Increasing the Sensitivity of Detection of Targeted MRI Contrast Agents using Bayesian Image Analysis Methods

H. C. Canuto[1,2], M. Velic[3], C. I. McLachlan[3], M. I. Kettunen[1,2], A. S. Krishnan[1], A. A. Neves[1,2], M. M. de Backer[1], D-E. Hu[1], M. P. Hobson[3,4], and K. M. Brindle[1,2]

[1]Biochemistry, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, [2]Cancer Research UK, Cambridge, Cambridgeshire, United Kingdom, [3]Metropolis Data Consultants, Cambridge, Cambridgeshire, United Kingdom, [4]Astrophysics, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom

Introduction

We have been developing a targeted MRI contrast agent for detecting cell death in tumors following drug treatment (1- 4). Quantitative assessment of contrast agent uptake has been based on the analysis of the whole tumor volume. However we know from histology that cell death is localized to specific regions within the tumor. The aim of this study was to use Bayesian image analysis methods to provide an objective assessment of contrast heterogeneity and thus potentially to enhance the sensitivity of localized contrast agent detection. The previously employed *k*-means clustering algorithm requires manual assignment of the number of expected clusters and as such has limited applicability within this area of research. In this study we have applied a Bayesian Multi-Region Segmenter (BMRS) to T_1-weighted MR images obtained from drug-treated and untreated control tumors 24 hours after intravenous injection of a Gd^{3+}-chelate-labeled targeted agent that binds to the phosphatidylserine exposed by dying tumour cells (4). The results were compared with those obtained using a conventional segmentation method, *k*-means, and with T_1-maps, which show the concentration distribution of the agent in the tumors.

Materials and Methods

Mice bearing EL4 murine lymphomas were either untreated or treated, by i.p. injection, with 67 mg/kg etoposide and then 24 h later injected i.v. with 200 mg/kg of a fusion protein (C2A domain of synaptotagmin fused to glutathione S-transferase) that had been conjugated with ca. 10 mols Gd^{3+}-DTPA. Twenty-four hours after injection of this targeted contrast agent, T_1-weighted images (TR 450 ms, TE 8ms, FOV 35x35 mm, data matrix 256x256, slice thickness 1mm) and T_1-maps (11 inversion times between 50 ms and 10s, 10 s relaxation delay, TR 5.5 ms, TE 2ms, data matrix 128x64, centre-out data collection) were acquired from the tumors. Previous work has shown that there is significantly greater accumulation of the targeted agent in treated tumors when compared to untreated tumors and also when compared to animals that had been injected with a site-directed mutant of the C2A domain, that is inactive in PS-binding (4). The BMRS was applied to drug-treated and untreated tumors injected with the targeted agent. The segmented images were compared with those obtained using a *k*-means clustering algorithm and also with T_1 maps obtained from the same tumors. The BMRS was developed as a region-growing segmentation method; it uses a conjugate prior that maximises evidence by taking into account multiple regions. The region is grown from a single voxel and each subsequent voxel is either added to the region or rejected, according to Bayesian inference. In this study each segmentation method was applied assuming a three-region model that included healthy tissue, tumor and possible subdivisions within these regions.

Results

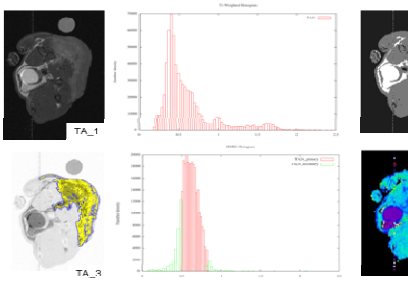

Fig. 1 **Drug treated** – T_1-weighted (TA_1), *k*-Means clustering (TA_2), BMRS (TA_3) and T_1 map (TA_4)

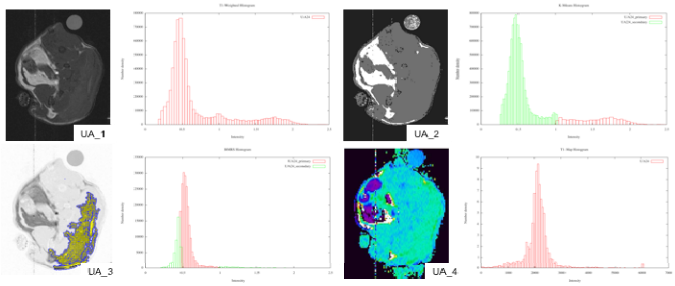

Fig. 2 **Control** – T_1-weighted (UA_1), *k*-Means clustering (UA_2), BMRS (UA_3) and T_1 map (UA_4)

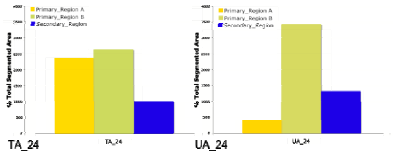

Fig. 3 Histogram Analysis of drug-treated and untreated control tumors showing the total area of segmentation for each region as a percentage of the total area segmented

T_1-weighted image (_1), *k*-means clustering algorithm and BMRS applied to the T_1-weighted image (_2 and _3) and a T_1 map (_4), together with the corresponding histogram analyses, are shown for drug-treated and control tumors in Figs. 1 and 2 respectively. In both the drug-treated (Fig. 1 TA_2) and control tumors (Fig. 2 UA_2) the *k*-means algorithm failed to make a distinction between healthy tissue and the tumor. Histogram analysis of the derived *k*-means cluster values clearly show the image to be segmented by assuming two Gaussian curve fits where the overlap is considered the dividing point between regions. The BMRS (Fig. 1 TA_3 and Fig. 2 UA_3) segmented the tumor (Primary A, yellow region) and a subdivision within the primary tumor region itself (Primary B, pale green region). BMRS assigned pixels to the secondary region (blue) in the regions immediately bordering the tumor as well as a few areas within the tumor itself. Histogram analysis of the BMRS segmentation shows the segmentation to have assigned pixels to the secondary region both above and below the intensity of the primary region.

Tumor segmentation by BMRS shows visibly different patterns of contrast agent accumulation and distribution in the drug-treated and untreated control tumors, a pattern confirmed by the T_1 maps (Fig. 1, TA_4 and Fig. 2, UA_4). The extent of subdivision within the primary region gives an indication of heterogeneity of contrast agent distribution within the tumor. It is interesting to note the ratio of Primary Region A to Primary Region B is higher in the drug-treated tumor compared to the control (Fig. 3). In the drug-treated tumor Primary Regions A and B make up 33% and 50% respectively of the total segmented area whereas in the untreated tumor Primary Regions A and B make up 8% and 66% respectively This is consistent with histological analysis of drug-treated tumors, which showed that tumor cell death was very heterogeneous and localized to specific regions.

Conclusions

BMRS clearly demonstrates the capability to extend the basic segmentation methods and provides a reliable automated segmentation. Application of the BMRS to T_1-weighted tumor images acquired from drug-treated and control animals that had been injected with a targeted Gd^{3+}-based contrast agent that binds to dying cells, showed that contrast agent accumulation was more heterogeneous in the drug-treated tumour, consistent with the heterogeneous nature of tumor cell death observed in tumor sections obtained post-mortem.

References

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