Diffusion Tensor Tractography in the Presurgical Assessment of Cerebral Gliomas

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SUMMARY – Glioma is the most common intra-axial brain tumor characterized by invasion into the surrounding white matter (WM) tracts. These tumors are usually diagnosed by conventional MRI, but this method is unable to describe the relationship between tumor and neighboring WM tracts. Diffusion tensor tractography (DTT) is a new imaging modality which can solve this problem. The current study evaluated the application of DTT imaging in the presurgical assessment of gliomas, and introduces this new modality and its importance to physicians and imaging centers in Iran. Ten patients with intra-axial brain tumor and suspicion of glioma underwent conventional brain MRI pulse sequences and DTT imaging between December 2011 and February 2013 with a 1.5 Tesla system using 64 independent diffusion encoding directions. Acquired images were assessed by the neuroradiologist and neurosurgeon. The treatment strategies were recognized and compared using data before and after the tractography. On the basis of DTT data, the treatment strategy changed from radiotherapy to the craniotomy in seven patients, and in one patient, the neurosurgeon preferred to avoid surgery. In one patient, the treatment technique did not change, and in the last one radiosurgery was replaced by craniotomy. As we can infer from this study, based on the tractography results, the treatment strategy may be changed, and the treatment technique could be devised more accurately and may lead to fewer postoperative neurological deficits and better outcomes.

Introduction

Glioma is the most common primary intra-axial brain tumor which is characterized by invasive growth along fiber tracts in the white matter (WM)¹⁻³. A significant challenge prior to surgery is to identify the extent of malignant cell infiltration within WM tracts because the WM fiber structures connect functional cortical regions. Delineation and characterization of fiber bundles are important to understand normal brain functions and changes due to pathologic processes⁴. Considering that most patients with tumors in eloquent areas such as the motor cortex (corticospinal tract: CST) are neurologically intact or slightly impaired, preservation of vital cerebral tissue while maximizing tumor resection is the principal goal in surgical

neurology^{5,6}. For this reason, it is essential to distinguish functional brain tissue from tumor-infiltrated tissue to avoid causing neurological deterioration during excision of these lesions^{6,8}. WM tract involvement adjacent to brain tumors can be classified as edema, infiltration, displacement or disruption. Although routine structural MR images can accurately demonstrate brain tumors, they do not give precise information on the involvement and integrity of the WM tracts in the immediate region surrounding the tumor^{4,6}. Currently, several functional approaches such as functional MR imaging and intraoperative mapping like functional mapping using somatosensory-evoked potentials (SEP) phase reversal, and subcortical mapping and monitoring using continuous cortical motor-evoked potentials (MEPs) are

used in the presurgical localization of eloquent cortex near brain tumors. Functional MR imaging will identify important functional areas of the cerebral cortex that may be invaded by a neoplasm. This imaging modality focuses on cortical structures but does not provide information on the subcortical gray and white matter, which in many instances may be invaded in invasive, intrinsic brain tumors^{5,6}. While cortical and subcortical electrophysiological mapping and monitoring using SEP phase reversal mapping, subcortical MEP mapping and cortical MEP monitoring are regarded as the gold standard in the treatment of lesions near the corticospinal tract, MRI-based diffusion tensor imaging fiber tracking (DTI-FT) is a recent technique used for presurgical planning and intraoperative localization of white matter tracts⁵. In ordered structures such as brain, water molecules diffuse with a non-uniform pattern called diffusion anisotropy. Using diffusion encoding gradients in at least six directions and acquiring diffusion-weighted images (DWI) from these directions, we can measure diffusion anisotropy, and then calculate the tensor and fractional anisotropy (FA) map of white matter tracts and then show the tracts and their orientations^{4,6,7,10-13}. On color-coded maps left-right orientation is usually represented in red, while anterior-posterior and superior-inferior orientations are usually represent in green and blue, respectively. However, depth information would not be shown clearly if the fiber tracts were rendered by lines with a constant width without visualizing the tumor and peritumoral tissue synchronously¹⁴. The aim of this study is to show the important role of DTI-FT for surgeons to know which and how WM tracts are affected by the tumor, and how they can approach the tumor to minimize post-operative neurological deficits. In the other words we aimed to assess the treatment strategy before and after tractography and also to suggest this method as a one of the useful imaging modalities in the presurgical assessment of tumors in some cases with gliomas in Iran.

