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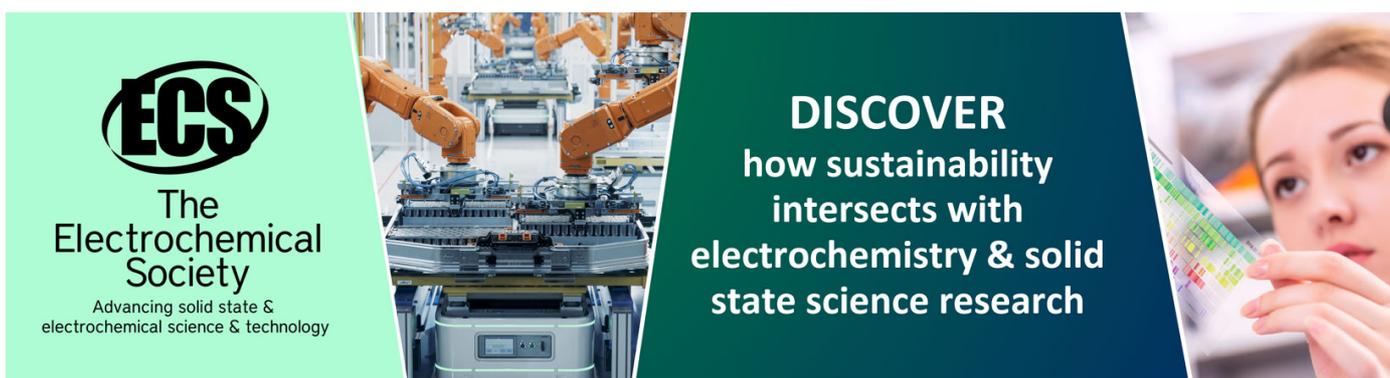
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Assessing local outcomes in heterogeneous gliomas

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Abstract. Tumours are known to be heterogeneous, yet typical treatment plans consider them as a single unit. This may influence treatment outcomes. However, treatment cannot be customised to intra-tumour variation without a method to establish outcomes at an intra-tumour scale. This work proposes a method to both assess and measure outcomes locally within tumours. **Methods:** Four patients were scanned at two post-surgery time points using contrast enhanced MRI and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-DOPA) PET. The shell of active tumour tissue is divided into a set of small subregions at both time points. Local outcome is measured from changes in subregion volume over time. The utility of the proposed approach is evaluated by measuring the correlation between PET uptake and documented growth. Correlation with overall survival time was also examined. **Results:** Local outcomes were heterogeneous and evidence of a positive correlation between local 18F-DOPA uptake and local progression was observed. **Conclusions:** Given that intra-tumour outcomes are heterogeneous the consistently positive correlation between FDOPA uptake and progression, local analysis of tumours could prove useful for treatment planning.

1. Introduction

It is known that even within individual tumours there is variation in biological behaviour [1]. Individual cell lines are highly adapted to their immediate environment, e.g. tumour cells in a hypoxic environment have different adaptations to those in normoxic conditions [2]. Tumour heterogeneity is important and is a determinant of patient outcome. However, most imaging studies of malignancy and therapeutic monitoring appear to examine tumours as a whole [3], [4], [5], [6] possibly because of the difficulty of establishing outcomes at an intra-tumour scale. The issue of heterogeneity is particularly appropriate to advanced glioma, which is an aggressive malignancy to which most patients succumb in less than a year [7]. Treatment involves maximal, safe surgical resection to debulk the tumour followed by radiotherapy and adjuvant chemotherapy [8] to control residual tumour. Even so, tumours typically, recur within months, because chemo-therapy and radiotherapy are limited by toxicity to normal tissues [8]; the blood brain barrier can limit access by chemotherapy agents[9]; and the tumour is microscopically infiltrative, which may result in geographic misses during radiotherapy.

This work attempts to address the above issues by introducing a polar spatial model for tumours similar to the polar map images used for myocardial perfusion imaging [10], to allow measurement of biological heterogeneity and to provide a method for comparison of serial follow up measurements.



The method is applied to clinical examples of PET scans in patients with advanced glioma, by using it to examine the predictive capabilities of PET one month after a course of radio- and chemo-therapy.

2. Materials and Methods

Four patients were scanned at two post-surgery time-points using contrast enhanced MRI and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (FDOPA) PET. Baseline scan was 4 weeks after a 6-week course of chemo-radio-therapy (12-weeks post-surgery). Follow up was 6 months later post-surgery. Scans at each time point were taken within a two day window. The study was approved by the Royal Brisbane and Women’s Hospital ethics committee. Informed consent was provided for study inclusion.

