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BRAIN TUMOR THERAPY-INDUCED CHANGES IN NORMAL-APPEARING BRAINSTEM MEASURED WITH LONGITUDINAL DIFFUSION TENSOR IMAGING

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Abstract

Purpose—To characterize therapy-induced changes in normal-appearing brainstems of childhood brain tumor patients by serial diffusion tensor imaging (DTI).

Methods and Materials—We analyzed 109 DTI studies from 20 brain tumor patients, aged 4–23 years, with normal-appearing brainstems included in the treatment fields. Those with medulloblastomas, supratentorial primitive neuroectodermal tumors and atypical teratoid rhabdoid tumors (n=10) received postoperative craniospinal irradiation (23.4–39.6 Gy) and a cumulative dose of 55.8 Gy to the primary site, followed by 4 cycles of high-dose chemotherapy. Patients with high-grade gliomas (n=10) received erlotinib during and after irradiation (54–59.4 Gy). Parametric maps of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were computed and spatially registered to three-dimensional radiation dose data. Volumes of interest included corticospinal tracts, medial lemnisci, and the pons. Serving as an age-related benchmark for comparison, 37 DTI studies from 20 healthy volunteers, aged 6–25 years, were included in the analysis.

Results—The median DTI follow-up was 3.5 years (range, 1.6–5.0 years). The median mean dose to the pons was 56 Gy (range, 7–59 Gy). Three patterns were seen in longitudinal FA and ADC changes: (1) a stable or normal developing time trend, (2) initial deviation from normal with subsequent recovery, and (3) progressive deviation without evidence of complete recovery. The maximal decline in FA often occurred 1.5 to 3.5 years after the start of radiation therapy. A full recovery time trend could be observed within 4 years. Patients with incomplete recovery often had a larger decline in FA within the first year. Radiation dose alone did not predict long-term recovery patterns.

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Conclusions—Variation existed among individual patients after therapy in longitudinal evolution of brainstem white matter injury and recovery. Early response in brainstem anisotropy may serve as an indicator of the recovery time trend over 5 years following radiation therapy.

Keywords

Diffusion tensor imaging; Brainstem; Radiation therapy

INTRODUCTION

The brainstem is a critical dose-limiting organ when in proximity to the targeted volume for patients with brain and head and neck tumors receiving high-dose irradiation. When irradiating the brainstem, there is a potential for severe neurological deficits and impairment of basic vital functions. Knowledge on the radiation tolerance of brainstem is extremely limited (1) and the potential impact of conformal radiation therapy on brainstem injury is not well understood. Due to the inability to discern brainstem substructures on conventional anatomic imaging and limited long-term clinical data, the brainstem has long been regarded as a single organ with a population-based tolerance constraint applied to all patients to achieve a <5% complication rate within 5 years after irradiation. To improve the therapeutic index of definitive treatment, there is a strong need to measure and understand how subvolumes of the brainstem respond to irradiation in individual patients and the contribution of treatment and clinical factors.

The brainstem contains densely packed motor, sensory, cerebellar, and cranial nerve pathways and nuclei. The primary motor pathways in the brainstem are the bilateral descending corticospinal tracts, which originate from the motor cortex and traverse through the brainstem and spinal cord to connect with lower motor neurons. They control voluntary body posture adjustments and limb movement. The posterior column medial lemniscal pathway and the anterolateral pathway are two major ascending sensory tracts passing through the brainstem. The former carries discriminative touch, vibration sense, and proprioceptive information, and the latter conveys crude touch, pain, and temperature sense from the body to the somatosensory cortex in the postcentral gyrus. Despite their importance and different functional roles, it has not been possible to noninvasively visualize and measure the integrity of these major white matter pathways until the emergence of diffusion tensor imaging (DTI).

