Quantification and spatial analysis of intra-tumoural perfusion heterogeneity in cervix cancer using DCE-MRI

M. A. Zahra[1], R. Black[2], E. Sala[3], A. N. Priest[4], M. J. Graves[4], S. S. Gupta[5], L. Tan[6], M. Arends[7], R. A. Crawford[8], J. D. Brenton[1], and D. J. Lomas[4]

[1]Oncology, University of Cambridge, Cambridge, United Kingdom, [2]Medical Physics, Addenbrooke's Hospital, Cambridge, United Kingdom, [3]Radiology, University of Cambridge, Cambridge, Cambridge, United Kingdom, [4]Radiology, University of Cambridge, Cambridge, United Kingdom, [5]Radiology, National Naval Medical Center, Bethesda, Maryland, United States, [6]Oncology, Addenbrooke's Hospital, Cambridge, United Kingdom, [7]Pathology, University of Cambridge, Cambridge, United Kingdom, [8]Department of Obstetrics & Gynaecology, Addenbrooke's Hospital, Cambridge, United Kingdom

Introduction:

Functional and architectural vascular abnormality is one of the hallmarks of neoplasia. It is the outcome of the various mechanisms involved in tumour vessel formation and results in intra-tumoural perfusion heterogeneity [1]. This has important implications for treatment response as hypo-perfused tumour regions are more likely to contain hypoxic cells which are radio-resistant and more likely to progress to metastatic disease, and also to have compromised delivery of systemic therapies [2]. This is particularly relevant in cervix cancer where concurrent chemo-radiotherapy is the treatment of choice for locally advanced disease and it has also been well documented that tumour hypoxia correlates strongly with poor response to treatment and increased risk of distant metastases [3]. Perfusion heterogeneity can potentially have a useful predictive value through its influence on the tumour micro-environment. If perfusion heterogeneity is going to be used for treatment individualization, as in the case of biologically adapted radiation therapy planning, information on the temporal changes in heterogeneity will be important. With the advent of anti-angiogenesis agents, accurate characterization of tumour perfusion and its spatial heterogeneity is becoming even more important as perfusion measurements are being used as biomarkers of tumour response [4]. The aim of this study is to use DCE-MRI to quantify the intra-tumoural heterogeneity and correlate it with radiological tumour response, and also to describe its spatial distribution and the temporal changes associated with treatment.

Methods:

Twelve patients with locally advanced cervix cancer (FIGO stage Ib2-IVa) treated with concurrent chemoradiotherapy were recruited into this study.

Imaging protocol: Examinations were performed on a 1.5T whole body MRI (Excite, GEHT, Milwaukee) using an eight-channel cardiac coil. Each patient had a DCE-MRI study done at three time-points: before starting treatment, after 2 weeks of treatment and in the fifth week of treatment. Each examination included pre-contrast, high resolution T2W FRFSE sequences (4mm thick, 1mm gap) for optimal tumour localization in axial and sagittal planes and axial T1WI. The dynamic sequence consisted of 3D T1w fast spoiled gradient echo (TR/TE = 4.8/1.5 ms, FA = 18°, bandwidth = 31 kHz, FOV = 24 cm) of 4 contiguous sagittal sections, section thickness 10 mm and positioned to maximally sample the tumour. The T1-weighted sequence is repeated every 3 seconds for a total of 180 seconds. A bolus of 0.1mmol/kg Gd-DTPA was machine-injected at 9mls/s 30 seconds after the start of imaging, followed by a 25ml flush of normal saline at the same rate. Tumour volumes were obtained by an experienced radiologist outlining the tumour on sagittal T2w images, and then calculating the in-plane area and multiplying it by the slice thickness.

Heterogeneity analysis: The relative signal intensity (RSI) was calculated on a pixel-by-pixel basis using GE-HT Cinetools software (version 5.1.4) and each region of interest (ROI) was divided into 5 concentric sub-regions spaced at equal intervals from the centre of the centre of mass of the ROI [5] (figure 1). Mean RSI for the whole ROI was calculated and the variance was used as a measure of the heterogeneity of RSI. These were correlated with radiological response and corresponding tumour volumes using Spearman's correlation coefficient. The RSI for the 10th and 5th percentiles was used to quantify the extent of hypoperfusion within each region [6]. The ratio of the RSI within the most peripheral and the central sectors was used to assess spatial distribution using the mean, 10th and 5th percentile SI values. The changes in the measured parameters over time were also assessed. Statistical analysis was carried out using SPSS (version 12.0.1).

