Radiomics analysis of multi-parametric MRI in human brain tumours

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Introduction: Gliomas are perhaps the most devastating of all tumours due to their debilitating nature and short median survival. There is however considerable variation in both treatment response and survival which appears to be related to intrinsic genetic factors and to the tumour micro-environment. Multi-parametric MRI has been employed with some success to characterise the micro-environment for grading and prediction of response and survival although the choice of the most useful parameters is still debated[1]. Here we use a radiomics[2] approach to identify associations between various MR parameters and to discover any relationship of the parameters to tumour histology and two common genetic markers, the IDH1 mutation and the 1p19q chromosomal co-deletion.

Methods: Multi-parametric MR data was acquired from 55 patients with suspected gliomas prior to any intervention. All diagnoses were subsequently proven histologically. Patients were scanned using a 3.0T MR system (GE 750 Discovery) and an eight channel phased array head coil. Morphological imaging in the form of T_2 FLAIR and T_1 FSPGR post-contrast imaging was acquired along with diffusion tensor imaging (directions=32), multi-flip angle T_1 volumes (3°,5°,10°,20°,40° flip angles) , T_1 dynamics (tdel=5sec, DCE-MRI) and EPI T_2* dynamics (tdel=2sec, DSC-MRI). DCE-MRI preceded DSC-MRI to preload the tissue with contrast, reducing leakage effects. Motion within and between datasets was minimised by applying a series of motion correcting registrations using FSL[3]. All data was subsequently processed using in-house software developed in IDL. DTI parameters were: apparent diffusion coefficient (ADC), fractional anisotropy (FA), anisotropic component of diffusion (Q), relative anisotropy (RA), longitudinal diffusivity (LD) and radial diffusivity (RD). Pharmacokinetic modelling to estimate K^{trans}, v_e, and v_b used a two compartment extended Tofts-Kety model and a population AIF applied to the DCE-MRI data transformed to contrast concentration using T_1 values calculated from the multi-flip angle data (R_1). DSC-MRI was processed using gamma variate and Boxerman[4] models. Cerebral blood volume maps were then normalised to global white matter ($rCBV_G$, $rCBV_B$). T_1 and T_2* dominant leakage rate (K_2) was also measured. Parametric volumes were created by registering the FLAIR, T_1 post contrast, ADC, FA, q, RA, LD, RD, R_1, K_{trans}, v_e, v_b, $rCBV_G$, $rCBV_B$, and K2 into a single 4D [x, y, z, parameter] volume[5]. Whole tumour volumes of interest (VOI) were manually contoured using the morphological images (T_2 abnormality + T_1 post contrast abnormality – necrosis/cyst – haemorrhage) and statistical metrics of each parameter within the tumour were recorded.

For cluster analysis the data for each parameter across all 55 tumours was standardized to the distribution of their medians. Dendrograms were then constructed in each dimension using the Euclidean distance between pairs and weighted pair-wise linkage. Probabilities for the distribution of minimum node lengths in each dendrogram were estimated from 10,000 Monte Carlo simulations of the data ignoring any correlation between parameters.

Results: Figure 1 shows the cluster heat map. It is immediately clear that distinct groups can be identified within both the parameter and subject dendrograms. The probability of each of these clusterings appearing by chance was found to be < 10^{-4}.

For the parameters, a minimum node length of 5 separates 7 clusters: (FA, RA, Q), R_1, (K^{trans}, V_e, V_b, STEALTH), ($rCBV_g$, $rCBV_b$, K1), FLAIR, (ADC, LD, RD) and K2. Clearly several of the parameters are correlated, for example FA with RA, and show redundancy in their ability to differentiate between lesions

Although this group of patients is small we were able to identify several distinct clusters, however it is apparent that a single minimum node length cut-off – the figure illustrates a value of 6.5 – is not the best means of cluster assignment. All but one of the low grade lesions [diffuse astrocytomas (dA) and oligodendrogliomas (O)] appear in one cluster with a distinctive parameter profile which unfortunately did not differentiate between those lesions with known prognostic genetic markers and those without.

