Whole body quantitative, multi-parametric characterisation of tumour heterogeneity for response evaluation

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Introduction. Inter and intra-tumour heterogeneity in patients with metastatic disease poses an important challenge to anticancer therapy. Multi-parametric, whole body (WB) MR imaging, combining excellent anatomic spatial resolution with functional MR techniques in the same examination may offer a viable solution. The purposes of this study were: a) investigate a new methodology to assess WB tumour heterogeneity; b) validate this hypothesis on a paired pre/post treatment data set.

Methods. *Patient population:* Patients enrolled in a phase II trial of a novel cMet &VEGF inhibitor were scanned pre and 6-week post treatment using 1.5T Siemens Avanto. For the purpose of this study two patients were chosen; Patient 1: A 71-year-old man with castrate resistant prostate cancer with nodal and bony metastases and a large prostate bed recurrence and; Patient 2: A 49-year-old woman with advanced ovarian cancer with liver and peritoneal metastases. *MR image acquisition:* A 3-stack acquisition (covering chest, abdomen and pelvis) of diffusion weighted imaging (DWI) and, respectively, T1w imaging (VIBE) pre (S_{pre}) and post (S_{post}) Gadolinium administration. A standard dose of contrast agent (Dotarem, 0.2 ml/kg) + 20 ml of saline were delivered by power injector. The post-contrast images were acquired at specific delayed time-points for each station following the first pass of contrast, i.e. 30s (chest), 65s (abdomen) and 120s (pelvis) after injection. The DWI parameters were: 2D EPI sequence, 46 axial slices, slice thickness 5mm, TR/TE=12700/69 ms, FOV=380 mm, 4 averages, matrix 150x150, phase partial Fourier 6/8, parallel acquisition (Grappa acc. factor 2, ref lines 32), b =50/900, aq. time ~6 min/stack. Pre/post T1w images were acquired using a 3D gradient echo sequence with: 52 axial slices, slice thickness 5mm, TR/TE=5.68/2.65 ms, FOV=400 mm, 24° flip angle, fat suppression (SPAIR), matrix 256x179, parallel acquisition (Grappa acc. factor 2, ref lines 24). *Segmentation/ mixture modelling:* ROIs were automatically drawn on computed high-b-value images (in-house software [1]) and reviewed by a senior radiologist. The DWI-based ROIs were subsequently applied to the processed T1w data (resampled to same spatial resolution) and Normalized Enhancement (NE = $\{S_{post} - S_{pre}\}/S_{pre}$) and Apparent Diffusion Coefficient (ADC) maps were calculated within these regions. The reported NE map is a pseudo-perfusion image which could reflect the real tissue perfusion if corrected by the local T1 value (not available here). Two-dimensional histograms of NE/ADC values were generated and Gaussian Mixture Modelling (GMM) was applied to the global multivariate data, using the Expectation Maximization (EM) algorithm for parameter estimation [2]. For each study the number of distributions ('classes') required to fit the data was chosen by eye (see right panel on both figures) and the EM algorithm was run over 100 iterations.

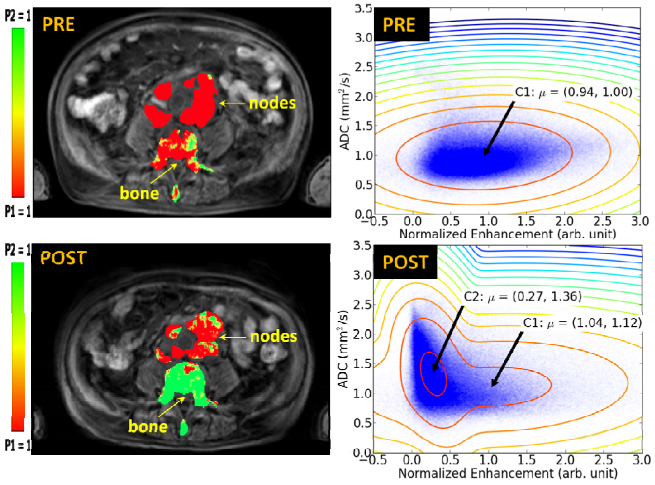

Figure 1. Patient 1. Pre and post treatment axial T1w with overlaid colour probability maps showing tumour heterogeneity and the corresponding scatter plots. Colours represent the probability of a voxel belonging of C1(red) or C2 (green), as defined in post-treatment data.