DTI is a quantitative magnetic resonance imaging technique that measures the preferential direction and magnitude of water diffusion in tissues. Water diffusion in white matter tracts is normally directionally dependent or anisotropic due to the ordered structure of axons and myelin sheaths. Changes in the structural integrity of white matter tracts because of disease or injury can be reflected on DTI-derived anisotropy and diffusivity indices. Numerous lines of evidence support the use of DTI as an imaging biomarker to noninvasively assess radiation-induced white matter injury (2-5). Animal histologic studies demonstrate a strong correlation between changes in DTI-derived indices and radiation-induced demyelination and axonal degeneration in the brain (3). Water diffusion anisotropy calculated from human in vivo DTI was also associated with the cumulative axonal membrane circumference, axonal density, and myelin thickness within the surgical specimen from supratentorial brain (6). We hypothesized that childhood brain tumor patients receiving radiation to the brainstem may show longitudinal patterns of diffusion property changes reflecting the evolution of therapy-induced injury and recovery when measured with serial DTI. Information revealed by these patterns may lead to a deeper understanding of the time course of therapy-induced brainstem injury and tract-specific radiation sensitivity. In this

study, we aimed to characterize therapy-induced changes in the brainstems of childhood brain tumor patients with DTI during the first 5 years after irradiation.

METHODS AND MATERIALS

Patients and healthy volunteers

This study was approved by our institutional review board. We retrospectively analyzed 109 DTI studies from 20 childhood brain tumor patients, 12 males and 8 females with normal-appearing brainstems, defined as no obvious signal abnormality on conventional T1-weighted images, and the longest follow-up enrolled in two institutional clinical trials (7, 8) between November 2004 and February 2008. The median age at the start of radiation therapy was 7 years (range, 4-23 years). Of the 20 patients, 7 had medulloblastoma, 2 had supratentorial PNET, 1 had atypical teratoid rhabdoid tumor (ATRT), and 10 had gliomas (6 anaplastic astrocytomas, 2 oligoastrocytomas, 1 ganglioglioma, and 1 glioblastoma multiforme). None of the patients in this study had clinical or imaging evidence of brainstem necrosis during the follow-up period. DTI studies were acquired at postoperative baseline as the first time point, at the completion of radiation therapy, and every 6 months thereafter up to 5 years. For comparison with irradiated brainstems, we also analyzed 37 DTI studies of 20 healthy volunteers (10 males and 10 females, aged 6-25 years, uniformly distributed) enrolled in an institutional functional imaging protocol between June 2008 and December 2009. Each healthy volunteer except the three oldest had two consecutive annual DTI studies. Healthy control data were used to construct a normal age-related benchmark. To circumvent the need to sedate young healthy children for minimizing head motion during imaging studies, we did not recruit volunteers younger than 6 years. These control subjects had no history of acquired brain injury, developmental delay, or learning disability.

Treatment characteristics

Medulloblastoma, supratentorial PNET, and ATRT patients in this study received definitive surgery, craniospinal photon irradiation of 23.4 Gy or 36-39.6 Gy, depending on risk-classification, followed by a cumulative 55.8 Gy boost to the primary site and 4 cycles of high-dose chemotherapy (vincristine, cisplatin, and cyclophosphamide), each cycle followed by infusion of peripheral blood stem cells or bone marrow-derived stem cells. Postoperative high-grade and unfavorable low-grade glioma patients received up to 3 years of erlotinib, a tyrosine kinase inhibitor, during and after 54-59.4 Gy radiation therapy. Radiation was delivered at 1.8 Gy per fraction 5 days per week.

