Fractal parameters derived from DCE-MRI data as markers of response to treatment

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Introduction: Response to treatment of cancer in MRI is assessed in a clinical setting using the RECIST criteria, which is based on an increase or decrease in the largest diameter of the tumour [1]. This technique suffers from a number of limitations, such as insensitivity to subtle variations in size and shape and does not consider changes in function. Any alternative methodology that includes tumour function must also characterise the structural and functional heterogeneity inherent in tumours [2]. Fractal analysis is an appropriate technique to characterise these properties. We present findings that demonstrate box-counting analysis can provide an additional measure of response to treatment.

Methods: DCE-MRI data were acquired from adult cancer patients with a variety of histologies, pre- and post-treatment, using a T1w gradient-echo FLASH sequence. Slice positions in the sequential studies were registered using fixed internal landmarks derived from high resolution T2w images. The imaging sequence included the following parameters: TE/TR/α = 10.2ms/4.7ms/3º for proton density and 35º for T1w. Images from three slices were reconstructed with a temporal resolution of 5s and a total duration of 250s. Injection of contrast agent (Magnevist, 0.2 mmol/kg body weight) at 5ml/s started 8s after the initiation of the sequence. T1w time series curves were converted to gadolinium concentration ([Gd]) using the method of Hittmair [3]. For the analysis, an ROI encompassing the whole tumour was defined in the central slice only, based on a post-contrast T1w image. AUC [Gd](0-90s) was calculated for each pixel in the central slice. AUC has the advantage over model-fitted parameters that it does not suffer from fit failures and erroneous parameter values. A second ROI corresponding to a large region of muscle (gluteals) was then defined. A threshold value equal to the mean AUC [Gd](0-90s) plus two standard deviations was calculated from the muscle ROI. Using this threshold value, the tumour ROI was converted into a binary mask such that pixels with a value less than the threshold were set to 0, and all remaining pixels set to 1. Box-counting was applied to evaluate the fractal dimension of the cluster [4]. A number of metrics were estimated from fractal analysis of the cluster: mass M, perimeter P, correlation distance ξ and the fractal dimension d_f. Mass is the number of occupied pixels within the cluster (a single occupied pixel has mass of 1). The perimeter includes both the external boundary and any internal boundaries resulting from holes (regions showing no gadolinium enhancement). d_f is a measure of how well the cluster fills its embedding space and ξ is the length scale at which the cluster changes from fractal (self-similar, scale-invariant) to Euclidean (space-filling) characteristics. The analysis was then repeated for each time point study.

Discussion: Figure 1 shows the binary clusters derived from a patient with angiomyolipoma. Three time points were studied: pre-treatment and at one week and three weeks following administration of an anti-VEGF agent. The tumour shows no significant change in size (0.02%, see Table 1) at study 3. According to the RECIST criteria, the maximum diameter of the tumour must increase by more than 20% to be termed progressive disease; the tumour is therefore be classed as stable here. However, visual inspection of the binary clusters shown in Figure 1 indicates a progressive reduction in [Gd] within the tumour. Such changes could be due to the tumour increasing in size without adapting its blood supply or successful treatment causing the blood supply to become disrupted. It is therefore noteworthy that the ratio M/P reflects these changes, and shows a decrease of 49.5% in study 3 (see Table 1). Other parameters from the fractal analysis, such as d_f and ξ also show a change, but not as significantly (ξ increases by 16.3%). However, it should be noted that it is assumed the uptake of contrast agent in muscle is unaffected by treatment and is constant across all studies.

Conclusion: Parameters derived from fractal analysis are able to characterise subtle variations in tumour morphology and function that are not characterised by normal radiological methods. The ratio mass/perimeter in particular appears to be a very sensitive parameter. This method analysis can be applied to any DCE-MRI acquired data.

Acknowledgements: This work was supported by Cancer Research UK (C1060/A808/G7643)

References: [1] Padhani AR. Br J Rad, 2001;74:983-987 [2] Jain RK, Adv Chem Eng, 1994;19:130-200 [3] Hittmair K et al. Magn Reson Med, 1994;31:557-567 [4] Bunde A., Havlin S., 'Percolation 1 and 2' in Fractals and Disordered Systems, 1991, Springer-Verlag, pp. 51-150

	Study 1	Study 2	Study 3
Mean AUC [Gd]	13.8	17.8	12.7
Number of pixels in ROI	8011	7806	8067
Mass (number of occupied pixels)	7434	7528	7608
RECIST			
Change in largest diameter	0%	0.01%	0.02%
FRACTAL ANALYSIS			
d_f	1.965	1.958	1.939
ξ (pixels)	32.88	34.29	39.30
P (pixels)	575	640	1183
M / P	12.93	11.76	6.53

Table 1: Values derived from the fractal analysis of each study. Note that both the RECIST criteria defines the disease as stable (<20%), yet M/P decreases by 49.5% and ξ increases by 16.3%.

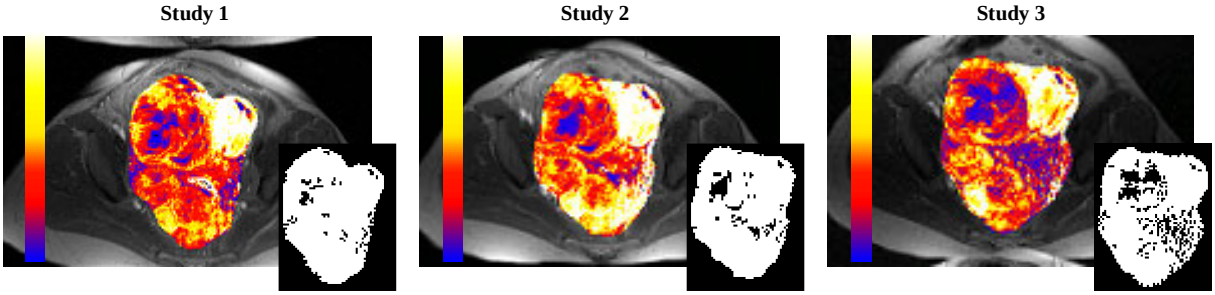

Figure 1: AUC [Gd] maps (overlaid onto T1w images) showing the tumour ROI, with binary maps shown inset, for each study