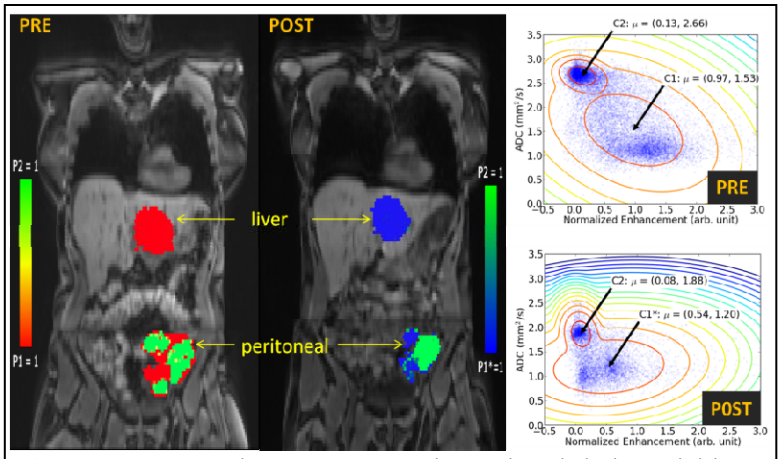

Figure 2. Patient 2. Pre and post treatment coronal T1w with overlaid colour probability maps showing tumour heterogeneity. Colour-coded red/green before treatment (representing probability of belonging to class C1 or C2 as derived from top scatter plot), and blue/green after treatment (C1* and C2 derived from bottom scatter plot).

Following estimation of these multi-modal probability distributions it is possible to derive the posterior probability, P*i*, of a voxel belonging to each class, C*i*, thus providing tissue classification maps.

Results and discussion. *Patient 1*: It is observed (**Figure 1**) that the pre-treatment data is represented by a unimodal Gaussian distribution, which is well fitted by GMM (contour lines). In contrast, the post-treatment data is represented by two Gaussian distributions (mean vectors shown on figure) suggesting the formation of a new tissue class after treatment. Left panel of fig.1 show maps of the posterior probabilities of class association for the classes defined after treatment (C1 and C2), on an image displaying regions of bone and nodal disease (see yellow arrows). Whilst before treatment the majority of pixels belong to class C1 (red), the formation of a second class (C2, green) associated primarily with bone is observed after treatment, suggesting differential response. *Patient 2*: Bi-model distributions are observed both before and after treatment (**Figure 2**) with C1 class believed to represent viable disease (ie low ADC, high enhancement); C2 class representing necrosis/cystic change (high ADC, low enhancement) and C1* class on the post treatment data representing post treatment changes (low ADC, low enhancement). Note the visible shift of NE to the left, from about 1 a.u. to less than 0.6 a.u. suggesting post-treatment lower enhancement. One possible explanation for the reduction in ADC values of class C2 on post treatment scans was thought to be the presence of intra-tumoral haemorrhage (confirmed by new high T1w signal on pre contrast images).

Conclusion. A new methodology successfully demonstrated pre and post-treatment tumour heterogeneity for two patients with different primary cancers and metastases. Such analysis allows observation of changes in the mean ADC and NE values after treatment for each tissue class independently and provides additional functional tumour response characterisation compared to using each method alone. This will be further explored in an on-going clinical study.

References. [1] Blackledge *et al*., Proc. 20th Annual Meeting ISMRM 2012, 255; [2] Pedregosa *et al*., JMLR 12, 2825-2830, 2011.

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