Patients and Methods

Ten patients (mean age: 48.6, ranging from 36 to 60 years old) participated in this study between December 2011 and February 2013. They had been diagnosed with intracranial tumors verified by conventional MRI. Nine patients had been selected for stereotactic biopsy

to determine the type and stage of the tumor and undergo radiotherapy or radiosurgery for treatment during the week after MRI examination; and one patient who underwent stereotactic biopsy four months earlier had been selected for craniotomy. All patients provided routine informed consent prior to the investigations.

Data acquisition

All patients underwent MRI examination by 1.5 Tesla, Siemens, Espree scanner with an eight-channel head coil. First anatomical T1-weighted images (3D fast spoiled gradient recalled echo sequences) were acquired to overlay the selected fibers on them. In addition T2-weighted images were acquired before fiber tracking for a better evaluation of tumor margins if necessary. After that, DWI were taken in the corresponding time period, covering the entire brain volume with the following parameters: single shot echo planar imaging sequences; TR:9000 ms; TE:106.2 ms; slice thickness: 2.3 mm; matrix size: 96×96; FOV: 180×180 mm; NEX:2; the number of diffusion-encoding directions for each slice was 64 with two b-values:0 and 1000 s/mm²; usually 60 axial slices needed for complete coverage of the brain.

DTI data processing

In addition to DWI data processing and 3D fiber tract reconstruction by scanner, all acquired data were transferred into our image-processing laboratory and processed with DTI Studio software (Johns Hopkins University, USA). FA and apparent diffusion coefficient (ADC) maps were generated with noise removal level 50, and tensor also calculated. A color-coded map was created using the FA map and eigen vector₀. Then we did fiber tracking by drawing the ROI on the selected fibers using color-FA images (which in most patients was the corticospinal tract). We extracted the corticospinal tract between the primary motor cortex and the midbrain using two ROIs. The first ROI defined the entire cerebral peduncle in an axial plane at the level of the decussation of the superior cerebellar peduncle. The most ventral axial slice that can clearly identify the cleavage of the central sulcus in the tracking result was selected and the bundle in the primary motor cortex was defined. The trajectories outside the two ROIs may cross the midline via the pontine crossing fibers and re-enter

Figure 1 Diffusion tensor tractography in a patient with a left parietofrontal oligodendrioma grade II. The tumor can be visualized in axial T1-w spin echo (A), T2-w spin echo (B), and T2-w TIRM dark fluid (C). The corticospinal tract is overlaid on the coronal b0 image (D). The corticospinal tract remains intact slightly deviated medially due to lesion pressure. In this patient the treatment technique changed from radiotherapy to craniotomy.

Figure 2 Diffusion tensor tractography in a patient with a right parieto-temporal lesion diagnosed as oligodendrioma grade I. Decreased fractional anisotropy (FA) at the site of the lesion indicating the infiltration or destruction of WM tracts can be easily seen on the FA map (A) and color-coded FA (B). The uncinate fasciculus was intact and with enough distance to tumor (C), but the corticospinal tract went through the tumor or disrupted it and in some places had no distance from the tumor. The treatment strategy in this patient after DTT was radiotherapy.

the contralateral hemisphere; these tracts were removed using the “NOT” operation across the entire mid-sagittal slice. Another tract requested by neurosurgeons based on the tumor location was the uncinate fasciculus. The best protocol for extracting the uncinate fasciculus is drawing a ROI over the entire temporal lobe in the most posterior coronal slice in which the temporal lobe is separated from the frontal lobe. The second ROI includes all projections toward the frontal lobe in the same slice chosen for the first ROI. The last step in DTI data processing was to overlay the selected fibers on T1 or T2-weighted anatomical images.

Evaluation

All acquired images (FA, ADC maps, color-FA and 3D reconstructed fibers) were evaluated by an expert radiologist to report which neuronal fibers were affected by the tumor and how. We categorized the type of involvement of WM tracts into four groups according to Witwer et al.’s criteria: 1) displaced (deviated) WM tracts: if they maintained normal anisotropy relative to the corresponding tract in the contralateral hemisphere but were situated in an abnormal location or with an abnormal orientation on color-coded orientation maps; 2) edematous: if they maintained normal anisotropy and orientation but demonstrated high signal intensity on T2-weighted MR images; 3) infiltrated: if they showed reduced anisotropy but remained identifiable on orientation maps; 4) disrupted (destroyed): if anisotropy was markedly reduced such that the tract could not be identified on orientation maps. Then, the anatomic images which included the selected fibers (overlaid images) were shown to the neurosurgeons: the treatment strategy was chosen after fiber tracking was noted. Finally, these results were compared with the tumor treatment techniques based on the conventional MR images.

