The Effects of Radiation Therapy on White Matter Fiber Tracts of the Limbic Circuit

Introduction

Radiation appears to affect different white matter fiber structures differently, as suggested by the selective late cognitive dysfunctions. WBRT, as a commonly used treatment modality for brain metastases, provides a platform to investigate this question. In this study, we focused on the cingulum and fornix, two fiber tracts in the limbic system which are efferent and afferent connections to the hippocampus, and compared the radiation effects on them with the corpus callosum, the largest white matter fiber bundle in the brain. Diffusion weighted magnetic resonance imaging is the most sensitive modality for evaluating the damage to the micro-structure of white matter tracts, which is not visible on any other imaging modalities. Extracting various fiber tracts from diffusion weighted images makes it possible to quantify their diffusion characteristics and thus monitor the therapy side effects on them.

Methods

We extracted structures of the cingulum posterior, superior, and anterior parts, the fornix, and the corpus callosum of the 12 patients, and examined the longitudinal percentage changes in the mean FA and MD for from pre-RT to end-RT and from pre-RT to 1-month post-RT.

Results

The results of the longitudinal changes in FA and MD are summarized in Table 1 and highlighted in Abstract.

To further reveal which diffusivity components contribute to the significant decreases in the FA in the cingulum posterior part, the fornix, and the corpus callosum, an analysis was applied to AD and RD, the first component is an indicator for axonal degradation and degeneration and the second one for demyelination In the cingulum posterior part, the means of the RD were increased by 11.4% at the end of RT (p <0.001) and by 10.5% 1-month post-RT from pre-RT(p< 0.008), while the means in the AD were not changed significantly at both time points, suggesting the radiation induced demyelination is predominant. Similarly, in the fornix, the means of the RD were increased by 7.1% at the end of RT (p=0.005) and by 4.9% 1-month post-RT (p=0.04) from pre-RT, while the means of the AD were changed neither substantially nor significantly at both time points. However, in the corpus callosum, the means of both RD and AD were increased significantly at the end of RT and 1-month post-RT from pre-RT. The means of RD were increased significantly by 17.0% (p<0.001) at the end of RT and to 21.8% 1-month post-RT. The increases in the mean AD, although significant, were in a much smaller extent, as 2.4% (p=0.001) and 2.6% (p=0.01) at the end of RT and 1-month post-RT, respectively, indicating radiation effects on the corpus callosum are predominant demyelination and mild axonal degradation.

Table 1. Longitudinal percentage changes in diffusion indices.
The absolute value of the mean and the estimation standard error for diffusion indices in pre-RT and the percentage changes in the mean, the estimation standard error, and the t-test p-value of the percentage changes in end-RT and 1-month post-RT with respect to pre-RT. Cg: cingulum, CC: corpus callosum. Fx: fornix. The letters P, S, A denote the posterior, superior, anterior, respectively.

Comparing the structures through the percentage changes in diffusion indices
We applied rigorous analysis to determine whether there were significant different radiation effects on these extracted structures by comparing different cingulum parts (posterior versus superior, superior versus anterior, and posterior versus anterior), the cingulum versus the fornix, the cingulum versus the corpus callosum, and the fornix versus the corpus callosum through the mean FA and MD percentage changes from pre-RT to end-RT and to 1-month post-RT. As can be understood from Table 2, at the end-RT and 1-month post-RT, there were significant differences between the cingulum posterior and superior parts in the terms of percentage changes in both the mean FA and MD, between the corpus callosum and the fornix in the terms of percentage changes of the mean FA, and between the corpus callosum and the cingulum in the terms of percentage changes of the mean MD. Moreover, despite their absolute values of the diffusion indices, their percentage changes were not significantly different on the superior and anterior parts of the cingulum. Furthermore, the cingulum and fornix were not significantly different, but they were both significantly different from the corpus callosum in the terms of the percentage changes of diffusion indices.

Table 2. Comparing different structures by t-test p-value on the percentage changes in diffusion indices.

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<tr>
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<th>p-value</th>
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<tr>
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<td>Cg P vs Cg S</td>
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<tr>
<td>end-RT %ΔFA</td>
<td>0.001</td>
</tr>
<tr>
<td>end-RT %ΔMD</td>
<td>0.001</td>
</tr>
<tr>
<td>1-month post-RT %ΔFA</td>
<td>0.000</td>
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<tr>
<td>1-month post-RT %ΔMD</td>
<td>0.008</td>
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Percentage changes in the mean FA and MD in end-RT (top) and 1-month post-RT (bottom) with respect to pre-RT. Cg: cingulum, CC: corpus callosum. Fx: fornix. The letters P, S, and A denote the posterior, superior, and anterior, respectively.

Conclusion
A previous report on the radiation effect on the genu and splenium in the patients received partial brain radiation shows a progressive increase in the radial diffusivity up to 45 weeks after starting RT.\(^4\)\(^3\) Also, a previous study reports the progress changes in both the radial and axial diffusivities in the posterior part of the cingulum up to six months after RT in the patients treated by partial brain radiation and the early change in the DTI index associated the memory function decline 18 months post RT.\(^1\)\(^1\) In the current study of the patients received whole brain RT, the percentage changes in the DTI indices of the posterior cingulum one month post RT are greater than the changes in the patients received partial brain radiation 6 months post RT.\(^1\) Furthermore, substantial cognitive dysfunction, especially in memory function, 4-6 months following WBRT has been reported.\(^5\)\(^5\)