an SNR of 20 is a minimum requirement, being 40 for tracts with lower FA values (0.45) [76]. The optimal FA threshold for integration of tractography in the neuronavigational device was suggested to be in the range of 0.15–0.2 [77], which needs an even higher SNR.

At lower SNR values the accuracy, precision and reproducibility of measured FA values is negatively influenced [78]. More noise has the effect that it converts diffusion isotropy to anisotropy and it augments anisotropy by an underestimation of the smallest eigenvalue ($\lambda_3$) and an overestimation of the largest eigenvalue ($\lambda_1$) [79,80]. Clearly, this has an effect on the tractography results. SNR appears to be underreported in the studies that investigated the value of DTI in neurosurgical planning. Several methods can be used to increase the SNR, such as scanning with a higher magnetic field, increase the number of repetitions, scan a $b_0$ image for every eight diffusion weighted images and cardiac gating [81–85].

**Method of tracking**

An important choice to be made is the method of tracking. Currently most studies perform tracking using a deterministic or probabilistic approach (for an example see Fig. 1). Most studies evaluating the use of DTI in neurosurgical planning use a deterministic approach, and only a few, such as in studies involving Meyer’s loop of the optic tract, use a probabilistic approach.
The deterministic method is based on the assumption that the orientation of fibers can be described by a single orientation. Clearly, this is an oversimplification as the millimeter-sized voxels contain thousands of axons, which can have different orientations. The probabilistic method can proceed in areas where the fiber direction is of lower certainty. Due to the fact that this is a very time-consuming method it is currently not possible to intraoperatively integrate this method in the neuronavigation. Furthermore, this method creates a 3D map of possible connectivity, which is not necessarily based on actual anatomy. Newer methods that account for crossing or kissing fibers are being developed. These methods take all the eigenvectors of a voxel into account and include high angular resolution diffusion imaging and diffusion spectrum imaging.

Figure 1. Posterior view of a deterministic tractography of a 34-year-old patient with a right-sided frontotemporoparietal gemistocytic astrocytoma prior to a planned fourth resection. The tumor is highlighted in yellow. We placed a region of interest in the right cerebral peduncle, without further adjustment to get nicer results. The left image shows the close relationship of the tractography of the pyramidal tract (green) projected on a T1-weighted MRI scan. The right image shows the same deterministic tractography projected on the fractional anisotropy map. The deterministic tractography approach follows only the principal diffusion direction. As a consequence, it is clearly visible that only part of the pyramidal tract is depicted, with the lateral and most medial aspect of the tract missing. Blue: superior–inferior tracts, green: antero–posterior tracts, red: right–left tracts.

User-dependent factors influencing the technique
Jones and Cercignani nicely illustrated these relevant aspects and numerous pitfalls in DTI. In addition to processing pitfalls, other factors should be considered as well. The choice of the fiber tracking program may influence the tractography results. A significant difference in anatomical accuracy was found when evaluating nine different programs. After the choice of a program the tracking results may vary due to different choices of vector step length, FA threshold and angular threshold. There is also a registration error of less than 3 mm for the fiber tracts when integrating it in the neuronavigation. Furthermore, the tracking depends on chosen location and size of the seed regions. To reduce user-dependence, fMRI activations can serve as an objective method to derive seed regions, although this cannot be updated intraoperatively. On the other hand, fMRI also...
has its flaws and pitfalls when it comes to identifying exact functional cortical regions. User-dependedness is often quoted as one of the major drawbacks of the technique. However, for the experienced individual neurosurgeon the user-dependedness may be expected to add value, because lessons can be learned from previous cases when using the same settings. It has been shown that experienced neurosurgeons have low intraobserver variability in generating tracts [23]. As with other surgical capabilities this is part of a life long learning process.

**Effect of brain shift**
A general problem of image-guided surgery with neuronavigation is that the preoperative coordinate system of the patient does not remain rigid. During the operation several factors may cause the brain to deform, such as patient positioning, the anesthesiology, the craniotomy, opening of the dura, resection of tissue, use of retractors, formation of edema, preoperative ischemic events, opening of tumor cysts or the ventricular system, and leakage of cerebrospinal fluid. As a consequence, the interpretation of preoperative data is affected. For example, at the cortical surface and near deep tumor margins brain shift can be up to 24 mm and 3 mm respectively [98]. Moreover, brain shift is unpredictable as it is a dynamic process that changes over time [99] and it does not necessarily move along the direction of gravity [100]. It therefore seems a logical step to correct for the brain shift to get an update of the real anatomy, because the preoperative tractography might lose its significance. For the specific situation of white matter tracts the brain shift has been well documented. Using intraoperative MRI Nimsky et al. [11] registered FA maps in the neuronavigation and showed that white matter tract shifting ranged from -8 to 15 mm, while it was unpredictable whether inward or outward shifting would occur. White matter tracts can also be localized by direct stimulation [101], bypassing the problem of brain shift. Without intraoperative updating, this resulted in a distance of +1.8 to +13.4 mm between the corticospinal tract assessed with DTI and the stimulated motor response point [28]. Furthermore, a combination of these techniques may lead to a better starting point for stimulation [22].

