

## Chemotherapy-Induced Structural Changes in Cerebral White Matter in Breast Cancer Patients: A Longitudinal DTI Study

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### Purpose:

With the improvement of breast cancer survival rates there has been an increased attention to understanding treatment sequelae. Among these complications is chemotherapy-related cognitive impairment (CRCI). However, the mechanisms underlying these cognitive deficits are poorly understood. Chemotherapeutic agents have been associated with damage to myelin in the CNS (1), hence investigating white matter changes in breast cancer patients following chemotherapy could aid in the understanding of CRCI. Previous diffusion tensor imaging (DTI) studies of white matter in these patients have identified widespread decreases in fractional anisotropy (FA, a measure of fibre tract integrity) in post-chemotherapy breast cancer patients (2, 3, 4); however, there have been few longitudinal studies, and, to our knowledge, none have provided a controlled longitudinal assessment at three time points. Thus, in this study we assessed FA in a group of breast cancer patients prior to and at two time points following chemotherapy treatment.

### Methods:

23 right-handed female patients (mean age:  $51.5 \pm 8.47$ ) and 23 individually sex-, age-, and education- matched controls (mean age:  $50.4 \pm 8.82$ ) were recruited (attrition resulted in 19 patients and 19 controls for baseline (t1) vs post-chemotherapy (t2), 17 patients and 19 controls for t2 vs. 1 year post-chemotherapy (t3)). Diffusion tensor images were acquired using a 1.5-T Siemens Magnetom Symphony MR scanner and the following parameters: spin-echo echoplanar parallel grappa diffusion weighted imaging sequence, with acceleration factor = 2, 12 non-collinear directions and 2 b-values (0, 600 s/mm<sup>2</sup>) and 2x2x7 mm<sup>3</sup> voxel resolution. Patients were imaged prior to chemotherapy, 2 weeks after treatment and 1 year post-chemotherapy completion. Controls were imaged at matched time intervals. A neuropsychological battery and 4 fMRI tasks were also administered with a focus on processing speed, response inhibition and working memory. The functional MRI of the brain (FMRIB) software library was used to analyse the raw data (5). Each diffusion weighted image was affine-aligned to its corresponding b0 image using FMRIB's linear image registration package (FLIRT v5.4) (6) to correct for motion artefacts and attenuate eddy current distortions. Brain masks of each brain b0 image were generated using the brain extraction tool (BET v2.1) (7) with fractional threshold,  $f=0.1$  and a vertical gradient,  $g=0$ . The FMRIB's diffusion toolbox (FDT v2.0) was then used to fit the tensor at each brain voxel and estimate the eigenvalues of the tensor from which the FA values were derived. Voxelwise whole-brain analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS v1.2) (8). Nonlinear registration of FA images into 1x1x1 MNI152 standard space was performed through direct registration to the FMRIB58\_FA template using FNIRT (9, 10). The transformed individual FA images were averaged to create a mean FA image, which was then thinned in order to produce a mean FA skeleton representing the centres of white matter tracts common to all subjects (threshold FA value of 0.2). The aligned FA images for each subject were then projected back onto this skeleton. Voxelwise statistics of the FA data were carried out using two sample paired t-tests. FA value changes between groups (patients and controls t1 vs t2, and t1 vs t3) were assessed using permutation-based non-parametric testing with 5000 random permutations. Threshold-Free Cluster Enhancement (11) was used to avoid having to arbitrarily define an initial cluster-forming threshold. Statistical maps were inspected at  $p < 0.01$  levels, uncorrected for multiple comparisons.

**Results:** Comparison of controls t1 vs. t2 and controls t1 vs. t3 showed no statistical differences in FA values ( $p < 0.01$ ). There was a significant reduction in FA ( $p < 0.01$ ) in the patient group post-chemotherapy in the dominant left hemisphere involving the left frontal white matter, anterior body of corpus callosum, Broca's area, contralateral right medial thalamus, right brachium pontis and cerebellar white matter (figure 1, first row). The FA changes were less prominent in the t1 vs t3 comparison (figure 1, second row).

### Discussion:

These results align with prior neuropsychological and fMRI results observed from previous analyses with these patients, suggestive of deficits in processing speed, working memory and verbal memory (12, 13, 14). fMRI results of cerebellar reductions in activation along with prefrontal and thalamic increases in activation coincide with these DTI results to demonstrate reductions in white matter integrity, altering blood flow patterns and cognitive functioning.

### Conclusions:

Chemotherapy significantly impacts white matter integrity in important areas of the brain that underlie cognitive processes like working memory and processing speed. This alteration in white matter structural organisation, as detected through changes in FA, recovers 1 year post-chemotherapy to near pre-chemotherapy levels. This study provides empirical evidence that chemotherapy alters white matter structural integrity but that this can be reversed with time. Quantitative DTI biomarkers, like FA, are sensitive to detect and follow the structural changes induced by chemotherapy in patients suffering CRCI.

### References:

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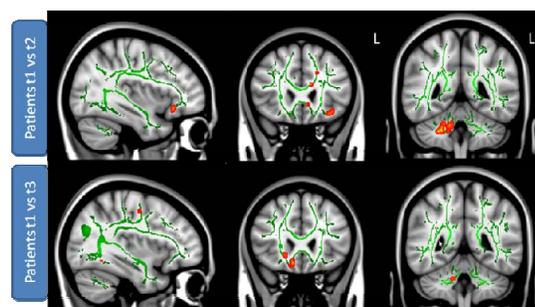


Figure 1: Areas of significant changes in FA ( $p < 0.01$ ) shown in red. Patients t1 vs. t2, top row. Patients t1 vs. t3, bottom row.