DTI acquisition

DTI studies for patients were performed on a 1.5-T Siemens Symphony MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a double spin echo, echo planar imaging (EPI) pulse sequence with the following parameters: TR/TE= 10 s/100 ms; FOV 192×192 mm²; matrix 128×128; 3-mm slice thickness; 40 slices; 4 repetitions. Diffusion encoding was applied along 12 non-collinear, non-coplanar directions in space (diffusion weighting factor $b=1,000$ s/mm²), and 1 reference image dataset was acquired without diffusion encoding ($b=0$ s/mm²). The total imaging time of each DTI study was approximately 8 minutes for 4 repetitions. T1-weighted three-dimensional (3D) sagittal MR images in MPRAGE sequence, a part of a standard clinical MR protocol, were acquired with a slice thickness of 1.25 mm in the same imaging session for each patient to facilitate registering DTI-derived parametric images to treatment planning CT images and three-dimensional radiation dose data. For healthy volunteers, the DTI acquisition technique was similar, except it was performed with TR/TE=6500/120 ms and a b -value of 700 s/mm² on a 3-T Siemens Trio MR scanner due to the need to conduct additional functional MRI activation studies that required a greater magnetic strength.

DTI processing

Acquired raw diffusion tensor data were processed to derive the two most widely used indices of anisotropy and diffusivity, FA and ADC, on a pixel-by-pixel basis. FA is a scalar index representing the directionality of water diffusion within each pixel, ranging from 0 for isotropic water diffusion to 1 for highly anisotropic diffusion in the tissue. ADC is a scalar measure of tissue water diffusivity in terms of the mean-square displacement of an ensemble of molecules within a unit of time, often expressed in mm^2/s . FA and ADC reflect the degree of alignment and organization of cellular structures within the neural fiber tracts and infer their microstructural integrity (3, 6, 9). Quantitative FA and ADC maps were computed from raw diffusion-weighted images using Siemens Neuro3D Syngo software. FA and ADC maps from multiple time points were registered to treatment planning CT through T1-weighted high-resolution 3D structural scans acquired at the same time.

Volumes of interest

Three volumes of interest were manually drawn on each axial slice of eigenvector-color-coded FA maps at the level of the pons. The first volume of interest contained the segments of bilateral corticospinal tracts in the pons. The second volume of interest was intended to include bilateral medial lemnisci and spinothalamic tracts. Since these two sensory tracts are immediately adjacent to each other and cannot be easily separated at the level of the pons, we drew a combined volume of interest to contain both fiber bundles. Other smaller adjacent fiber tracts were probably included in this volume of interest, such as rubrospinal tracts, central tegmental tracts, and ventral trigeminothalamic tracts. However, for simplicity, we will refer to this volume of interest as medial lemniscus/spinothalamic tracts. The third volume of interest was the entire pons. In the caudal-to-cranial direction, the most caudal and cranial slices determining the extent of the pons are those at which the middle cerebellar peduncle first appears and at which it is no longer visible, respectively. Fig. 1 shows an example healthy subject with volumes of interest overlaid on T1-weighted, FA, and ADC images. Fig. 2 is an example eigenvector-color-coded FA image of a 15-year-old male illustrating that major fiber bundles in the pons can be identified when the principal eigenvector at each image pixel, suggesting the fiber tract orientation, is assigned a specific color based on its direction. The volumes of interest drawn on the baseline DTI study were projected onto spatially-registered DTI studies from subsequent time points. For younger patients whose brainstem size may have changed over the follow-up period, we redrew volumes of interest to ensure the pons and the fiber tracts were properly contained at each time point.

Age-related normal changes in DTI indices

We recruited 20 healthy volunteers from 6 to 25 years old to generate DTI datasets for deriving age-related normal changes in FA and ADC of the developing brainstem. Average FA and ADC over each volume of interest were computed for all healthy volunteers and plotted against the subject's age at the time of DTI scan. These scatter plots of FA and ADC versus age were then fitted with logarithmic functions using the least squares approach. Longitudinal changes of FA and ADC of individual patients were compared with these fitted normal benchmarks.

Statistical analysis

Statistical analysis and curve fitting on healthy volunteer data were performed with Matlab version 7.6 (The MathWorks, Inc., Natick, MA). Two-sample paired *t*-test was performed to assess statistically significant differences in DTI-derived indices between left and right, corticospinal tracts, and medial lemniscus/spinothalamic tracts in healthy volunteers. To determine whether trends in the recovery time of motor and sensory tracts in the pons of

childhood brain tumor patients were different, we used linear mixed effect models to fit the longitudinal FA and ADC ratios of medial lemniscus/spinothalamic tracts to corticospinal tracts.

