Mapping radiation dose distribution on the fractional anisotropy map: Applications in the assessment of treatment-induced white matter injury

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We describe a method to map whole brain radiation dose distribution on diffusion tensor MR (DT-MR) fractional anisotropy (FA) images and illustrate its applications for studying dose–effect relationships and regional susceptibility in two childhood medulloblastoma survivors. To determine the FA changes voxel-by-voxel in white matter, the post-treatment follow-up FA maps were coregistered to baseline pretreatment FA maps and automatic segmentation for white matter was carried out. ΔFA maps representing relative FA change in white matter were hence generated for visual inspection and quantitative analysis. The radiation dose distribution, calculated from radiotherapy plan and exported as images, was coregistered to baseline FA images. DT-MR imaging and processing noise was small with root mean square value of 1.49% for mean ΔFA. We evaluated the mean ΔFA changes of regions-of-interest according to radiation dose regions to provide an estimate of the dose–response and found increasing reduction in mean ΔFA with increasing radiation dose up to 45 Gy after which there was a reversal in the mean FA trend and mean FA approached baseline value. We also found more severe mean FA reduction in the frontal lobes compared to the parietal lobes despite the same radiation dose, suggesting regional susceptibility in the frontal lobe, and mean FA increase in the brainstem after radiation in both patients. We conclude that the method described may be useful in estimating dose–effect relationships and studying regional susceptibility of the brain to radiation in medulloblastoma survivors.

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Introduction

Medulloblastoma (MED) survivors commonly suffer from neurocognitive deficits which impact significantly on their quality of life (Mulhern et al., 2004). Treatment using whole brain radiotherapy is considered to be the major contributory factor that causes these deficits (Johnson et al., 1994; Mulhern et al., 1998; Silber et al., 1992). It has been shown that white matter (WM) is predisposed to radiation-induced injury and that it may be the substrate of neurocognitive deterioration. There is emerging evidence that diffusion tensor MR (DT-MR) imaging, using fractional anisotropy (FA), is sensitive in detecting and monitoring white matter injury in these patients (Khong et al., 2003, 2005, in press; Leung et al., 2004). We have shown in our previous studies that WM FA is reduced in post-treatment MED survivors and that the reduction in WM FA correlates significantly with known risk factors of neurotoxicity, including age at irradiation (Khong et al., 2005). Although we found a trend of reduced FA with higher irradiation dose, the dose effect on FA was limited by the small dose range of whole brain irradiation among the subjects (Khong et al., 2005). We also found that the reduction in WM FA correlates significantly with IQ scores, suggesting that WM FA can be used as a biomarker of post-treatment WM damage in this cohort of subjects (Khong et al., in press).

In this study, we describe a method which maps whole brain radiation dose distribution to the FA images of MED patients. With this tool, we are able to study voxel-by-voxel, the FA changes over a wider dose range and also to evaluate regional susceptibility to irradiation, between and within subjects. Dose correlations with FA change are valuable as they could conceivably provide a threshold for brain damage. Knowledge of regional susceptibility and dose threshold is important in radiotherapy planning, especially with the widespread usage of conformal radiotherapy as well as intensity-modulated radiotherapy in treatment protocols nowadays. This is
particularly true for the inverse planning approach used in intensity-modulated radiotherapy. We illustrate these applications in two MED patients who underwent sequential DT-MR imaging scans prior to and after whole brain irradiation.

Materials and methods

Patients and control subjects

Two newly diagnosed MED patients (A and B) were recruited for the study with informed consent obtained from the patients and parents. This study was approved by the Institutional Review Board of the hospital. Patient A was female, aged 10.7 years at treatment and she received 23.4 Gy of crani-o-spinal irradiation followed by a boost to the posterior fossa to give a total dose of 56 Gy. Patient B was male, aged 9.4 years at treatment and he received 36 Gy of cranio-spinal irradiation followed a boost to the posterior fossa to give a total dose of 56 Gy. Both patients also had prior surgical excision of the tumor and subsequent chemotherapy, which comprised CCNU (lomustine), cisplatin and vincristine (CCV protocol). CT scan was performed for radiotherapy planning and dose calculations. The patients underwent DT-MR imaging before the commencement of radiotherapy and subsequently three DT-MR imaging follow-ups at approximately 3 months, 6 months and 1 year after completion of radiotherapy.

