Studying breast tumour heterogeneity with a fractal analysis tool, a prognostic indicator of tumour pathological response before chemotherapy treatment

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INTRODUCTION

World wide breast cancer is the main cause of death amongst young women; dynamic contrast enhanced MRI (DCE-MRI) has been shown to be a sensitive and predictive technique for the characterization of breast lesions. During a DCE-MRI study the contrast agent spreads into the interstitial space of the tumour where it stays until renal filtration occurs. Having two high resolution T1-weighted 3D fast spoiled gradient echo images of the lesion, one before and one after Gd-DTPA injection allows the generation of a 3D subtraction image which is a contrast distribution map. One way to assess heterogeneity and structure of a tumour is by fractal analysis which has already shown to be a powerful tool in other biomedical applications[1-4]. The aim of this study is to investigate if a goodness of fit into the fractal model of contrast maps has a prognostic value in terms of pathological response to chemotherapy.

MATERIALS AND METHODS

A group of 41 women with primary breast cancer was imaged by DCE-MRI before undergoing chemotherapy. Two 3D slabs of both breasts in the coronal plane were acquired on a 1.5T GE scanner by a high resolution (0.9 mm in plane) FSPGR sequence with a flip angle of 35° and TR/TE of 9 and 4.2 ms respectively. The first slab was taken before contrast injection, the second one approximately 6 minutes after injection. By subtracting these two images a contrast distribution map was obtained, within this 3D matrix a large ROI around the tumour was drawn manually and in house IDL (Research Systems, Inc, Boulder, Colorado) software was used to localize the tumour boundaries. From the original 3D matrix a slab of 12 slices across the tumour is chosen. The slab is spatially under-sampled along the 3 axes by the factors 2-3-4-6-12; at each resolution a measure of contrast variation is extracted and scaled on the original resolution contrast variation. The fractal dimension D was calculated using the following equation[5-6]: $\ln\left(\frac{Cv\_res}{Cv\_ref}\right) = (1-D)\ln\left(\frac{Vox\_res}{Vox\_ref}\right)$ where *Vox_res* represents the total number of tumour pixels (p) at the under-sampled resolutions, *Vox_ref* represents the total number of tumour pixels at the original resolution, *Cv* was calculated as follows: $Cv = \frac{stdev\ (p1,...,\ pn)}{\sum_{i=1}^{n} p\ i}\ n$

where *Cv_res* is the contrast distribution of the under-sampled matrix while *Cv_ref* is the contrast distribution of the original resolution matrix.

RESULTS

Of the available 42 primary breast lesions only 39 were used for the fractal analysis. In two patients it was not possible to distinguish between enhancing and non enhancing tumour voxels probably due to movement artefacts; in one patient most of the lesion area was occupied by non enhancing pixels. For each patient a value of fractal dimension *D* and goodness of fit was extracted. Figure 1 shows a logarithmic scale plot of the linear regression fractal fit for a tumour with a large homogenous region with a poor fit into the fractal model, while Figure 2 shows a heterogeneous tumour with a good fit into the fractal model. A significant correlation was found ($p < 0.01$, Spearman's rho = 0.42) between the tumour pathological response and its goodness of fit into the fractal model. A boxplot of tumour pathological response from no response to a complete response (1 to 5 respectively) versus goodness of fit (measurement of chi-square) is shown in Figure 3. No significant correlation was found between tumour fractal dimension *D* and pathological response. The response to chemotherapy was pathologically assessed using the Miller Payne scale[7].

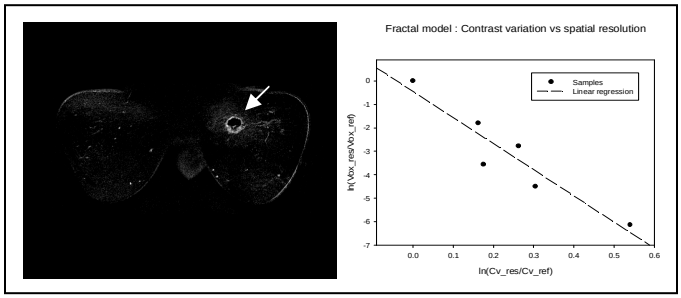

Figure 1. A tumour which is homogeneous in the centre and shows a poor match to the fractal model

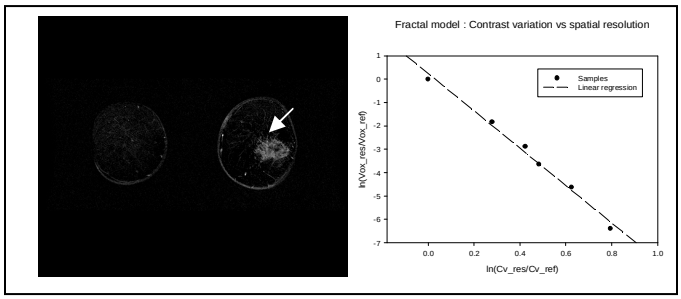

Figure 2. A tumour which is highly heterogeneous and shows a good match to the fractal model

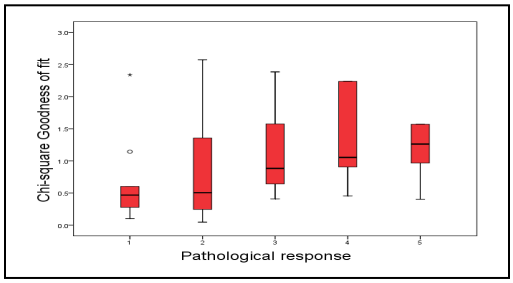

Figure 3. Boxplot of tumour pathological response (ranked from no response equal to 1 to a complete response equal to 5) versus goodness of fit into the fractal model. Two outliers from rank 4 and 5 are not included in the graph for clarity.

DISCUSSION AND CONCLUSION

The main finding of this work is that fractal analysis of contrast distribution map within a breast lesion has some prognostic predictive value. Tumour heterogeneity measured using goodness of fit to a fractal model shows correlation with the tumour's pathological response. A possible explanation might be that in the case of a tumour which has a very heterogeneous distribution of contrast, showing pixels enhancing at various different levels of intensity, there is a more hypoxic microenvironment which leads to a less effective response to chemotherapy[8]. If the tumour has a uniform distribution of contrast across its volume it does not fit the fractal model well and has a poor goodness of fit. The approach could perhaps be improved in two ways. First the contrast distribution map would be more accurate if the spatial resolution was increased; secondly, the timing of the post-contrast image has not been optimised for the use of fractal type analysis methods. In conclusion we have shown that a fractal approach to measuring heterogeneity is possible in DCE-MRI and those fractal parameters predict pathological response in this patient group.

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