The effect of brain shift does not withhold many neurosurgeons from using neuronavigation during the operation, keeping in mind that the interpretation of DTI should be put into this perspective. A mental update of the neuronavigation can be made using anatomical landmarks and intraoperative neuromonitoring. DTI can also be of value in providing additional information. Intraoperative updating, whether real, mental or mathematical [102], seems to be important. Intraoperative MRI is not widely available due to financial and practical limitations, although it seems to have benefits through a reduction in repeat surgery, length of stay in the hospital and costs [103]. A different option would be to use ultrasonography for intraoperative updating, which has also been used for tractography-based neuronavigation [104].

**White matter tract organization**
Several groups have tried to find changes in white matter tracts adjacent to a tumor using DTI metrics, mostly the FA. Field et al. [105] classified four patterns of tumor induced alteration of white matter tracts, namely displacement with a normal FA, normal tract locations and tensor directions with a decreased FA, decreased FA with abnormal tensor directions and near isotropy. Witwer et al. classified the tracts adjacent to tumor as displaced, disrupted, edematous or infiltrated [19]. Others invented a relative anisotropy index as a measure for white matter organization [106]. This index was significantly lower in areas of white matter adjacent to high-grade gliomas, but not with low-grade gliomas or metastases, which suggested
white matter disruption in the high-grade gliomas. Several others tried to use DTI metrics to distinguish low-grade gliomas, high-grade gliomas and metastases or to distinguish related vasogenic edema from tumor infiltration, disruption or displacement [107–121]. Both tumor infiltration or disruption and vasogenic edema lead to a decreased FA. Compression of a tract leads to an increased FA [5]. In cats it was shown that a cortical cold lesion model inducing vasogenic edema enhances diffusion [122]. In order to demonstrate tumor infiltration in white matter tracts, Stadlbauer et al. correlated FA and fiber tracking results with histopathological findings from stereotactic biopsies, although not corrected for brain shift [77,123]. They suggested an FA threshold of 0.15–0.2 is most favorable to minimize faulty tracking, but to include infiltrated fibers [77]. This is an important comment, because earlier Kinoshita et al. showed that the size of a fiber tract was not accurately estimated and relying on it led to more neurological deficit in one patient [4]. As mentioned earlier, when using such a low FA it is a challenge to obtain an adequate SNR for bias-free FA measurement, which stresses the importance of measurement of the SNR [76]. While DTI metrics such as the FA may help in the differentiation of normal, invaded and disrupted white matter tracts, the effects for tracking can be detrimental, because sometimes the reconstructed fibers cannot pass through an area of peritumoral edema, while the real fibers can [17,44,124,125]. The interpretation of the significance of the tractography becomes even more complex because it has been shown that pathologically infiltrated white matter can have preserved function [126,127]. Current DTI metrics are thus not capable of estimating exact white matter organization, nor white matter ‘integrity’ [69]. Fig. 2 shows an example of a case with normal, displaced and disrupted tracts due to a large tumor.

**Discussion**

Currently, DTI is the only technique that creates in vivo depiction of white matter tracts. Although there are many limitations and pitfalls associated with this technique, it can provide the neurosurgeon with additional valuable morphological/anatomical information. As with many new techniques, its introduction gives rise to skepticism [128]. Although the results look very promising, the problem is that DTI-studies, by definition, cannot be blinded. The technique definitely needs further standardization, validation and technical improvement. Every increase in information about the tumor and the vital tracts will be of use to optimize decision-making before and during the operation. As suggested by Duffau, it seems that DTI is not reliable enough to base decisions on in the operating theater, given the current limitations of the technique [129]. However, we do not share the opinion that the technique is merely a research tool [130]. As with any diagnostic test, one needs to be able to interpret and to integrate the different findings. No specific test is infallible. DTI gives additional information that needs interpretation. Just like high signal intensity adjacent to tumor on a T2-weighted images needs interpretation to determine whether it represents edema or tumor invasion that should be resected. Direct electrical stimulation, that could be considered the current gold standard, also has drawbacks, such as variation of the responses, due to anesthetic regimens and susceptibility to electrical excitability [131,132]. Furthermore, in our experience direct stimulation not always leads to unequivocal determination of functional areas to base the ongoing surgical strategy on. Ultimately, however, direct neurostimulation is the best we currently have. Unlike direct stimulation, DTI can provide additional preoperative information, which may help in determining the best surgical approach. Especially with non-invasive lesions, and in the absence of significant edema, others found that assessment of white matter tracts had influence on the initial surgical approach as it provided additional
Figure 2. Preoperative DTI images of representative tracts of a 40-year-old patient with a large left-sided diffuse gemistocytic astrocytoma that presented with focal epileptic seizures (dysphasia). All images are made with deterministic tractography with an FA threshold of 0.18. R denotes the right side of the brain. (A) 3D graphical lateral view of the tumor (blue/purple) and the relation with the left arcuate fascicle (yellow). These deep structures are projected on the surface of the cerebral cortex. (B) The same tract projected on a transversal T2-weighted FLAIR MRI, showing that there is space between the arcuate fascicle and the tumor, although there seems to be a close relationship. (C) The cingulate fasciculi projected on a coronal T1-weighted MRI (without gadolinium contrast). (D) The pyramidal tracts projected on a coronal T2-weighted FLAIR MRI, which shows that the left tract has a close relationship with the tumor, but does not seem to be displaced or disrupted. (E) This picture clearly shows that the left inferior fronto-occipital fasciculus is disrupted by the tumor and there is a stop in the tractography. (F) 2D illustration of the displacement and also disruption of the left uncinate fascicle by the tumor.
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Information [31,34].