MRI data was acquired using a 3T Siemens Trio employing a Magnetization-prepared Rapid Acquisition Gradient-echo (MPRAGE) sequence with the following parameters (FOV 24x25.6x17.6 cm, TR/TE/TI 2300/2.26/900 ms, flip angle of 90, 1 mm isotropic resolution). Images were acquired before and after administration of contrast agent Gadovist, (Bayer HealthCare Pharmaceuticals). FDOPA was synthesised according to the method in [11]. An FDOPA activity of 151MBq on average was administered intravenously (range 138 to 164MBq). PET imaging was performed using a Philips Gemini GXL scanner. A transmission CT scan was acquired first. Subsequently, FDOPA was administered intravenously and a 75-minute acquisition initiated. The images were reconstructed using ordered subset expectation maximisation with corrections for attenuation and scatter. The final volume has a matrix size of 128x128, consisting of 90 planes of 2x2x2mm³ voxels.

The follow-up MRI was registered to baseline using standard multi-scale mutual information rigid registration [12], and the remaining images within each time-point were registered to their respective pre-contrast MRI. Afterwards, a standard non-rigid registration algorithm [13] was applied at a coarse level (40mm node spacing) to account for brain shift.

An experienced nuclear medicine physician (PT) manually contoured each tumour at each time point using fused FDOPA PET and MR images, to define the outer extent of the tumour. The contour of the tumour cavity was obtained by thresholding away the central regions below the median PET intensity on the outer surface. A tumour centre point was defined by calculating the centre of gravity in the baseline study. The tumour centre was reused in the follow-up images. Rays corresponding to each combination of longitude and latitude are projected from the tumour centre to its outer extent, and used to divide the tumour up into a set of small subregions at both timepoints as shown in Fig. 1.

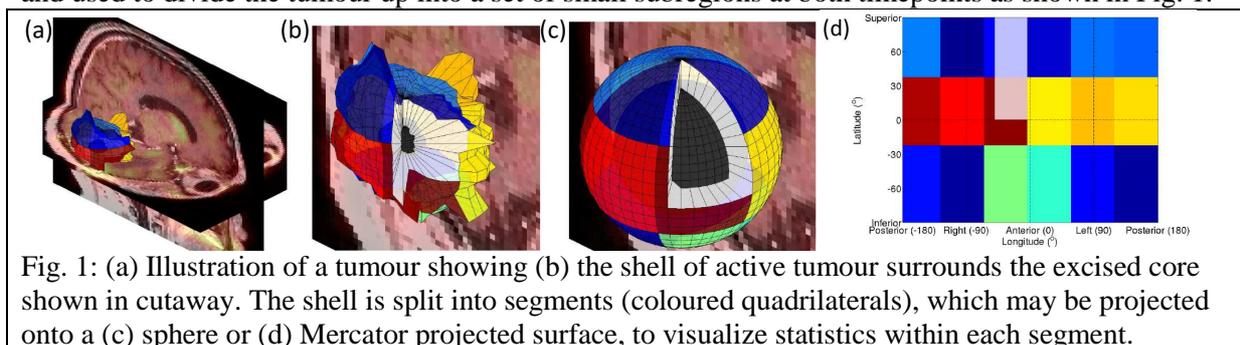


Fig. 1: (a) Illustration of a tumour showing (b) the shell of active tumour surrounds the excised core shown in cutaway. The shell is split into segments (coloured quadrilaterals), which may be projected onto a (c) sphere or (d) Mercator projected surface, to visualize statistics within each segment.

Local outcome is measured in terms of the changes in the volume of each subregion between the baseline and follow-up images. Volume changes are reported in percentage terms relative to the regional volume at baseline. The mean PET uptake within each subregion was also computed. In order to make inter-patient comparisons, PET uptake was measured as Standardized Uptake Value (SUV) ratio, where all PET intensities are divided by the mean PET intensity within the ipsilateral cerebellum. A value of one indicates uptake identical to normal tissue.

3. Results and discussion

Several angular resolutions were applied to find the optimal number of latitudes and longitudes using Receiver Operator Curve (ROC) analysis. The Area of each Curve (AoC) was measured and the

results are shown in Fig. 2a. Three latitudes and six longitudes gave the largest area of curve of 0.83. Variation in performance occurs because errors arise from grouping heterogeneous biological regions. Also, changes in both metabolism and location occur, which registration cannot disambiguate. A trade-off between these errors exists: larger segments risk grouping more heterogeneous tissues but reduce correspondence error, and *vice-versa*. Unbiased segment correspondences rely on movements in the tumour centre point, caused by brain shift, remaining small (below 10% of diameter). Although such shifts did not occur in this dataset, this should be checked for and corrected if necessary.

Cox hazard analysis was used to examine correlation between survival time, max segment intensity, and whole-tumour mean for the four patients. Despite the low sample size, an r^2 of 0.23 was obtained (versus 0.59 for the whole-tumour mean). More samples are needed to properly evaluate segments' correlation with survival.

