DCE-MRI parameters are predictive of tumour regression in cervix cancer

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Introduction

Over the last decade there have been considerable technological advances in radiation oncology, both in the planning and also in the delivery of treatment. Despite this progress treatment is still prescribed in an empirical method. Standard risk factors like stage and histology are used to guide management, even though there is a significant and unpredictable variation in the outcome of patients within the same prognostic group. Unless the biology of the individual tumours is taken into account real individualisation of treatment will not be possible. This is particularly relevant in advanced cervix cancer where the gold standard treatment is concurrent chemoradiotherapy and where there is ample scope for individualisation of the treatment including the use of hypoxic sensitizers, alternative fractionation regimes or the novel sequencing of treatment modalities. Also it is well established that the rate of tumour regression in cervix cancer correlates strongly with local control and overall survival, thus providing a clinically relevant early endpoint. DCE-MRI is a technique that can generate parameters that reflect the tumour micro-environment such as perfusion and permeability indices (1). These are related to the response to treatment as poorly perfused tumours are more likely to contain hypoxic regions that are known to be resistant to radiotherapy and also to have compromised delivery of chemotherapy (2). The aim of this study is to assess the value of DCE-MRI parameters for predicting radiological tumour response.

Materials / Methods

Patients with locally advanced cervix cancer (FIGO stage Ib2-IVa) referred to our oncology department for treatment with concurrent chemoradiotherapy were eligible for recruitment to the study, this was approved by the local ethics committee. Each patient had a DCE-MRI scan done at 3 time points; prior to the start, on the third and on the fifth week of external beam radiotherapy treatment.

Imaging protocol: The examinations were performed on a 1.5T whole body MRI (Excite, GEHT, Milwaukee) using an 8-channel cardiac array. At each time point high resolution FRFSE sequences using T2 axial and sagittal scans (4mm thick 1mm gap) were obtained for accurate assessment of the extent of tumour involvement and volumetric measurements. The dynamic sequence consisted of a 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, each 10mm thick and positioned to cover all or most of the tumour, and repeated every 3 seconds for a total of 180 seconds. Contrast was injected 30 seconds from the start of the sequence, as a bolus of 0.1mmol/kg Gd-DTPA using an MR compatible power injector at a rate of 9mls/s followed by a flush of 25mls of 0.9% sodium chloride solution at the same rate.

DCE-MRI analysis: Tumour volumes were obtained using the sagittal FRFSE images and multiplying the in-plane area by the slice thickness. The percentage regression was then calculated by finding the difference in tumour volume between the first and the third scans. The region of interest was outlined by an experienced radiologist using the FRFSE images for guidance. For each of the 4 sagittal slices semi-quantitative parameters were obtained using GE-HT Cinetools software (version 5.4.1) these consisted of the contrast enhancement ratio (CER), maximum slope of the signal intensity-time plot, time for peak enhancement and the area under the curve at 90seconds (AUC90). Quantitative perfusion parameters were calculated using a model vascular input function and an estimated tissue T1 value of 860ms, these included the volume transfer constant (K^{trans}) and the rate constant (k_{ep}). Spearman's correlation coefficient was used to assess the correlations between the DCE-MRI parameters and the percentage tumour regression and the corresponding tumour volumes. Statistical software package SPSS (version 12.0.1) was used for the analyses.

Results

11 patients were recruited and had a total of 32 scans. The pre-treatment tumour volumes ranged between 1.1cm^3 and 197cm^3 (median 39cm^3; s.d. 51cm^3). The percentage tumour regression after 5 weeks of radiotherapy ranged between 35% and 100% (median 76%; s.d 21%). All the parameters from the pre-treatment DCE-MRI scan showed a significant correlation with tumour regression (figures 2 & 3), but the parameters from the second and third scans did not correlate (Table 1). There was a significant difference in the pre-treatment perfusion parameters between tumours using a 75% regression cut-off. Overall there was an increase in the value of the perfusion parameter measurements by the time of the second scan, which then decreased by the time of the third scan. There was no correlation between the DCE-MRI parameters and the corresponding tumour volumes.

DCE-MRI parameters	1st study	2nd study	3rd study
peak time	-0.875* p = 0.001	-0.267 p = 0.455	-0.964 p < 0.001
slope	0.742* p = 0.014	0.383 p = 0.275	0.286 p = 0.535
CER	0.9* p < 0.001	0.085 p = 0.815	0.036 p = 0.939
K^{trans}	0.754* p = 0.012	0.36 p = 0.342	0.179 p = 0.702
k_{ep}	0.778* p = 0.008	0.377 p = 0.283	0.643 p = 0.119
AUC90	0.857* p = 0.002	0.055 p = 0.881	0.036 p = 0.939

Table 1: Correlation between DCE-MRI parameters and percentage tumour volume regression using Spearman correlation coefficient and two-tailed significance testing
** significance at 0.005 level*

Conclusions :

The pre-treatment DCE-MRI parameters showed a significant correlation with radiological tumor response, indicating that tumors that are well perfused as reflected by higher DCE-MRI perfusion values respond better to radiotherapy. The increase in perfusion as measured by the 2nd MRI parameters would indicate that DCE-MRI could reflect perfusion changes that are secondary to treatment. Since the DCE-MRI measurements did not correlate with the corresponding tumor volume, it would appear that this technique can provide biological information about the tumor that is not available using standard staging imaging sequences and which could be used for biological adapted treatment individualization. This study supports the further exploration of the predictive value of DCE-MRI.

References :

1) Mayr N et al 2000 2) Gillies RJ et al 1999

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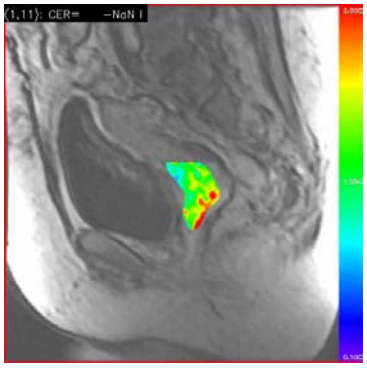

Figure 1: perfusion map showing intra-tumoural heterogeneity

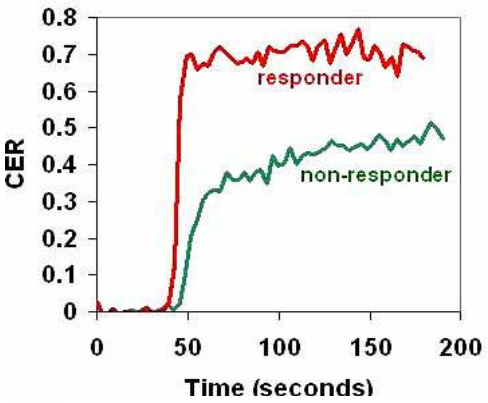

Figure 2: Plot of contrast enhancement ratio with time for 2 patients with different tumour responses

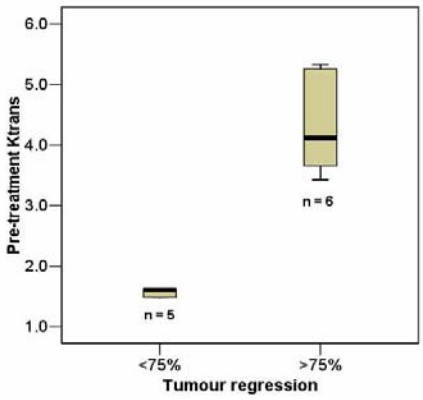

Figure 3: K^{trans} showing correlation with percentage volumetric tumour regression