Dynamic contrast-enhanced MR imaging and tumour oxygenation measurements in cervical cancer

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Introduction
Evidence suggests that tumour hypoxia is important in determining cancer treatment outcome. The Eppendorf pO2 histograph system is regarded as the ‘gold standard’ for measuring tumour oxygenation [1], although the method has limitations in that the technique is not widely available, limited to accessible tumours and invasive. Recently there has been increased interest in using dynamic contrast enhanced (DCE) MRI to assess tumour microcirculation, based on the temporal and spatial change in signal. As tumour oxygenation is dependent on the microcirculation, the technique may be useful to identify hypoxic tumours. We have performed DCE MRI in 30 patients with locally advanced carcinoma of the cervix pre- and post-external beam radiotherapy and compare the findings with the level of tumour oxygenation measured using polarographic needle electrodes.

Methods
The patients underwent pre-radiotherapy DCE MRI followed by pre-radiotherapy oxygenation measurement using the Eppendorf pO2 histograph system. Imaging was performed a maximum of 24 hours before pO2 measurements except for 3 patients where it was performed 2-48 hours prior. In 9 patients repeat oxygenation measurements and imaging was performed following external beam radiotherapy.

MRI studies were performed on a Siemens 1.0 Tesla clinical MR using the body and phased array pelvic coils. The protocol included T1 and T2 weighted images for tumour staging, volume and nodal status. The dynamic sequences used Gd-DTPA, 0.1mmol/kg body weight, injected via the antecubital vein as a fast bolus injection followed by a 5ml saline flush. Gradient-echo T1-weighted 5mm sagittal sections through the tumour (TR=130ms, TE=6.5ms) with a temporal resolution of 25 secs were obtained serially before and after injection of contrast. The ROI’s for analysis of dynamic data were defined on T2 images by a single radiologist (BMC). A second individual then transferred these onto GE images. ROI’s were defined on the central sagittal slice to correlate approximately with the 12 and 6 o’clock positions of the oxygenation measurements. The ROI encompassed the maximum amount of tumour at these two positions but avoided areas of high signal intensity that could indicate necrosis. Time-intensity curves were then generated along with the maximal signal intensity increase over base line (SI-I; obtained by subtracting the pre-contrast from the maximal value) and the steepest rate of signal intensity increase (SI-I/sec). Finally, the maximum tumour diameter was measured using the pre-treatment MR images.

Details of the tumour oxygenation measurement methods have been described in detail elsewhere [2]. Measurement tracks were performed at the 12 and 6 o’clock position and results were expressed as the median pO2 and as the proportion of values less than 5mmHg (HP5).

Results and Discussion
Two time-intensity curves were obtained for every tumour (representing the two ROI’s studied), illustrating the level of intra- compared to inter-tumour heterogeneity. The average SI-I for the 39 measurements was 2.60 with a range of 0.72-4.48. The average SI-I/sec for the 39 measurements was 8.45 with a range of 2.90-21.70. There was a significant positive correlation between the two MRI parameters (r=0.43, p<0.005). Tumours that were well oxygenated had a better magnitude of enhancement than tumours that were poorly oxygenated (Fig. 1). There was a significant negative correlation between SI-I and HP5 and positive correlation between SI-I and median pO2 levels. Repeating these analyses on the 30 values that were obtained before treatment did not alter the findings for either HP5 (r=-0.45, p=0.011) or median pO2 (r=0.47, p=0.008). These findings are difficult to explain, as both parameters relate to tumour perfusion, however, the SI-I may give a better indication of tumour perfusion as a whole (intravascular and interstitial) whereas SI-I/sec may be a better reflection of the number of blood vessels present. It may be that dynamic MRI could be used to measure both angiogenesis (ROI selected from imaging whole tumour and selecting those that enhance maximally) and hypoxia (ROI selected to capture regions of poor blood supply). As both measures of angiogenesis and hypoxia are independent prognostic factors for treatment outcome in carcinoma of the cervix. For 9 patients imaged post-radiotherapy, there was a trend towards a correlation between SI-I measurements obtained before and after external beam radiotherapy (SI-I (r=0.60, p=0.088). There was no correlation for SI-I/sec (r=-0.03, p=0.93).