Volume transfer constants spatial distribution across breast tumors: evidence of interstitial fluid pressure?

P. Di Giovanni[1], T. S. Ahearn[1], S. I. Semple[2], C. A. Azlan[1,3], F. J. Gilbert[1], and T. W. Redpath[1]
[1]Radiology, University of Aberdeen, Aberdeen, Scotland, United Kingdom, [2]Medical Physics, University of Edinburgh, Edinburgh, Scotland, United Kingdom,
[3]Biomedical Imaging, University of Malaya, Kuala Lumpur, Malaysia

INTRODUCTION

It is well known that high interstitial fluid pressure (IFP) can be present in the central areas of a tumor[1]. This can lead to tissue necrosis and causes a barrier to drug delivery[2]. IFP can be assessed invasively with the wick-in-needle procedure, this is not a suitable technique in clinical practice. MRI is a non-invasive technique which has shown to be highly sensitive in the detection of breast tumors and has the potential of generating spatial distribution maps of pharmacokinetic parameters linked to IFP. In the previous work of Dadiani[3] an attempt of imaging pressure driven parameters in inoculated mice tumors was made by fitting a T1-weighted dynamic contrast enhanced dataset to the standard Tofts' model[4], this produced an imbalanced estimate of K^{trans}_{in} and K^{trans}_{out} across the tumor. These quantities represent the volume transfer constants from the intravascular space into the lesion leakage space (K^{trans}_{in}) and in opposite direction (K^{trans}_{out}). They were fitted assuming a fixed value for the fractional volume of interstitial space v_e. In this work we have generated parametric maps of breast cancers obtained from patients showing the spatial distribution of the two transfer constants across the lesions.

MATERIALS AND METHODS

A group of 18 patients with large or locally advanced breast cancer was scanned at 1.5T (GE, Waukesha WI, USA) before chemotherapy treatment. DCE-MRI was performed with 10 seconds temporal resolution using a T1-weighted 2D fast spoiled gradient echo (FSPGR) sequence (TR/TE/α = 8.4 msec /4.2 msec /35°). A set of 9 slices covering the lesion area was acquired in the coronal plane. Dynamic images were acquired for over 6 minutes after the Gd-DTPA bolus injection (0.2 mmol/kg). Using the Tofts' model[4] the T1-weighted MR signal samples were fitted to the FLASH equation obtaining a tissue contrast concentration dynamic curve. Free parameters in the fitting were K^{trans}_{in} and K^{trans}_{out} according to the following model:

$$C_t(t) = DK^{trans}_{in} \sum_{i=1}^{2} a_i^T \frac{e^{-(K^{trans}_{out}/v_e)t} - e^{-m_i t}}{m_i - (\frac{K^{trans}_{out}}{v_e})}$$

where D, a_i^T and m_i are the quantities describing the plasma biexponential decay[5]. The plasma fractional volume was assumed to be negligible ($v_p = 0$). The interstitial fractional volume v_e was fixed to 0.3 which was in the range of values estimated in a patients study by Hayes et al[6]. The fitting algorithm was implemented in IDL (Research Systems, Inc, Boulder, Colorado, USA) and different starting points for the fitted pharmacokinetic parameters were used in order to avoid the routine falling in local minima[7]. For each pixel within the lesions a parametric map expressed as $K^{trans}_{out}/K^{trans}_{in}$ was generated together with a scatter plot of K^{trans}_{in} versus K^{trans}_{out}.

RESULTS

Amongst the lesions we noticed how the ones showing a non-enhancing region within the tumor's core were characterized by a marked imbalance between the fitted volume transfer constants. Figure 1 shows two lesions, the parametric maps are color coded to show where the two quantities are balanced (blue and green), where $K^{trans}_{out} > K^{trans}_{in}$ (green, yellow and red) and where $K^{trans}_{out} < K^{trans}_{in}$ (blue and aqua). A high value of K^{trans}_{out} in respect to K^{trans}_{in} appears in a rim pattern around the non-enhancing areas while higher values of K^{trans}_{in} in respect to K^{trans}_{out} are observed at the tumor's periphery. Next to each parametric map is a scatter plot of K^{trans}_{in} versus K^{trans}_{out}.

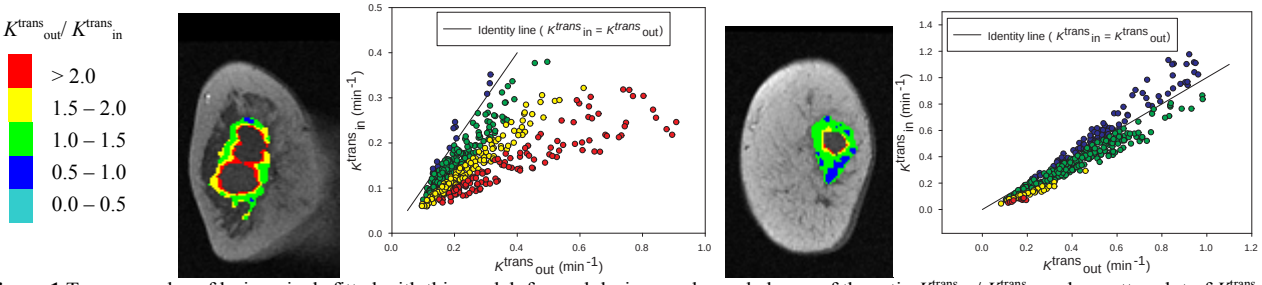

Figure 1 Two examples of lesion pixels fitted with this model, for each lesion a color coded map of the ratio $K^{trans}_{out}/K^{trans}_{in}$ and a scatter plot of K^{trans}_{in} vs K^{trans}_{out} is given. The non-enhancing pixels here are substituted by a pre-contrast T1-weighted image.

DISCUSSION

We have found an imbalance between K^{trans}_{in} and K^{trans}_{out} which is particularly marked around non-enhancing tumor areas. We argue that these regions are characterized by a high IFP. This would explain why, next to these areas, the volume transfer constant going from the intravascular space into the lesion interstitial space is lower than the transfer constant in opposite direction due to the higher resistance exerted by the high IFP within the tumor interstitial space. Unfortunately there are not non-invasive ways to assess IFP within tumors and thus we could not verify that what we are measuring is a direct effect of high interstitial fluid pressure. However, a common assumption made in pharmacokinetic modeling is to consider $K^{trans}_{in} = K^{trans}_{out}$, we believe that important information can be extracted from these quantities if a measure of v_e is available. In a recent work[8] a pressure driven flow model was proposed based on a distinct pattern observed among breast tumor scatter plots of k_{ep} versus K^{trans} (provided $K^{trans} = K^{trans}_{in} = K^{trans}_{out}$). In the present study we have assumed a homogeneous v_e across the lesion, however, we expect a certain degree of variation across the tumor from our chosen value. Further work investing the relationship between v_e and the $K^{trans}_{out}/K^{trans}_{in}$ ratio is required. Interstitial space volume fraction has been measured using injections of an intravascular and then an extravascular agent[9]. A different approach based on diffusion weighted images was successfully implemented with mice tumors and a separation between the extravascular extracellular compartment from the intracellular compartment was observed. This idea is based on the fact that water molecules diffuse at different rates in the two environments[10]. The efficiency of the latter method in clinical practice has still to be demonstrated but it represents an attractive non-invasive approach which could be introduced among the imaging sequences of a clinical breast DCE-MRI exam.

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