Survival Analysis for Apparent Diffusion Coefficient Measures in Children with Embryonal Brain Tumours

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Introduction: Apparent diffusion coefficient (ADC) measures have been used in various tumour analyses and of particular importance here, ADC has been used as a biomarker for inferring tumour cellularity [1]. Increased tumour cellular densities as well as increased nuclear to cytoplasm ratios are believed to restrict diffusion of water molecules and hence imply a lower ADC value [2]. We investigated a previously described ADC measure [3,4,5], the Apparent Transient Coefficient in the Tumour (ATCT), to study whether it correlates with survival outcome in childhood embryonal brain tumours. The ATCT is a measure of the gradient change of ADC from the peri-tumoural oedema into the tumour core.

Methods: 58 patients (31 male, 27 female, aged 3 weeks to 14.6 years, mean 5.7 years) with histologically proven embryonal brain tumours and who had diffusion-weighted imaging (DWI) as part of their clinical imaging, were enrolled in a retrospective study that correlated ADC measures (ATCT, mean ADC and minimum ADC) with survival. Kaplan-Meier survival curves were constructed for tumour location, extent of surgical resection and age less than 3 years at diagnosis. A multivariate survival analysis was carried out considering ATCT (Fig 1a) and variables found to be significant in the Kaplan-Meier analysis, as covariates. The ATCT was further analysed using Kaplan-Meier survival analysis by dividing the patients into four equally-sized groups of increasing ATCT values. A reproducibility study was also carried out on a random selection of 10 patients. Statistical analysis was performed using R software.

Results: Results are shown in Figure 1b and 1c. ATCT showed a significant correlation with survival ($R = 0.37$, $p = 0.002$). The Cox proportional hazard regression model indicated that the only statistically significant covariate was ATCT ($p << 0.001$). Kaplan-Meier curves showed that more negative values of ATCT were related to a lower chance of survival ($p << 0.001$). The coefficient of reproducibility was found to be 30.1 and 28.4% for the intra- and the interobserver analysis respectively.

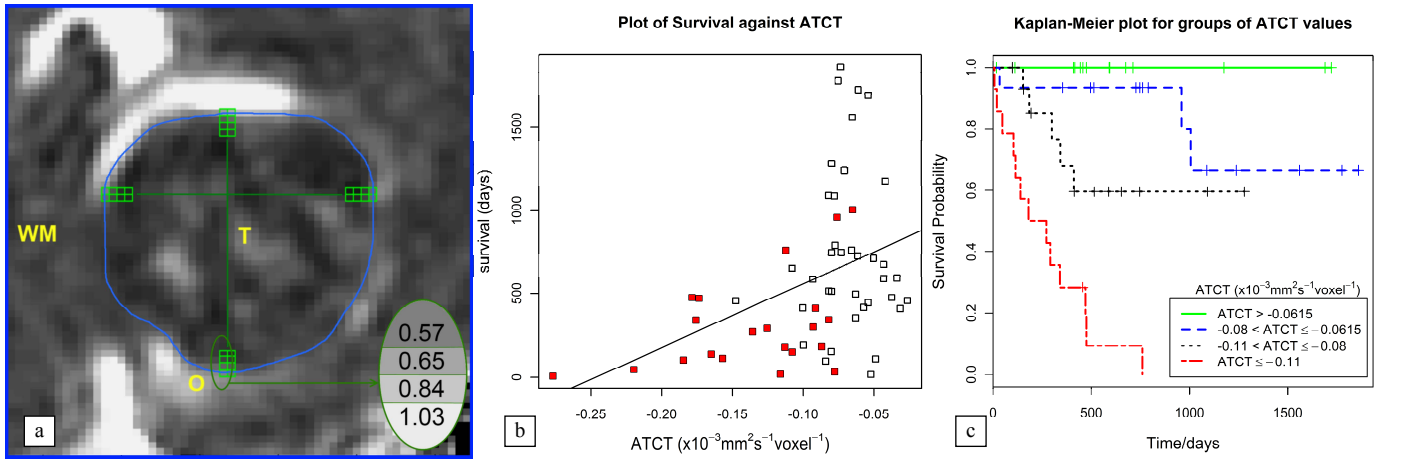

Figure 1: (a) Method for ATCT measurement: The oedema-tumour boundary is identified as marked by the blue contour. The white matter (WM), peri-tumoural oedema (O) and tumour core (T) are also shown. In order to measure the ATCT, the slice with the largest visible tumour area was selected. The ATCT is measured at 4 different locations using a 2 voxel width as shown by the voxels highlighted in green. The gradient change in ADC is calculated by applying a linear fit to the ADC values for the vertical column of four pixels on the left, at the posterior side of the tumour and circled in green. The gradient change in ADC is measured in all eight locations and the mean of these is the ATCT. (b) Scatter plot showing all ATCT values and survival data for each of the patients. Patients who died are shown in red. (c) Kaplan-Meier survival curves, dividing ATCT into four groups of equal size, showed lower survival probabilities for patients whose ATCT was more negative.

Discussion: A statistically significant difference was observed for survival data in children with embryonal brain tumours with respect to the change in ADC from oedema into the tumour volume. The results indicate that more negative values of ATCT are related to lower survival, whilst changes closer to zero indicate a higher survival. As ADC has been shown to correlate with tumour cellularity, the change in ADC over the oedema-tumour boundary could be an indication of how rapidly the tumour cellularity is increasing. Alternatively, the result can also be explained if a tumour is surrounded by more oedema which would imply a higher oedema ADC value and therefore increased ATCT values. In conclusion, ATCT is a sensitive biomarker that correlates with survival in childhood embryonal brain tumours.

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