As DTI is an anatomical (and not a functional) determinant, its combination with direct stimulation provides important functional validation of the anatomy involved. In fact, with slow growing lesions, cortical reorganization may take place resulting in anatomically evident but functionally rudimentary tracts, which thus appeared to be resectable [133–135]. However, this dichotomy between functional and anatomical tracts does not hold. With DTI a reorganization of white matter tracts, induced by training, has been depicted [136], which provided evidence for the plasticity of the neural circuits. The underlying mechanisms of these changes are not clear. Also, one should bear in mind that damage to small blood vessels adjacent to a tract may result in ischemic injury, leading to a neurological deficit [137].

An additional advantage of DTI is that it facilitates the identification of tracts of interest, especially in combination with electrical stimulation, because one can have better expectations where to find the tract. In this respect, the combination of DTI with electrical stimulation appears to be synergistic [18]. As a result, mapping during awake surgery can be more effective and efficient, leading to less discomfort and less fatigue for the patient [27].

The aforementioned limitations of the technique, combined with the effect of brain shift and edema, brain displacement, disruption or tumor-invasion of tracts, may all lead to false negative or false positive estimation of tracts. The limitations and potential benefits of DTI are summarized in Table 1. This is why the DTI findings, especially in the clinical situation, should be interpreted with great caution [69]. In this light, the critical safety distance of 5 mm seems to be arbitrary [22,138]. It is wiser to apply the gold standard of direct electrical stimulation to assess the accuracy of the tractography [6,139,140]. There is a high concordance between DTI tractography and direct electrical stimulation (sensitivity of 92.6% and specificity of 93.2% in the study of Zhu et al.), which validates the tractography findings [6,20,27,141]. In another study it was found that the probability of eliciting a motor response during subcortical stimulation depends on the distance between the tractographic estimate of the pyramidal tract and the tumor [142]. If the distance of stimulation is closer to the tractography of the pyramidal tract, indicating close proximity of the pyramidal tract to the resection cavity, there seem to be more neurological deficits [143]. In fact, the largest study involving 238 patients reported less postoperative deficit, higher Karnofsky scores and a positive effect on the survival when surgery was guided by FA maps (not tractography) during the operation [7].

Conclusion

DTI has shown to be a promising technique in pre- and intraoperative navigation in tumor surgery. A thorough knowledge of its limitations and potential pitfalls is indispensable for the interpretation and safe application of this promising new technique. For bias-free FA measurement, a sufficiently high SNR is important in the clinical use of DTI. As pointed out, a thorough knowledge of the pitfalls of the tractography in the pre- and intraoperative situation is of utmost importance. We believe that DTI has a role in multimodal navigation, especially in combination with intraoperative direct neurostimulation. The functional validation of DTI tracking by intraoperative stimulation provides synergistic use of both techniques. It has the potential to aid in maximal tumor resection, without increasing morbidity. Intraoperative neurostimulation remains the gold standard to determine the anatomical and functional borders.
### Chapter 9

**Table 1.** Limitations and potential benefits of DTI in neurosurgical resection of tumors.

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<tr>
<th>Limitations</th>
<th>Potential benefits</th>
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<tr>
<td>Variability in data acquisition, possibly leading to low SNR’s</td>
<td>Defining optimal surgical approach</td>
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<td>Tractography depends on used software, tracking method, seed region and other user-specified variables</td>
<td>Potential beneficial role in multimodal navigation to maximize tumor resection, without causing more morbidity</td>
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<td>Registration error</td>
<td>Synergy with other modalities</td>
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<td>Brain shift affects tractography reliability</td>
<td>Possibility of intraoperative updating may guide in optimal resection strategies</td>
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<td>False negative tracts by white matter tract alterations</td>
<td>Improved orientation for direct stimulation</td>
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<tr>
<td>False positive tracts (tracts without function)</td>
<td>Confirmation with direct stimulation</td>
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