MR Multiparametric Analysis for Tumour Heterogeneity Characterisation. Framework & Initial Experiment in Liver Metastases.

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INTRODUCTION: As a tumour evolves, cells undergo heterogeneous structural changes from alterations in the tumour microenvironment, leading to diverging pathologic phenotypes, differing growth rates and consequently susceptibility to specific drug therapies. Although histopathologic examination of tissue biopsy specimens remains the most trusted method for tissue characterisation, it is prone to sampling error. MR technology offers multiple contrast mechanisms, each informing on a different aspect of tumour pathophysiology, from which parameter maps can be derived. Combining the multiparametric MR information could provide accurate non-invasive tissue characterisation, allowing global assessment of a tumour, while also highlighting regional differences that may be biologically meaningful. Multiparametric approaches in animal models have yielded promising results in tumour segmentation and subtypes discrimination [1]. Tissue characterisation based on multiparametric MR imaging data can be harnessed to evaluate tumour heterogeneity and their response to conventional and novel therapies, depict biologically active disease for radiotherapy planning and improve understanding of tumour behaviour in-vivo. At present, there is no framework and application to enable these complex datasets to be displayed and correlated with each other. This makes multiparametric analysis a time consuming and difficult task in practice. Development of such a platform is critical to the development of bioinformatics and radiogenomics.

AIMS: (a) To create a framework to support the non-invasive multiparametric imaging characterisation of tumour tissue ['virtual biopsy'] and its application in clinical trials. (b) To enable exploration of multiparametric imaging data and correlate quantitative MR measures. (c) To define in the multiparametric space tissue type "signatures", and investigate various classification schemes for specific discrimination tasks.

MATERIAL & METHODS: 1. Framework (fig 1) **–** We have developed an evaluation framework that allows spatially synchronised 3D visualisation and analysis of anatomical, diffusion-weighted and dynamic contrast enhanced MR data in multi-planar orientations. *Data Processing:* (i) A fusion toolbox enables the alignment of all datasets at the tumour of interest. (ii) A Diffusion toolbox allows computation of ADC maps (based on various ranges of b-values). (iii) A DCE toolbox allows the computation of relative enhancement and time to peak. With a proton density reference scan, gadolinium concentration can be calculated, enabling T1, M0, onset time and area under the gadolinium enhancement curve (AUC) maps to be derived. *Exploration:* A scatter plot interface (fig 2) provides the tools to explore the correlations between combinations of parameters in both image and feature spaces, allowing to analyse the distributions within a common ROI defined across the different datasets or to map clusters in the feature space back to the original data. The interface enables the definition of feature descriptors. *Classification:* Various classification methods using or based on the feature descriptors are incorporated in the application. All presented modules are integrated with advanced linking and brushing of the data in a highly interactive way. Application state can be stored for comparative analysis or split workflow. ROIs, quantitative maps and template classifier descriptions can be imported and exported across multiple applications, studies and clinical trials. The framework also allows additional methods to be plugged-in in simple steps. **2. Tumor Heterogeneity Evaluation in Liver Metastases –** *Data:* 10 patients with neuroendocrine liver metastases undergoing a clinical trial. Each patient had 2 baseline scans prior to treatment and 2 follow-ups. Each study included two anatomical scans (T1w, T2w) and 6 b-values DWI (0, 50, 100, 250, 500, 750 s.mm^{-2}), acquired axially, a pre-contrast PD and 40-dynamic DCE-MRI (0-230s) acquired coronally. *Exploration:* All baseline datasets were used to define "normal liver" signature on ADC, T1 and AUC maps, based on manual delineation on the scatter plot interface. *Classification:* Each parametric map was partitioned into 3 fuzzy classes based on the "normal liver" distributions (fig 3), then merged using ternary bit combination to obtain a final probabilistic heterogeneity map (fig 4). The merge process resulted in 26 "abnormal" classes, labeled in different colours in fig 4, one of which directly corresponding to necrotic tissue. **3. Validation –** Necrotic areas were compared to ROIs manually drawn in the environment. Validity of the "normal liver" signature was tested on 10 patients from a different clinical trial.

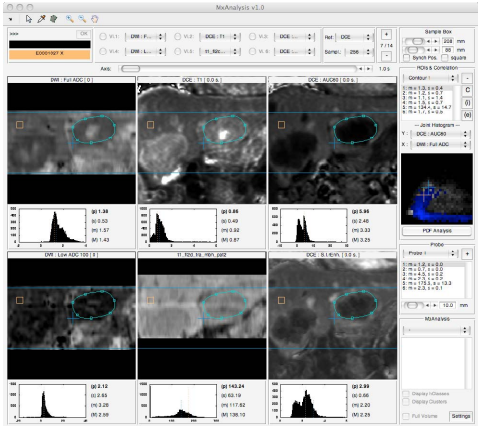

Fig 1: Multi-parametric Framework

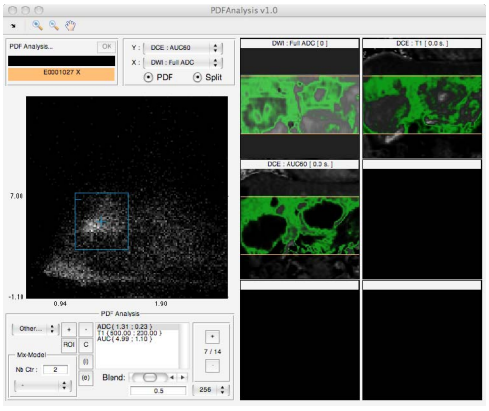

Fig 2: Scatter plot Interface

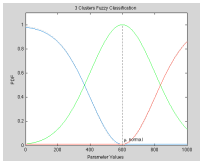

Fig 3: 3-Class Fuzzy Classification

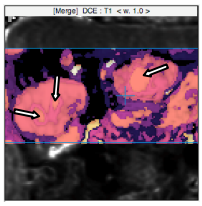

Fig 4: Heterogeneity Map

RESULTS: "Normal liver" distributions for each parameter were (mean μ, standard deviation σ) $\{\mu{:}1.3, \sigma{:}0.16\}_{ADC,1e\text{-}3.mm2.s\text{-}1}$, $\{\mu{:}600, \sigma{:}200\}_{T1,ms}$ and $\{\mu{:}6, \sigma{:}2.0\}_{AUC60}$. From the probabilistic heterogeneity map, necrotic areas, defined as high ADC, high T1 and low AUC were automatically identified (arrows on fig 4), matching expert manual delineation on combination of T2-weighted MR imaging and contrast enhanced images. In the other clinical trial, the descriptors gave similarly good results in identifying tissue subtypes. However, in 4 cases, the "normal liver" signature had to be tuned slightly in the scatter plot interface to improve cluster boundaries.

CONCLUSION: We have built a functional imaging framework to link analysis of multimodality and multiparametric data, explore and characterise tumoural tissues types. The 3-class fuzzy classification / ternary bit combination merging method that we introduced not only allowed normal vs. tumour segmentation, but also identification of heterogeneous tumoural tissues. Further work is being carried out to validate the use of this platform in imaging studies with histopathological comparison, and integrate more automated feature extraction / tissue segmentation methods.

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[1] **Henning EC**, Azuma C, Sotak CH, Helmer KG. Multispectral tissue characterization in a RIF-1 tumor model: monitoring the ADC and T2 responses to single-dose radiotherapy. Part I & II. MRM 2007; 57(3): 501-12 & 513-9.