Results

Ten patients diagnosed with intra-axial brain tumor were referred to the imaging center. Diffusion tensor imaging was performed. In a first step, FA, ADC and directional maps (color-coded FA map) were calculated; then fiber tracking was performed (Figures 1 and 2). The calculated maps and images were reported by a neuroradiologist expert in reporting the results of tractography images. The reports are noted below:

Patient # 1: A 36-year-old man with an intra-axial brain tumor in the left frontoparietal and right parietal lobes. MR tractography showed deviation of WM tracts medially, posteriorly and laterally due to the left frontoparietal lesion. Diminished FA and color brightness was also noted in these tracts especially in the medial WM tracts, but no significant changes in color hues were noted; findings could be due to edema. Similar changes with less severity were noted in the right frontal lobe FA and directional maps. The lesion was diagnosed as oligodendrioma grade II. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 2: A 60-year-old man with an intra-axial brain tumor in the left frontal lobe. The mid-frontal central and parieto-occipital fibers and genu of corpus callosum were shown intact on tractography. Medial displacement without distortion of frontal corpus callosum fibers but destruction and distortion of the left high frontal fibers of the mid-frontal and small part of the superior frontal connecting fibers were also shown, and other tracts were normal. The lesion was diagnosed as glioblastoma. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 3: A 51-year-old man with an intra-axial brain tumor in the left parietal lobe. DTI and DTT results showed compression and deviation of white matter tracts at the anterior and posteromedial aspect of the lesion with decreased and absent anisotropy at the cystic area suggestive of WM tract destruction. The lesion was diagnosed as malignant gliosarcoma/glioblastoma grade IV. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 4: A 48-year-old man with an intra-axial brain tumor in the left frontal lobe. DTI and DTT results showed deviation of white matter tracts at the anterior, medial and posterior aspects of the lesion with diminished and absent anisotropy indicative of infiltration and destruction of some WM fibers. The lesion was diagnosed as astrocytoma grade II. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 5: A 60-year-old woman with a left temporo-occipital mass lesion in the brain. MR tractography results showed compression and deviation of the left internal capsule (posterior tracts) and posterior corticospinal tracts (corona radiata) and also optic radiation were seen anterolaterally and in contact with the

mass. Posteromedial deviation of the splenium of corpus callosum was also seen that were in contact with the lesion. The lesion was diagnosed as oligodendrioma grade I. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 6: A 39-year-old man with a right frontal intra-axial brain tumor. The tractography results showed diminished FA in the right frontal lobe lesion indicative of infiltration and destruction of WM tracts and also deviation and compression of tracts at the lateral and posterior aspect of the lesion. The lesion was diagnosed as oligodendrioma grade II. The treatment strategy before DTT was craniotomy.

Patient # 7: A 49-year-old woman with a right temporoparietal intra-axial brain tumor. The tractography results showed compression and deviation of corticospinal and other WM tracts at its medial, anteroposterior and craniocaudal aspects. Deviation of the splenium of corpus callosum at its posteromedial aspect was also seen. The lesion was diagnosed as oligodendrioma grade II. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 8: A 56-year-old man with a mass lesion in the right parieto-temporal lobe. The tractography results showed deviation and compression of WM tracts at the anteromedial and posterior aspect of the lesion. Foci of diminished or absent FA at the site of lesion could be suggestive of infiltration or destruction of some WM fibers. The lesion was diagnosed as oligodendrioma grade I. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 9: A 47-year-old woman with a lesion in the right parietal lobe. The tractography results showed compression and deviation of WM tracts at the anterior and posteromedial aspect of the lesion. The lesion was diagnosed as astrocytoma grade II. The treatment technique before DTT was radiotherapy following stereotactic biopsy.

Patient # 10: A 40-year-old man with a left parietal intra-axial mass lesion. The tractography results showed the retrolenticular part of the internal capsule was distorted (deviated) but not involved. The angular gyrus was involved by the mass including fiber and cortex. The lesion was diagnosed as astrocytoma grade I. The treatment strategy before tractography was radiosurgery.

These reports with fiber tracking images were then shown to the neurosurgeons and the treatment procedures before and after

fiber tracking were recorded (Table 1). As seen in Table 1, in seven patients (nos 1-5,7,9) the treatment technique changed from radiotherapy to craniotomy which is more effective to make a better prognosis for patients, and in patient number 6, physicians preferred to avoid surgery because of many connections between tumor and adjacent WM tracts. The operation strategy before tractography in this patient was craniotomy. In patient 8, the corticospinal tract went through the tumor, so the treatment plan did not change in this patient. In patient 10 the operation strategy changed from radiosurgery to craniotomy. According to DTT results, the treatment technique changed in approximately all patients, and in one patient helped to plan a treatment procedure with more assurance. No significant additional neurological deficits occurred after surgery except in patient 1 who was temporarily hemiplegic for one week after surgery.