RESULTS

Age-related normal changes in FA and ADC

We tested the left and right symmetry in the mean FA and ADC values of corticospinal tracts and medial lemniscus/spinothalamic tracts at the level of the pons based on 20 DTI studies of 20 healthy volunteers. If the subject underwent more than one DTI study, the first study was used. We found no statistically significant differences between the left and right corticospinal tracts (paired t -test, $p=0.152$ for FA and $p=0.171$ for ADC) or medial lemniscus/spinothalamic tracts ($p=0.171$ for FA and $p=0.153$ for ADC) in healthy volunteers. When dividing 20 subjects into two gender groups (10 males and 10 females), the only asymmetry present was in the mean FA values of corticospinal tracts in males ($p=0.017$). On average, FA was 2.6% greater in the left corticospinal tract than in the right for males. All healthy subjects were either strongly or mixed right-handed based on the Edinburgh Handedness Inventory performed at the time of imaging studies.

Averaging left and right volumes of interest for corticospinal tracts and medial lemniscus/spinothalamic tracts, we plotted the mean FA and ADC values versus the subject's age at the time of DTI study using 37 DTI studies of 20 healthy volunteers, as shown in Fig. 3. Logarithmic fits to the population data indicated a gradually increasing trend in FA and a decreasing trend in ADC with age from 6 to 25 years in corticospinal tracts, medial lemniscus/spinothalamic tracts, and the entire pons. For all ages of study, the mean FA was higher in the medial lemniscus/spinothalamic tracts than in the corticospinal tracts ($p<0.001$). However, these tracts had similar ADC values ($p=0.617$).

Temporal changes in FA and ADC in patients

Twenty brain tumor patients underwent a median of 5 DTI studies (range, 4-9) with a median follow-up of 3.5 years (range, 1.6-5.0 years). Longitudinal evolution of FA and ADC in the pons was highly variable among individual patients. For illustrative purposes, we loosely categorized the time trends of FA into three groups as shown in Fig. 4: (1) rising or relatively stable time trends similar to those observed in healthy volunteers; (2) initial decline during the first three years followed by a rebound to baseline values; (3) progressive decline without evidence of recovery. Though generally opposite to FA patterns, ADC patterns were less distinctive. They included a normal decreasing pattern, an abnormal increasing pattern, and a pattern with an initial increase followed a subsequent decrease. The percentage change from the baseline FA in the pons for all patients is plotted in Fig. 5 with three colors representing three temporal patterns. For patients whose pons showed an initial decline in FA with or without complete recovery, the maximal percentage decrease from the baseline value ranged from 10% to 35%. The maximal decline was most likely to occur 1.5 to 3.5 years after the start of radiation therapy. Patients with incomplete recovery, as represented by red curves in Fig. 5, seemed to exhibit a higher rate of decline in the first year than patients with no decline or with complete recovery during the follow-up period, represented by green and blue curves. This observation suggests that the early response in brainstem anisotropy may serve as an indicator of the recovery time trend over 5 years following radiation therapy.

Corticospinal tracts vs. medial lemniscus/spinothalamic tracts

To determine whether the degree of structural integrity change resulting from therapeutic insult for major motor and sensory tracts of the brainstem in patients was different, we

