The Median of Modelling Parameters K^{trans} and v_e in a Tumour ROI Best Characterises Breast Cancer Response to Treatment

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Introduction

In the evaluation of response to therapy of cancer using DCE-MRI, pharmacokinetc parameters resulting from modelling such data are summarised using a number of approaches. A common approach is to fit each pixel within a region of interest (ROI) and characterise the resultant distribution using summary measures such as the mean or median. Alternatively, the mean contrast agent uptake curve in the ROI is calculated and parameters derived from the fit to this curve used to characterise the whole tumour, an approach known as whole-ROI analysis. However, which of these approaches offers the greatest ability to identify responders and non-responders has only been considered to date using simulations [1]. In this pilot study, the ability of each parameter derived from the pharmacokinetic modelling of DCE-MRI data to categorise clinically responding and non-responding breast cancer patients following treatment with chemotherapy is evaluated.

Materials and Method

Clinical Study: 14 women with locally advanced breast cancer were treated with neoadjuvant chemotherapy. Patients were assessed clinically using bi-dimensional clinical measurements of the primary breast tumour, both prior to and at completion of chemotherapy. Clinical responders were defined as those patients with complete response or partial response; clinical non-responders were defined as those patients with stable disease or progressive disease.

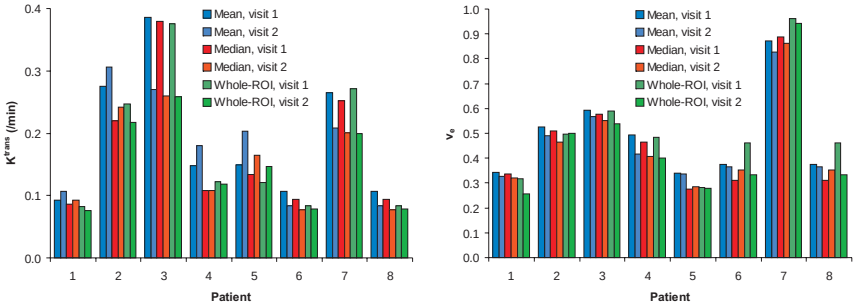

Figure 1: Barcharts of the pre-therapy mean, median and whole-ROI values of K^{trans} and v_e.

MRI Measurement: DCE-MRI data were acquired using a FLASH sequence (TE/TR/α = 11ms/4.7ms/35º for dynamic T1w images and 350ms/4.7ms/6º for reference proton density-weighted images (required for conversion to Gd-DTPA concentration)). Images from four slices were reconstructed with a temporal resolution of 12.1s and total duration 607s; contrast agent (Gd-DTPA, 0.1 mMol/kg body weight) was injected at 4ml/s. Two reproducibility studies were acquired in 8 of the patients, prior to therapy. All patients had at least one pre- and one post-therapy study (following two cycles of chemotherapy).

Phamacokinetic Modelling: The modified Kety model with a bi-exponential VIF taken from the literature [2,3] was fitted on a pixel-by-pixel basis, within a region of interest corresponding to the tumour. Mean and median values of each model parameter within the ROI were calculated. By estimating the mean signal intensity-time curve from the ROI, whole-ROI estimates of each model parameter were then measured.

Statistical Analysis: Mean, median and whole-ROI estimates of each model parameter were compared using the t-test and Pearson correlation coefficient. Reproducibility thresholds were defined for each parameter using the coefficient of variation (COR, 1.96 times the standard deviation of the percentage change between pre-therapy values [4]), from which changes in each parameter following therapy greater than the COR were considered significant. The ability of each parameter to separate responders and non-responders was evalated using the metrics n_1 = TP/(TP+FN) and n_2 = TN/(TN+FP) (analogous to sensitivity and specificity), where TP, TN, FP and FN are the number of true positives (clinical responders with values *outside* reproducibility thresholds), true negatives (clinical non-responders with values *inside* reproducibility thresholds), false positives (clinical non-responders with values *outside* reproducibility thresholds) and false negatives (clinical responders with values *inside* reproducibility thresholds), respectively. Following an approach analogous to ROC analysis, the product $n_1 \times n_2$ was used to summarise both measures (a large value of both n_1 and n_2 represents optimum accordance with clinical response).

Results

Reproducibility: Table 1 shows reproducibility statistics for each parameter, which reveals that the COR was smallest when the whole-ROI was used to summarise K^{trans} and when the mean was used to summarise v_e. Figure 1 shows a bar chart of the pre-therapy values of each parameter. Median and whole-ROI values were consistently smaller than mean values, but were comparable with each other (t-test significance >0.05, Pearson significance <0.01), which agrees with previous studies [5].

	Mean	Median	Whole-ROI
K^{trans}	49.1%	36.9%	31.2%
v_e	8.6%	18.8%	23.2%

Table 1: Reproducibility statistics (COR) for each parameter and summary measure.

Response to Therapy: Table 2 shows values of $n_1 \times n_2$ for each parameter, which shows that the median consistently offered the best combination of both properties, whilst whole-ROI analysis offered the poorest.

	Mean	Median	Whole-ROI
K^{trans}	16%	24%	8%
v_e	24%	48%	18%

Table 2: Values of $n_1 \times n_2$ for each parameter, measured against clinical response following 6 cycles of chemotherapy. A value of 100% indicates perfect accordance with clinical response, whilst a value of 0% indicates no accordance.

Discussion and Conclusionss

In this study, the response to therapy of breast cancer was evaluated using DCE-MRI and compared against a clinical measure of response. Three summary measures were used to characterise each tumour: the mean, the median and the whole-ROI value. It was found that the reproducibility of each model parameter depended on the summary measure used. The parameter most able to identify responders and non-responders was consistently given by the median, whilst whole-ROI analysis gave the poorest combination. This agrees with previously reported results from simulations [1]. It is likely that median summary measures offer optimal categorisation due to their greater central tendency compared with the mean. This study therefore provides evidence that median summary measures should be used in preference to mean or whole-ROI values in the context of the assessment of response. Furthermore, it shows that summary parameters with the best reproducibilty do not necessary provide the most sensitive assessment of response.

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