In order to validate the reliability and estimate the accuracy of the method, two normal healthy control subjects (two males, aged 23 years and 33 years) were recruited with informed consent, and each underwent DT-MR imaging twice at different time-points using the same imaging protocol as the patients’.

DT-MR imaging

MRI was performed using a Signa 1.5 T imager (General Electric Medical Systems, Milwaukee, WI, USA) with a standard head coil. DT-MR imaging data were acquired using single-shot spin-echo echo-planar imaging with TR = 10 000 ms, TE = 100 ms acquisition matrix = 128 x 128 and field of view = 28 cm. Using a slice thickness of 5 mm with 1.5 mm gap, images were acquired parallel to the orthogonal axial plane through the entire brain (19 images). Diffusion-sensitizing gradient encoding was applied in 25 directions by using a diffusion-weighted factor $b = 1200$ s/mm$^2$, and one image was acquired without use of a diffusion gradient, i.e. $b = 0$ s/mm$^2$. Twenty-six images were obtained at each section giving a total of 494 images. The patient and control subject heads were positioned using a standardized procedure that minimized the effect of dose on FA. The means of relative FA change ($\Delta$FA) of different dose regions were calculated using following equation

$$\Delta FA = \frac{(followupFA - baselineFA)}{baselineFA}.$$

CT for radiotherapy planning

Radiotherapy consisted of two phases, lateral opposing field whole brain irradiation and 3D conformal boost to the posterior fossa. Based on the CT images which were acquired parallel to the orbito-meatal line, both phases were planned using Cadplan (version 6.27, Varian Medical Systems, Palo Alto, CA). To facilitate the post-processing work, these plans were reproduced with identical CT images sets, plan data and dose calculation algorithms on Eclipse (version 7.3.10, Varian Medical Systems, Palo Alto, CA) which is featured with DICOM-RT export capability. The resultant dose distribution was exported in ASCII format for further processing. For control subjects, similar but pseudo radiotherapy planning based on MR images was carried out. A CT number of zero (0 HU) was assigned to the whole MR brain for dose computation.

Imaging processing and analysis

The diffusion tensor imaging data were processed using FUNCTOOL (GE Medical Systems, USA) to obtain the fractional anisotropy (FA) map. All image manipulations were done using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UK) and MATLAB 6.5 (The MathWorks, Inc., Natick MA).

Radiotherapy planning was based on CT images for patients but on MR images for control subjects. We will describe the procedure using CT for planning. For the method validation analysis of control subject data, MR images were used in place of CT images.

The dose distribution of the whole brain in ASCII format was read in and transformed to Analyze format using Matlab script (referred as plan image in subsequent description). The plan images were smoothed with a 3-mm Gaussian kernel to account for the patient position variation during the course of radiotherapy. As plan images were produced based on CT images, they were in register intrinsically. For patients, since CT images were scanned with patients prone in the bed, we then re-oriented the CT and corresponding plan images so that they were consistent with MRI images. In order to evaluate the FA change in regions of different doses, it was necessary to make the plan images in register with the baseline and follow-up FA images. Since nondiffusion-weighted ($b=0$) images were in register with FA inherently and provided better tissue contrast, we used $b=0$ images in the following registration procedure. The CT images were coregistered to the baseline $b=0$ images using normalized mutual information method. The warps derived were then applied to the plan images. As a result, the plan images and the FA images were in register. Similarly, the follow-up $b=0$ images were coregistered to the baseline $b=0$ images and the warps were applied to the follow-up FA images. Third order spline interpolation method was used in all coregistration procedures to achieve better accuracy. We chose to use coregistration rather than normalization because normalization would allow scaling, which was not desired for intrasubject registration. The $b=0$ images were segmented in ‘native’ space to give white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) images. The segmented images of each tissue class were averaged among follow-up scans and employed to produce a highest probability WM mask (HIWMM) using the equation we proposed previously (Leung et al., 2004). The HIWMM was further edited manually to remove the cerebellum because in that region the segmentation was not satisfactory due to anatomical distortion after surgery. Baseline FA image, follow-up FA images, plan image and HIWMM image were read into Matlab. All FA changes were calculated with respect to baseline FA and confined to white matter using HIWMM. A 5-Gy dose window was used to study the effect of dose on FA. The means of relative FA change ($\Delta$FA) of different dose regions were calculated using following equation:

