Cross-visit tumour sub-segmentation may reveal localised response to anti-angiogenic treatment in DCE-MRI data

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Introduction Parameters derived from quantitative dynamic contrast enhanced MRI (DCE-MRI) are increasingly used to support early decisions on the viability of emerging anti-angiogenic and vascular-disrupting agents[1]. Standard practice[2] is to report statistics only for a volume of interest (VOI) that identifies the target tissues, e.g. median $IAUC_{60}$ or K^{trans} for a whole tumour. We present a pilot study that makes use of recent developments in the segmentation of DCE-MRI data sets[3,4] to access the rich spatially- and temporally-heterogeneous information in the 3-D parametric maps, and so supplement the information available from whole VOI statistics.

Data Patients in a clinical trial of a VEGF inhibitor had 6 DCE-MRI scans: 2 pre-treatment visits (within 7 days before administration); and 4 post-treatment visits (4 hours, then 2, 8 and 12 days after administration). At each visit we acquired 3-D spoiled gradient echo (SPGR) images on a Philips 1.5 T Intera scanner for baseline T_1 estimation (3 acquisitions with flip angles of 2°, 10° and 30°; required to convert MR signal to contrast agent concentration for cross-visit normalisation) and for DCE-MRI (75 acquisitions: flip angle 20°, temporal resolution 4.97 s, voxel matrix 128 x 128 x 25). We manually defined tumour VOIs in 3-D on co-localised T_1-and T_2-weighted image volumes. All patients had metastatic tumours in the liver, resulting from colorectal primary tumours. We selected 4 tumours (in 4 patients) with acceptably low motion—where multiple tumours were present in the same patient, only the largest tumour was analysed.

Methods Following a procedure similar to Ref. 4, we converted the raw DCE-MRI data to contrast agent concentrations and for each patient we pooled the data for all visits. We reduced the dimensionality of the resulting multivariate data space using correlation matrix-based principal components analysis (PCA), retaining the subset of principal components indicated by the "broken stick" technique[5]. We performed 10 repetitions of *k*-means clustering (with k = 15) in the data space of the retained principal components. Cluster centres were initialized randomly and we selected the solution (from the 10 initialisations) that minimised the sum of the squared Euclidean distance from each data point to its cluster mean vector. To focus on the main per-cluster trends, we rejected all clusters with fewer than 2% of the total number of voxels in the tumour VOI. We used the *k*-means cluster labels to generate a set of single-cluster VOIs which we used to obtain cluster volumes and per-cluster statistics from 3D maps of K^{trans}, generated from the DCE-MRI data using in-house software. We applied a Bland-Altman analysis to the cluster volumes for the two pre-treatment visits and used those visits to calculate the repeatability, expressed as a 95% confidence interval for percent change in volume.

Results The Bland-Altman analysis found no correlation between the volume differences and means for the two pre-treatment visits and the 95% confidence interval for percent change in volume was 123%. Fig. 1 shows 3-D cluster label images for tumours in two patients. Fig. 2 shows graphs of cluster volume against visit for all clusters with significant volume changes (left panel—non-significant volume changes removed for clarity), and bar charts of mean K^{trans} for each cluster and for the whole tumour VOI (right panel—T = whole tumour VOI). Eight of the 9 clusters that decreased in volume had mean $K^{trans} > 0.127$ min^{-1} (with one exception at 0.084 min^{-1}) while 5 of the 6 that increased in volume had median $K^{trans} < 0.046$ min^{-1} (again with one exception at 0.190 min^{-1}).

Discussion Although the clustering procedure did not incorporate spatial information, the segmentations demonstrated a high level of spatial contiguity (Fig. 1).

Each patient data set had a subset of clusters that showed volume changes from the pre-treatment baseline that were statistically significant by the repeatability criterion for at least one visit (Fig. 2). Most clusters can readily be identified in Fig. 1—e.g. Clusters 10 and 11 in Fig. 2 for Patient 2 correspond to the regions coloured yellow and orange in Fig. 1 (a) and the statistically significant post-treatment volume changes in these clusters are evident in both the graphs and the images. Similarly the cluster volume changes for Patient 4 can be seen both in the graphs of Figure 2 and in the images of Fig. 1 (b).