Discussion

Intracranial neoplasms may invade both functional cortical gray and white matter (WM) tracts⁶. In the surgery of patients with brain tumors preservation of vital cerebral functions is as important as maximizing tumor resection. The associated morbidity of aggressive resection can be significantly reduced by careful preservation of vital cerebral function so that the quality of life of these patients will be greatly improved. Simultaneously maximizing tumor resection can reduce the chance of tumor recurrence and improve longer patient survival and long-term functional status^{15,16}. So a comprehensive assessment of the extent of the tumor is vital to all neurological and surgical therapies. Magnetic resonance imaging has a key role in neuroimaging for diagnosing any brain pathologies, such as tumors. Tumor can be easily detected using conventional MRI (cMRI). Enhanced MRI using contrast medium such as gadolinium shows the margins of the tumors, and also their different enhancement patterns indicate the tumor stage and to some extent help differentiate some pathologies from others. These methods in cMRI are unable to show the eloquent cortex and functional white matter tracts in the brain. fMRI is a relatively new imaging modality which can show the functional areas in gray matter cortex by applying specific task/ stimulation related to each cortex, but fMRI does not give precise informa-

Table 1 Patient information and treatment strategy before and after diffusion tensor tractography.

<i>Pt. NO</i>	<i>Age/ Sex</i>	<i>Pathology</i>	<i>Tumor location</i>	<i>WM involvement</i>	<i>Treatment technique before DTT</i>	<i>Treatment technique after DTT</i>	<i>Post op. deficit</i>
1	M-36	Oligodendrioma, grade II	Lt. parito-frontal	Deviation and edema involvement of WM tracts	Radiotherapy	Craniotomy	Temporary hemiplegia
2	M-60		Lt. frontal	Displacement of frontal CC*, destruction and distortion of SFC* fibers	Radiotherapy	Craniotomy	None
3	M-51	Gliosarcoma (GBM), grade IV	Lt. parietal	Destruction of WM tracts near tumor	Radiotherapy	Craniotomy	None
4	M-48	Astrocytoma, grade II	Lt. frontal	Infiltration and destruction of WM tracts near tumor	Radiotherapy	Craniotomy	None
5	F-60	Oligodendrioma, grade I	Lt. temporo-occipital	Deviation of Lt. internal capsule, posterior CST*, splenium of CC	Radiotherapy	Craniotomy	None
6	M-39	Oligodendrioma, grade II	Rt. frontal	Infiltration and destruction of WM tracts near tumor	Craniotomy	No operation	–
7	F-49	Oligodendrioma, grade II	Rt. temporo-parietal	Deviation of CST and splenium of CC	Radiotherapy	Craniotomy	None
8	M-56	Oligodendrioma, grade I	Rt. Parieto-temporal	Deviation and compression of WM tracts at the antero-medial and posterior aspect of lesion	Radiotherapy	Radiotherapy	–
9	F- 47	Astrocytoma, grade II	Rt. parietal	Deviation and compression of WM tracts near tumor	Radiotherapy	Craniotomy	None
10	M-40	Astrocytoma, grade I	Lt. parietal	Deviation of retrolenticular part of internal capsule and involvement of angular gyrus	Radiosurgery	Craniotomy	None

*CC: corpus callosum, SFC: superior frontal connecting fibers, CST: corticospinal tract

tion on WM tracts which are as important as cortical eloquent areas and might be involved in intra-axial brain tumors. The development of accurate, noninvasive and *in vivo* methods like tractography to map WM fiber tracts is of critical importance. Knowledge of the exact location of eloquent WM pathways with respect to a lesion is of great value to neurosurgeons in

planning the appropriate treatment strategy. A key assumption is that the results are a faithful representation of the underlying axonal microstructure and thus the WM tracts themselves¹⁶⁻¹⁹. Applying DTT to depict WM neural fibers started in 2002. These early studies verified the utility of this technique for treatment planning in patients with intra-axial brain tumors.

Figure 3 Parameters needed to define a 3D diffusion ellipsoid (Mori S. Introduction to Diffusion Tensor Imaging. Amsterdam: Elsevier; 2007).