$$\Delta FA = \frac{(followupFA - baselineFA)}{baselineFA}.$$
By grouping voxels in this way, we evaluated the mean white matter FA response to each dose region. As we recognize that heterogeneous response in FA may occur within each dose region, standard deviation (SD) of \( \Delta FA \) in each dose region was also calculated to reflect the spatial heterogeneity and 95% confidence interval (CI) of mean \( \Delta FA \) was calculated to reflect the reliability of each mean \( \Delta FA \) value.

This calculation was repeated for all three follow-up DT-MR imaging scans for each patient. \( \Delta FA \) was calculated at each voxel using the equation above and the \( \Delta FA \) map was created. For better illustration, the \( \Delta FA \) map was smoothed with isotropic Gaussian kernel of 8 mm FWHM to reduce noise.

In order to quantify regional FA changes so as to study regional susceptibility, we created masks for the frontal lobe, parietal lobe and brainstem. These regions were selected based on visual inspection of the \( \Delta FA \) map that suggested regional differences in these parts of the brain. We compared the frontal lobe FA change to the parietal lobe FA change in the sections cranial to the level of the anterior commissure where the dose to both lobes is almost uniform. We created masks of the frontal lobe and parietal lobe by manually delineating the lobes in the baseline \( b0 \) images. These masks were subsequently combined with HIWMM to give HIWMM in the frontal lobe and parietal lobe and mean \( \Delta FA \) of these regions were calculated accordingly. The mean \( \Delta FA \) of the brainstem was quantified similarly.

In the validation analysis using normal subjects, additional evaluation was made to assess the reliability of our method. Since SD of \( \Delta FA \) over each pseudo dose region only reflects the heterogeneity within the region-of-interest, root mean square (RMS) of mean \( \Delta FA \) value of each region was calculated in addition to CI, so as to assess the possible bias of our method towards certain dose regions and to reflect the reliability of mean \( \Delta FA \). RMS was used instead of SD of mean \( \Delta FA \) value of each region because in the control subjects, mean \( \Delta FA \) should ideally equal zero.

Results

Radiation dose distribution map superimposed on \( \Delta FA \) map

Fig. 1 shows the iso-dose lines superimposed on the \( \Delta FA \) map of patient B’s first follow-up at the level of the basal ganglia. For the grayscale of the \( \Delta FA \) map, black indicates more severe FA reduction and white indicates less severe reduction. The severity of FA drop can be appreciated pixel-by-pixel and this can be evaluated for the whole brain.

Method validation

Fig. 2A shows the mean \( \Delta FA \) and associated 95% CI of each pseudo dose region for both control subjects. For both control subjects, the overall mean \( \Delta FA \) were \(-0.0022\) and \(0.0047\); and the RMS were \(0.0147\) and \(0.0151\), respectively. The root mean square of the RMS from the two control subjects was calculated as \(0.0149\). Fig. 2B shows the SD of the \( \Delta FA \) for each pseudo dose region for both control subjects. The SD ranged from \(0.2621\) to \(0.3951\). The distribution of SD across the pseudo dose regions was quite uniform, suggesting that each dose region consists of comparable proportion of heterogeneous voxels. The overall mean SD were \(0.315\) and \(0.298\) for the control subjects, respectively.