plotted the longitudinal evolution of the mean FA of bilateral corticospinal tracts, bilateral medial lemniscus/spinothalamic tracts, and the entire pons in Fig. 6. In general, these two motor and sensory tracts followed a time trend as similar to that of the pons. However, discrepancy arose in three patients (cases 6, 8, and 9 in Fig. 6) with the corticospinal tracts and the pons showing a pattern of initial decline with subsequent recovery in FA while their medial lemniscus/spinothalamic tracts continued a normal increasing trend. On the other hand, the reverse has not been seen in this cohort of patients, i.e., a normal time trend for corticospinal tracts but abnormal for medial lemniscus/spinothalamic tracts. We further performed linear mixed effect model fitting to determine whether recovery time trends were different for these motor and sensory tracts. For each time point for each patient, we calculated the ratio of mean FA and ADC in medial lemniscus/spinothalamic tracts to mean FA and ADC in corticospinal tracts, both first normalized to their individual baseline values. This ratio indicates which neural tract suffered a larger decline in FA and a larger increase in ADC relative to their baseline values. The linear mixed effect model equation fitting the longitudinal data was: $FA\ ratio = 1.01 + 0.016 \times t$, where t is the time since the start of therapy in years and $p < 0.01$ for the slope. This suggests that FA of the medial lemniscus/spinothalamic tract recovered slightly better than that of the corticospinal tract. For ADC, the difference in recovery time trends for these two tracts was not statistically significant ($p = 0.41$).

Radiation dose and changes in FA and ADC

Because measures considered in this study were mean FA and ADC over the entire pons and two major neural tracts at the level of the pons, here we inspected the corresponding mean rather than maximal radiation dose to these structures. The median mean dose to the pons, corticospinal tracts, and medial lemniscus/spinothalamic tracts was 55.5 Gy (range, 7-59 Gy), 55.7 Gy (range, 6-59.3 Gy), and 56.3 Gy (range, 6-60 Gy), respectively. Two patients who received < 20 Gy to the pons had a normal increasing trend in FA and a normal decreasing trend in ADC for the pons and two major motor and sensory tracts. For 6 patients who received 35-54 Gy to the pons, which was considered below the conventional brainstem tolerance dose, their time trends were mixed, including all three patterns shown in Fig. 4. Surprisingly, the patient who had the largest decline in FA (30-40% from baseline values) in our patient cohort received only 45, 40, and 46 Gy to the pons, corticospinal tracts, and medial lemniscus/spinothalamic tracts, respectively. For the remaining 12 patients who received 54-60 Gy, one had a fairly stable pattern, 4 showed a complete recovery pattern, and 7 did not completely recover to baseline values during the follow-up period. Results suggested that using the conventional brainstem tolerance dose of 54 Gy as a threshold cannot completely ensure the long-term recovery pattern in FA of nerve fibers.

DISCUSSION

Our findings in this study support that brain tumor therapy-induced structural integrity changes in cerebral white matter, including the brainstem, can be detected and quantified in vivo with DTI-derived anisotropy and diffusivity indices. Several earlier studies showed that patient DTI acquired at a single time point after irradiation was statistically different from those of age-matched healthy controls (10-13). More recent studies of serial DTIs performed from before radiation therapy to 14 months after revealed that FA changes in cerebral and cerebellar white matter of adult patients can be detected during and at the end of radiation therapy (2, 14, 15). Progressive changes persisted beyond the end of radiation therapy. Further expanding knowledge on the long-term evolution of therapy-induced white matter injury, our data showed that differences existed among individual patients in the recovery pattern of DTI changes, at least in the brainstem. For patients who showed an initial decline in FA, many presented a time trend reversal 1.5 to 3.5 years after the start of chemotherapy

and radiation therapy and even recovered to their baseline values by year 4. However, patients who had a larger decline within the first year of therapy appeared to have a consistently lower FA over the follow-up period. Our DTI findings suggest a slightly longer recovery time in the brainstem from a mean dose of 56 Gy than what was reported based on reirradiation data of animal spinal cords (16, 17). Since we previously identified surgical morbidity and tumor extent as important risk factors for incomplete recovery of brainstem function after radiation therapy (18), we hypothesize that the variation in white matter response to therapy-induced injury is a combined effect of the radiation dose delivered, clinical risk factors, and the individual patient's ability to repair therapeutic damage.