Results:

12 patients were recruited and had a total of 33 studies. The mean RSI for the pre-treatment studies was 2.52 and the mean variance was 0.2, the significant heterogeneity across each ROI can be appreciated from the perfusion maps generated (figure 1). The degree of heterogeneity (as quantified by the variance) showed no correlation with the corresponding tumour volumes (r = -0.27, p = 0.42), nor with the percentage tumour regression (r = -0.27, p = 0.54). When analysing the spatial distribution of heterogeneity, there was no significant difference in the mean RSI between the different ROI sub-regions as exemplified by the pre-treatment peripheral-to-central ratio of 1.01 (s.d. 0.09). However, when using the peripheral-to-central ratio for the 10th and 5th percentile RSI values there was a clear trend showing an increase in the extent of hypo-perfusion in the peripheral sectors, with ratios of 0.83, 0.87 and 0.83 respectively for the first, second and third study 10th percentile values (figure 2). There was a consistent temporal increase in perfusion (Table 1) between the first and second studies as shown by increases in the mean, 10th and 5th percentile RSI measurements, which then decreased by the time of the third study (figure 3).

Parameters	1st study	2nd study	3rd study
Mean RSI	2.52 (s.d. 0.41)	2.99 (s.d. 0.65)	2.76 (s.d. 0.57)
RSI variance	0.2	0.21	0.16
10th percentile RSI	1.88 (s.d. 0.35)	2.19 (s.d. 0.62)	2.1 (s.d. 0.42)
5th percentile RSI	1.7 (s.d. 0.36)	2.0 (s.d. 0.63)	1.9 (s.d. 0.4)
Mean RSI ratio peripheral-to-central	1.01 (s.d. 0.09)	1.02 (s.d. 0.13)	0.97 (s.d. 0.14)
10th percentile RSI ratio peripheral-to-central	0.83 (s.d. 0.18)	0.87 (s.d. 0.22)	0.83 (s.d. 0.18)
5th percentile RSI ratio peripheral-to-central	0.78 (s.d. 0.19)	0.79 (s.d. 0.23)	0.75 (s.d. 0.16)

Table 1: Relative signal intensity measurements

Conclusions:

There is significant heterogeneity in the RSI within each ROI and this was not determined by tumour volume, indicating that it might reflect the intrinsic biology of the tumour. There appears to be a radial component in perfusion with the regions that are most poorly perfused being mainly in the periphery, this remained consistent with time and can have important implications when planning additional radiation boost to the tumour. The increase in perfusion parameters in the first 2 weeks of treatment reflects the acute effects of radiation on the perfusion and permeability within the tumour. Future work will involve correlation of RSI heterogeneity measurements with histopathological parameters using biopsies taken at similar time-points as the DCE-MRI studies.

References:

1. Vaupel P, 2004;**14**:198-206
2. Gillies RJ et al, 1999;**1**:197-207
3. Fyles AW et al, 2000;**57**:13-9
4. Checkley D et al, 2003;**89**:1889-95
5. Graff BA et al, 2003;**88**:291-7
6. Mayr N et al, 2000; **12**:1027-33

Acknowledgements: Fund and Friends for Addenbrooke's, Radiographers of the MRIS Unit, Addenbrooke's Hospital.

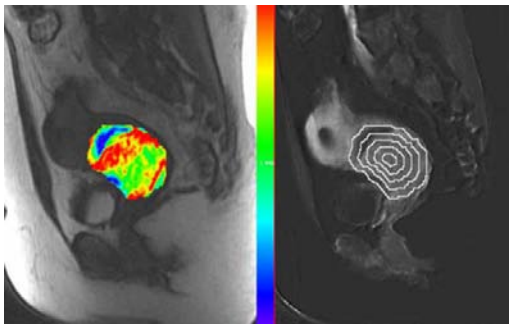

Figure 1: Perfusion map showing heterogeneity and image of ROI sub-volumes used for analysis

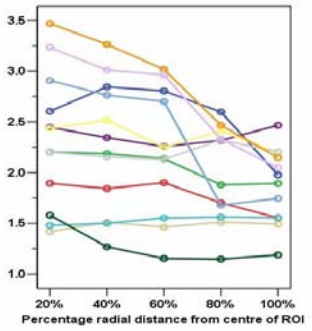

Figure 2: Change in 10th percentile RSI with radial distance from centre of ROI

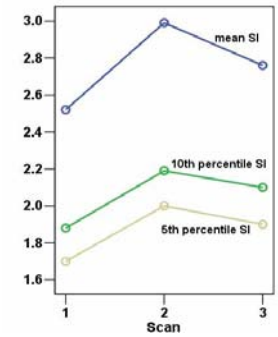

Figure 3: Change in mean, 10th and 5th percentile RSI with time