Applications

Dose–effect on mean FA relationships

Fig. 3A shows the relationships between mean \( \Delta FA \) and 95%CI of the voxels in the dose regions and the dose received for three follow-up scans for patients A and B, respectively. For both patients, reduction in mean FA (i.e. negative mean \( \Delta FA \)) increased with increasing radiation dose up to 45 Gy, after which the reduction in mean FA became less severe and approached baseline value. For patient A, there was a trend of progressive reduction of mean FA with time, but this pattern was not found in patient B. Although the regions receiving [35,40]Gy dose were similar for both patients, patient B suffered a more severe drop in mean FA in [40,45]Gy and [45,50]Gy dose regions compared to patient A. For patient A, the mean FA of the region receiving [20,25]Gy dose did not drop from the baseline value. For all follow-ups, the 95% CI was within an acceptable range reflecting the reliability of the value and was generally narrower for low dose regions than for high dose regions. Fig. 3B shows the SD of the \( \Delta FA \) of the follow-ups of both patients and this reflects the spatial heterogeneity of the voxels within the dose regions. This could be contributed by inherent heterogeneity in FA between voxels and the heterogeneous effect of radiation. The overall mean SD for both patients A and B were \(0.335\) and \(0.480\), respectively.

Regional FA change

By visual inspection of the \( \Delta FA \) map, we found marked reduction in FA in the frontal lobe white matter and genu of the corpus callosum. In both patients, there were differences in FA reduction between the frontal regions and posterior regions in the supratentorial white matter despite exposure to the same radiation dose (Fig. 4). This was confirmed by quantitative \( \Delta FA \) measurements of the frontal lobe and parietal lobe WM at each follow-up (Table 1). The mean difference of \( \Delta FA \) between frontal lobe and parietal lobe was \(-0.056\) although frontal and parietal lobes were irradiated with the same radiation dose.
In the brainstem, the ΔFA map showed less reduction in FA despite the high radiation dose exposure in the posterior fossa (>45 Gy) (Fig. 5). We calculated the quantitative mean FA and mean ΔFA of the brainstem of the patients and found that mean FA in the brainstem in fact increased after irradiation in both patients, by up to 26.0% (Table 2).

Discussion

We have successfully mapped radiation dose distribution onto FA images to study the dose effect on mean FA change and regional susceptibility in individual subjects, thereby allowing the analysis and the comparison of dose effect within and between subjects. It should be emphasized that the calculated mean FA change for each dose region is the result of both radiation dose effect and regional susceptibility/spatial heterogeneity within the voxels of the region, which we have shown to occur in this study. As it is not possible to separate these two factors which affect mean FA change, we cannot determine if the mean FA change is purely a dose effect, and therefore, the confounding factor of regional susceptibility, as assessed on the ΔFA maps, should be considered in the interpretation i.e. visual inspection of ΔFA map should complement dose–effect calculations. However, we expect that FA

Fig. 2. Graphs showing fairly narrow range of imaging and processing noise (mean ΔFA) in the pseudo dose regions (A) of the normal control subjects and fairly uniform distribution of standard deviation of ΔFA over pseudo dose regions (B).

In the brainstem, the ΔFA map showed less reduction in FA despite the high radiation dose exposure in the posterior fossa (>45 Gy) (Fig. 5). We calculated the quantitative mean FA and mean ΔFA of the brainstem of the patients and found that mean FA in the brainstem in fact increased after irradiation in both patients, by up to 26.0% (Table 2).

Fig. 3. Graphs showing the results of application of dose–effect in patients A and B. Panel A shows the relationship between mean ΔFA with associated 95% CI in the dose regions and the dose ranges of all three follow-up scans for patients A and B (A). There is increasing mean FA reduction with increasing dose up to 45 Gy after which the trend in FA reverses and approaches normal. Note that for patient A, the mean FA of the region receiving [20,25] Gy dose did not drop from the baseline value. Panel B shows SD of ΔFA over dose regions for patients A and B.

Fig. 4. ΔFA map superimposed on T1-weighted image, taken at the level above the basal ganglia of patient A’s first follow-up showing more severely reduced FA in the frontal lobe (darker regions) compared to the parietal lobe. Radiation dose to both lobes was uniformly 25 Gy.
should mainly reduce after irradiation, and thus mean FA does provide an indication of the averaged dose–effect. Although heterogeneity was quite high between individual voxels, the reliability of the mean ΔFA will increase by averaging over a number of voxels and this was at an acceptable level in our analysis as revealed by the 95% CI.