A large cluster of high grade lesions [glioblastomas (GBM), anaplastic astrocytomas (AA) and oligodendrogliomas (AO), gliosarcomas(GS)] appear at the bottom of the dendrogram but there is also another cluster of lesions with similar histologies closely linked to the cluster of low grade lesions and possessing an intermediate parameter profile. Although all the deaths, as expected, occurred amongst patients with high grade lesions there was no difference in proportion between the two major high grade clusters.

Discussion: Multi-parametric MRI is a powerful technique which has the potential to provide useful diagnostic and prognostic information. The wealth of data it produces can be overwhelming and methods of identifying associations will need to move beyond simple statistical comparison tests. Radiomics provides a framework within which associations between parameters and disease characteristics can be readily assessed. In this study we demonstrated some redundancy amongst the parameters but equally it is worth noting that each MRI paradigm we employed provides at least one useful parameter. As a minimum set we might suggest Q, R_1, K^{trans}, $rCBV_b$, FLAIR, ADC and K2. We choose Q over FA since it is less influenced by the presence of oedema.

A significant limitation arises from the known heterogeneity of gliomas; our parameters are sampled for the whole tumour volume yet the histological classification is provided by a small tissue sample from an unspecified location within the tumour. This discrepancy of scale may account for few occurrences of a lesion within an apparently inappropriate cluster.

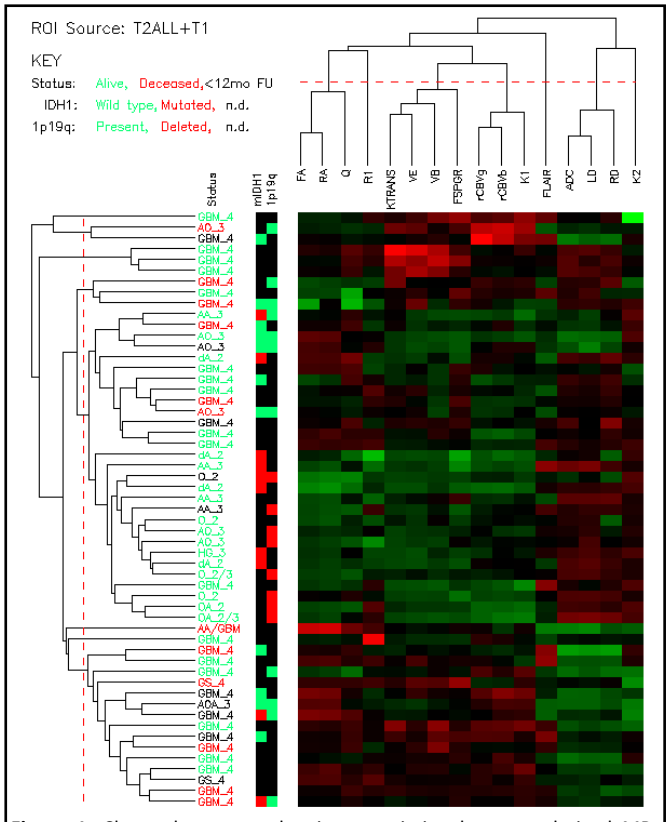

Figure 1. Cluster heat map showing association between derived MR parameters, genetic markers and survival. Green represents parameter values below the median and red those above; the range from brightest green to brightest red is 7.2 standard deviations. Dashed red lines on the two dendrograms show the position of the two cut-offs discussed.

Conclusion: Radiomics analysis of multi-parametric physiological MRI data can provide useful insights that could allow a considered choice of parameters for further investigation. It is possible that a similar analysis of early post-treatment parameter change profiles may be predictive of subsequent survival.

References: 1. Roy B *et al* (2013) Neuroradiol. **55**: 603-613 and references therein. **2**. Kumar et al (2012) MR Imaging **30**: 1234-1248. **3.** Jenkinson *et al*. Medical Image Analysis. (2001) **5**: 143-156. **4.** Boxerman *et al*. Am J Neuroradiol. (2006) **27**: 859-67. **5.** Kenning *et al.* Proc. 21st ISMRM. (2013). 975.