The kinetic model parameter K^{trans} reflects higher blood flow/vessel permeability and is likely to take higher values in actively growing tumour regions where angiogenesis is progressing, as these regions are likely to contain higher densities of immature blood vessels[6]. The observation of reduced post-treatment volume in clusters with "high" K^{trans} (> 0.127 min^{-1}) is therefore consistent with the hypothesis of a post-treatment reduction in the volume of actively-angiogenic tumour regions, as would be expected with a VEGF inhibitor.

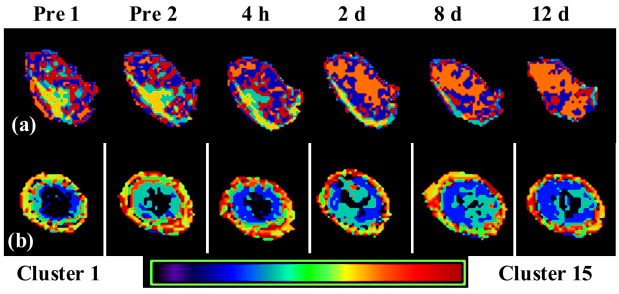

Fig 1 Cluster label images for (a) Patient 2 and (b) Patient 4.

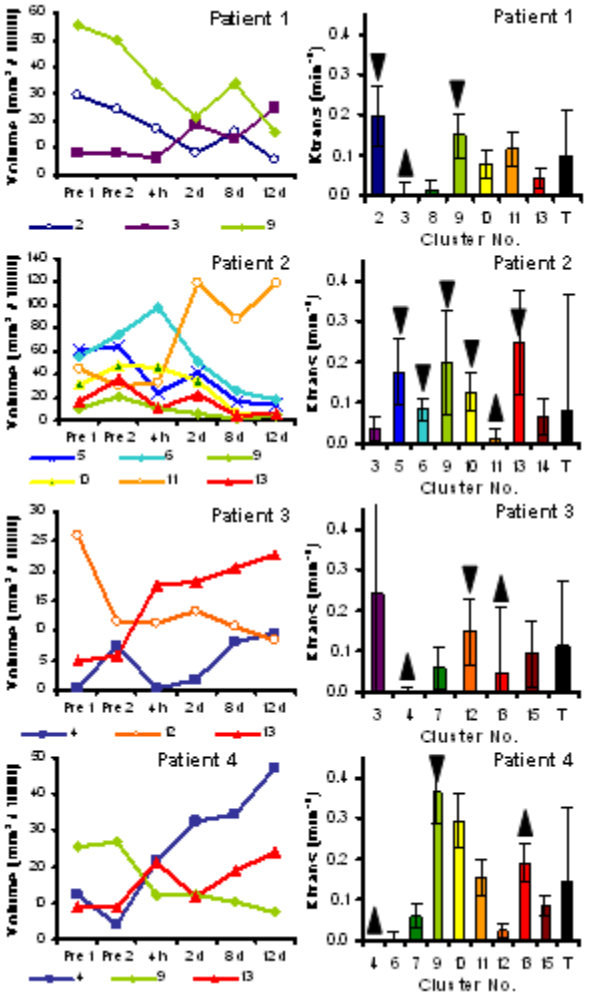

Fig 2 Cluster volume at each scan visit (left) and mean within-cluster K^{trans} ± standard deviation (right). Left panel: horizontal axis is scan visit; legends show cluster numbers. Right panel: triangles indicate statistically significant volume increase (▲) or decrease (▼). Line and bar colours match the cluster colour map of Fig. 1.

Conclusions Segmentation of DCE-MRI time series data from 4 patients enrolled in a trial of a VEGF inhibitor showed statistically-significant changes from pre-treatment baseline in visit-by-visit cluster volumes (Fig. 2) that corresponded to visible alterations in cluster-labelled images (Fig. 1). In trials using DCE-MRI-based biomarkers to study the biological effect of anti-angiogenic or vascular-disrupting agents, the segmentation methodology has the potential to uncover subtle effects that would be masked when using whole tumour VOI statistics.

References 1. Leach MO, Brindle KM *et al*. Br. J. Cancer **92**:1599-1610 (2005). 2. Evelhoch JL, LoRusso PM *et al.* Clin Cancer Res **10**:3650–3657 (2004). 3. Zöllner FG, Sance R *et al*. CMIG **33**:171-181 (2009). 4. Buonaccorsi GA, O' Connor JPB *et al*. Proc ISMRM **16**:2788 (2008). 5. Joliffe IT. *Principal Components Analysis*. Springer, New York (2002). 6. Carmeliet P, Jain RK. Nature **407**: 249–257 (2000).