Our method is closely related to the one described by Steen et al. (2001) who use one slice from the T1 map for the evaluation of radiation dose dependent T1 change in medulloblastoma survivors. There are, however, two main differences in the methods; firstly, we evaluated the whole brain using FA maps. Hence, larger numbers of voxels were studied and the results were less likely to be influenced by noise, leading to a more sensitive detection of subtle changes. Secondly, we applied a registration method to correct for repositioning displacement in order to improve the accuracy of comparing the same regions between different scans.

Some pitfalls about this method should be emphasized. Firstly, the misregistration that remains after registration of pre- and post-treatment images will introduce some inherent noise to the result. Since averaging the result over a region of voxels with the same expectation value will reduce the noise, the size of the region of analysis should be chosen according to the registration accuracy; the higher the accuracy, the smaller the size is allowed. In our analysis, a 5-Gy dose window was chosen such that there was a substantially large number of voxels in each dose region. Inaccuracies in registration will also occur if there are changes in brain morphology before and after treatment, in which case perfect matching may not be possible. In our analysis, only rigid body transformation is used. Hence, it is required that the brain shape does not change significantly in order to achieve good registration. Misregistration will also occur when the brain size and shape change markedly between scans. For example, if the scans are done far apart in children, then there may be substantial growth in head size. For long-term studies where brain growth is substantial, affine or nonlinear transformation may be used for a better mapping of images (Shen and Davatzikos, 2002; Thirion, 1998). Secondly, imaging conditions which cannot be perfectly controlled between scans will also introduce some noise such as differences in head positioning between the scans. Cercignani et al. (2003) compared interscan variabilities and reported that the coefficients of variation range from 1.81% to 14.3% for average mean diffusivity and FA. The authors suggest that different patient repositioning could account for this variation. Thirdly, imperfect segmentation will include some GM and CSF voxels in the analysis, thus reducing the sensitivity of the method in the detection of FA change in WM. However, we believe that the effect of inaccurate segmentation on the result is minor so long as we use a consistent segmentation method throughout the study. Fourthly, interpolation has a smoothing effect on the resultant image and may introduce some error. In order to achieve better resampling accuracy, high order interpolation method should also be used.

We have illustrated two applications of this tool with two MED patients who underwent sequential DTI scanning prior to and up to 1 year after whole brain irradiation. The findings are specific to these patients and cannot be generalized because of the small sample size.

Our results suggest a more severe reduction in mean FA with increasing dose up to 45 Gy whereby an unexpected reverse trend in mean FA change occurs. Further analysis of these regions with >45 Gy exposure by visual inspection of the ΔFA maps revealed the brainstem to be the main structure to have been exposed to these doses. We propose two possible explanations for this increase in mean FA after radiation; this may be due to the presence of hemorrhage/hemosiderin or the selective damage of fiber tracts at the regions of fiber crossing. Hemosiderin causes elevated FA due to susceptibility effects. Hemosiderin deposits in the brainstem may be secondary to the relatively high dose of irradiation and this is found in animal models of radiation injury (Benczik et al., 2002) or it may be due to hemorrhage as a consequence of surgery. Radiation may selectively damage specific tracts at regions of fiber

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### Table 1
Mean ΔFA of frontal lobe and parietal lobe of patient A and patient B at the three follow-ups

<table>
<thead>
<tr>
<th>Patient</th>
<th>First follow-up ΔFA of frontal lobe</th>
<th>First follow-up ΔFA of parietal lobe</th>
<th>Difference of ΔFA between lobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>−0.052</td>
<td>0.010</td>
<td>−0.062</td>
</tr>
<tr>
<td></td>
<td>−0.057</td>
<td>0.007</td>
<td>−0.064</td>
</tr>
<tr>
<td></td>
<td>−0.058</td>
<td>−0.024</td>
<td>−0.034</td>
</tr>
<tr>
<td>Patient B</td>
<td>−0.055</td>
<td>−0.010</td>
<td>−0.045</td>
</tr>
<tr>
<td></td>
<td>−0.028</td>
<td>0.039</td>
<td>−0.067</td>
</tr>
<tr>
<td></td>
<td>−0.047</td>
<td>0.016</td>
<td>−0.063</td>
</tr>
</tbody>
</table>