Changes in DTI-derived indices of white matter tracts in the brainstem may have a significant clinical relevance since an association with neurologic function has been reported in various diseases (19-22). Given that DTI-derived indices reflect radiation-induced histologic changes; these indices may serve as important quantitative imaging biomarkers of brainstem injury if the association with neurologic functional outcome can also be established in patients receiving radiation therapy. Due to the large variation observed, we continue to accrue patients to increase the sample size. To demonstrate the clinical relevance, we have started to prospectively evaluate brainstem neurologic functions and extremity motor and sensory functions in parallel to serial imaging studies. A link between DTI changes and neurologic deficits will create a new, objective and sensitive strategy for monitoring therapy effects and anticipating the progression from occult injury to clinical symptoms. The ability to quantitatively measure neural tract recovery from previous treatment might help select patients for reirradiation if they experience local-regional tumor recurrence near the brainstem.

The EPI-based DTI acquisition is known to suffer from eddy current distortion and geometric distortion due to inhomogeneities in local magnetic fields. Without applying sophisticated algorithms for correction of susceptibility artifacts, our experience indicated that the quality of DTI datasets in children is sufficient for visualizing and delineating major motor and sensory neural tracts in the brainstem (23-24). However, continued improvements in DTI acquisition, distortion correction, and fiber tractography are needed to further resolve brainstem nuclei, fiber tracts of small caliber, and decussating fibers in the medulla and cerebellar peduncles.

Because potential bias may exist between DTI indices measured with 1.5-T and 3-T systems, we caution readers not to directly compare the absolute values of these indices between patients and healthy subjects. Instead, we encourage readers to focus on comparing the time trends. Our observed time trends of gradually increasing FA and decreasing ADC with age from 6 to 25 years in healthy subjects from 3-T data are in agreement with previous publications using 1.5-T MR systems (25-26), also consistent with the fact that white matters of the central nervous system mature during childhood and adolescence, involving increases in white matter myelination, density, and organization (27, 28). Additional pediatric subjects are currently being recruited to undergo DTI scans on both 1.5-T and 3-T systems for estimating and correcting the effects of magnetic field strengths and scan protocols on DTI-derived indices.

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Fig.1. Spatially-registered T1-weighted MR, FA, and ADC images of an example subject at mid pons. Overlaid are contours containing bilateral corticospinal tracts (red), medial lemniscus/spinothalamic tracts (green), and the pons (blue).

Fig. 2.

An example eigenvector-color-coded FA image at mid pons. ML, medial lemniscus; STT, spinothalamic tract; CTT, central tegmental tract; RST, rubrospinal tract; CST, corticospinal tract; TPF, transverse pontine fiber; MCP, middle cerebellar peduncle.

Fig. 3.

Age-related normal changes in (a) FA and (b) ADC of corticospinal tracts, medial lemniscus/spinothalamic tracts, and the entire pons of 20 healthy volunteers. Solid curves are logarithmic fits to these population data. ML/STT, medial lemniscus/spinothalamic tract; CST, corticospinal tract.

Fig. 4. Longitudinal patterns of FA (left panels) and ADC (right panels) of the pons of 20 brain tumor patients. Medulloblastoma, supratentorial PNET, and ATRT patients are in crosses and glioma patients are in circles. Top two plots are patients with a rising or stable pattern in FA. Middle plots represent a pattern of initial decline with a rebound. Bottom plots represent a pattern of progressive decline with no evidence of complete recovery. Dashed lines are fitted time trends for healthy volunteers.

Fig. 5.

The percentage change from baseline FA of the pons for 20 brain tumor patients. Patients with a fairly normal pattern, a pattern of initial decline with a rebound, and a progressive decline pattern in Fig. 4 are represented here in green, blue, and red, respectively.

Fig. 6. Longitudinal evolution of mean FA of corticospinal tracts (solid blue), medial lemniscus/spinothalamic tracts (dashed green), and the entire pons (thick solid red) of 20 brain tumor patients.