They showed that it is possible for anatomically intact neural fibers to be located in abnormal areas in the brain, and removing these tracts might have neurological deficits. In 2005, researchers used DTT in intra-operative studies and showed that major neural fibers near anatomical data with high resolution provided trustable directions to approach the tumor to increase the extent of safe resection, and consequently improve patient prognosis. In spite of these studies, a shortage of valid information on the reliability of fiber tracking results regarding impaired anatomical location led to further research. Studies investigating the relationship between DTT and histopathological information in 25 patients with gliomas grades I and II showed the consistency of tumor infiltration into surrounding WM tracts with neurological outcomes¹⁶⁻¹⁹. Despite these studies, some researches could not show the efficiency of DTT in treatment planning, but nonetheless recommended performing DTT in presurgical tumor assessment because of the potentially useful effects of this imaging modality.

However, we are aware of the utility and important role of this new modality in neuroim-

aging to help neurosurgeons choose treatment plans more accurately and thereby reduce post-operative neurological deficits. fMRI and DTT are not routine imaging modalities and they are performed in very few imaging centers in Iran. Therefore approximately all neurosurgery departments operate on patients with intra-axial brain tumors completely blind and without any information on the eloquent cortex and WM tracts. In the Shohada neurosurgery department that co-operated with us in this study, the treatment strategy in patients with intra-axial brain tumor located in or near motor or language areas is radiotherapy following stereotactic biopsy. Based on the opinion of our neurosurgical team, if the distance between the tumor and neural fibers is at least one gyrus, they can do craniotomy with little concern about post-operative neurological deficits. As we mentioned before, maximum resection of the tumor is a valuable treatment in patients with brain tumor, offering patients a better prognosis and reducing the chance of tumor recurrence.

This study compared the treatment strategy before and after fiber tracking in ten patients with intra-axial brain tumor suspicious of gli-

oma. The strategy changed after tractography in approximately all patients or was chosen with more assurance. No neurological deficits were shown two months after surgery in all nine patients who underwent craniotomy. It should be mentioned that there was temporary hemiplegia in patient 1, but this deficit disappeared one week after surgery. Finally, we consider that tractography may have many advantages for patients, and also for neurosurgeons to devise accurate and more reliable surgical strategies.

Conclusion

Diffusion tensor imaging allowed the identification of multiple viable WM pathways within hemispheres involved by intra-axial tumors. Involvement of WM tracts may be important in surgical planning and in predicting the extent of safe resection in patients with intrinsic brain tumor. We should bear in mind that diffusion tensor tractography is a new powerful method to extract specific WM tracts. Although this modality is highly sophisticated, and more studies should be done to optimize and simplify fiber tracking, its potential possibilities to help neurosurgeons access tumors with minimal post-operative deficits is an important issue that cannot be ignored.

Recommendation

In some cases in addition to tractography, neurosurgeons requested fMRI of the motor cortex. Finally they suggested DTT and fMRI may be complementary, and if both of these pre-surgical assessments are used, physicians can choose a better treatment technique with more assurance. This idea has been proved by many studies: utilizing these imaging modalities synchronously may improve lesion localization and targeting within the cortical gray matter (functional anatomy) and along deep WM structures (connectivity). In addition, seed point placement (drawing ROIs) based on anatomical landmarks in the diffusion data may be prone to random errors, while fMRI activations offer the possibility of operator-independent placement.

So, it seems necessary to carry out more studies on various aspects of fMRI in combination with DTT to evaluate the value and validity of these methods in brain lesion assessments.

Appendix

Diffusion tensor imaging (DTI) provides information in a three dimensional space on water molecules diffusion in a given direction at the cellular level due to restrictions such as the myelin sheath covering neural axons. Water molecules diffuse more easily parallel to the WM tracts rather than perpendicular to them; consequently the measured image signals are higher for diffusion-gradient encoding perpendicular to the WM tracts than parallel. This directional variation in the signal intensity is termed "diffusion anisotropy". In tractography we measure diffusion anisotropy in each pixel using a matrix called "tensor" by acquiring DW images with at least six non-collinear gradient-encoding directions. The next task is to determine the six parameters (λ_1 , λ_2 , λ_3 , v_1 , v_2 , and v_3) from the six diffusion constant measurements or in the other words from the diffusion ellipsoid. The three parameters, λ_1 , λ_2 , and λ_3 , are called eigenvalues and the three vectors (v_1 , v_2 , and v_3 , are called eigenvectors (Figure 3). The principle eigenvector (principle vector of diffusion ellipsoid) in each pixel represents the direction of greatest diffusion which also corresponds to the fiber tract axis. With this directional information, the WM tract organization may be represented using directionally color-coded schematic maps of major eigenvector orientation^{4,6,7,10-13,17,18}.

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