### Table 2
Mean FA and mean ΔFA of the brainstem of patient A and patient B at baseline and at the three follow-ups

<table>
<thead>
<tr>
<th>Patient</th>
<th>FA</th>
<th>ΔFA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.393</td>
<td>/</td>
</tr>
<tr>
<td>First follow-up</td>
<td>0.440</td>
<td>0.120</td>
</tr>
<tr>
<td>Second follow-up</td>
<td>0.495</td>
<td>0.260</td>
</tr>
<tr>
<td>Third follow-up</td>
<td>0.432</td>
<td>0.099</td>
</tr>
<tr>
<td>Patient B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.391</td>
<td>/</td>
</tr>
<tr>
<td>First follow-up</td>
<td>0.404</td>
<td>0.033</td>
</tr>
<tr>
<td>Second follow-up</td>
<td>0.445</td>
<td>0.138</td>
</tr>
<tr>
<td>Third follow-up</td>
<td>0.430</td>
<td>0.100</td>
</tr>
</tbody>
</table>

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Fig. 5. ΔFA maps of patient A’s first follow-up taken at the level of the posterior fossa with iso-dose lines superimposed showing increased FA in the brainstem despite a high dose of >45 Gy.
crossing in the brainstem such as in the rostral pons, preferentially affecting the descending corticospinal tract or transverse pontine fibers, leading to more coherently oriented fiber tracts and hence, increased FA despite the degeneration of fibers (Pierpaoli et al., 2001). It is unlikely that the brainstem is ‘resistant’ to the effects of radiation. Our findings suggest that the dose threshold for FA change of patient A was around 25 Gy. Thus, this dose level could be considered “safe” in terms of FA change. However, it would be more convincing if information of FA changes at lower dose levels are available. In our study, patients received lateral opposing irradiation and conformal irradiation, and the former phase determines the minimal dose received by the brain. This limited our ability to observe the FA change pattern below that minimal level. However, the usefulness of dose threshold as measured by FA change should be further evaluated by histopathological correlates of white matter damage/demyelination to determine its sensitivity and significance.

The ΔFA maps provide visual information of the FA changes and areas of regional differences that may indicate that susceptibility can be easily appreciated. This is important in the interpretation of the dose–effects as regional susceptibility, if seen, should be taken into account. The apparent ‘susceptibility’ of the frontal lobe compared to the parietal lobe to radiation injury in both our patients warrants further evaluation. While it is possible that this is a chance occurrence, we propose the following explanation; the vascular hypothesis of radiation injury considers vascular damage secondary to radiation to be the main cause of white matter demyelination/necrosis. It has been shown that radiation induces decreases in regional cerebral blood volume and this reduction in intravascular volume could result in radiation-induced injury (Fuss et al., 2000). It has also been shown that there are perfusion differences between frontal and parietal lobes as demonstrated using positron emission tomography and arterial spin labeling methods, albeit with high intersubject variability (Ito et al., 2003; Parkes et al., 2004). It is therefore possible that regional susceptibility may be related to these perfusion differences which affect compensating mechanisms in the microvascular circulation. It would be interesting to evaluate intersubject variability in response to irradiation and to determine if the increased susceptibility of the frontal lobe white matter in individual subjects is related to more severe cognitive deterioration. We found the ΔFA changes in the genu of the corpus callosum to be marked, as in the rest of the frontal lobe white matter. While the corpus callosum has been found to be more ‘resistant’ to radiation effects on conventional T2-weighted MR imaging (Edwards-Brown and Jakacki, 1999), this has not been found on DTI (Leung et al., 2004) or quantitative volumetric studies (Palmer et al., 2002). Possibly, relatively compact fibers of the corpus callosum limit the increase in interstitial edema which has been proposed as a cause of increased signal on T2-weighted imaging (Constine et al., 1988).

Finally, apart from the applications for studying dose–threshold relationships and regional susceptibility, this tool can also provide a means of assessing the associations between regional FA changes with subsets of the cognitive scores, potentially to obtain more sensitive correlations with cognitive function.

References