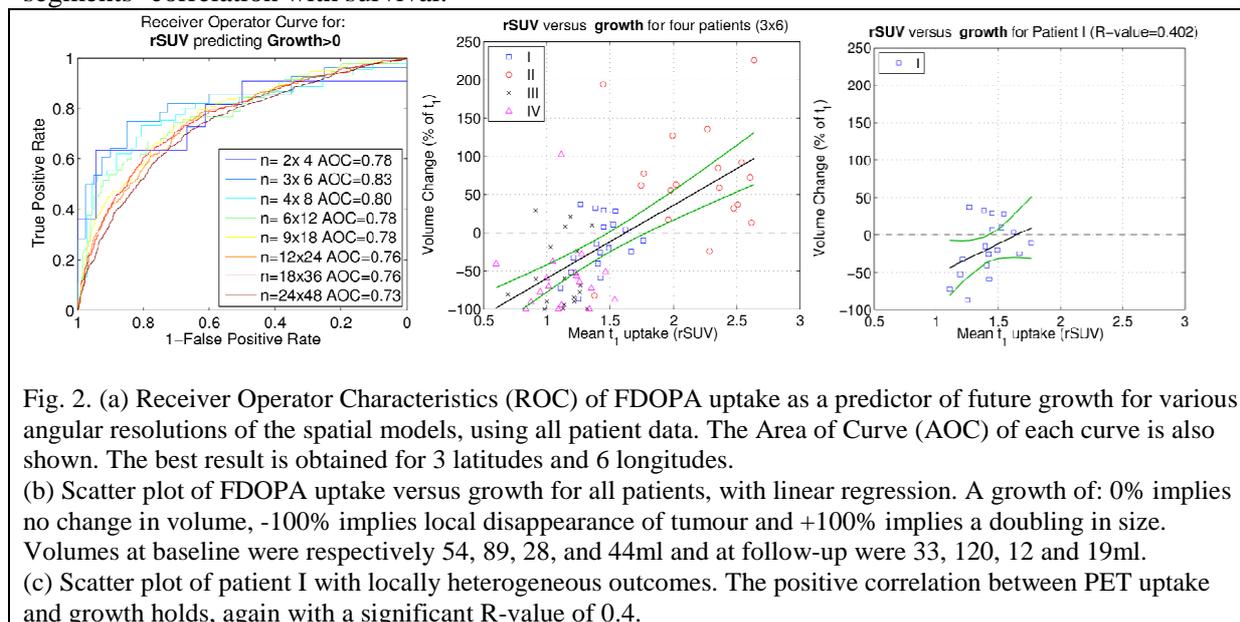


Fig. 2. (a) Receiver Operator Characteristics (ROC) of FDOPA uptake as a predictor of future growth for various angular resolutions of the spatial models, using all patient data. The Area of Curve (AOC) of each curve is also shown. The best result is obtained for 3 latitudes and 6 longitudes. (b) Scatter plot of FDOPA uptake versus growth for all patients, with linear regression. A growth of: 0% implies no change in volume, -100% implies local disappearance of tumour and +100% implies a doubling in size. Volumes at baseline were respectively 54, 89, 28, and 44ml and at follow-up were 33, 120, 12 and 19ml. (c) Scatter plot of patient I with locally heterogeneous outcomes. The positive correlation between PET uptake and growth holds, again with a significant R-value of 0.4.

The linear regression applied to the SUVr and growth values of the four patients is shown in Fig. 2b. The Pearson correlation coefficient (or R-value), was 0.656, indicating that uptake is a predictor of future growth. The 95% confidence interval was also relatively narrow. Inter-patient variation had substantial influence on the results. Patients III and IV had lower uptake and general shrinkage. Considering patients individually, positive correlations between SUVr and growth occurred in all cases with respective R-values for patients I to IV of 0.402, 0.135, 0.048 and 0.016. The correlation indicates significant correspondence between FDOPA uptake and future growth. This is a useful result, because it means FDOPA could potentially be used as an early marker of treatment response. In the remaining patient with a mixture of growth and shrinkage, the correlation between uptake and volume change was more significant, implying that local analyses are not only possible but useful, and provide an advantage over analyses of tumours as a whole.

Although positive correlations between uptake and local volume changes were found, a limitation of this study is the low number of patients. In particular, more patients with heterogeneous growth are needed. Even so, the positive correlations in patients with relatively uniform behaviour globally imply that local analysis has potential utility, because it allows a better interrogation of the data, with reduced tissue heterogeneity within each segment relative to the tumour as a whole.

4. Conclusion

A method for dividing tumours into subregions and evaluating outcomes locally in longitudinal studies has been introduced. This may be useful in removing some of the confounding effects of tumour heterogeneity. It may also facilitate research into risk adapted local therapies (such as radiotherapy boost doses to local tumour areas at risk) by identifying and localizing risk biomarkers.

In testing on four longitudinal FDOPA PET studies of patients with advanced glioma, heterogeneity was consistently evidenced both in local outcomes and local PET uptake. Although two patients showed general tumour regression everywhere in all cases positive (if weak) correlations between FDOPA and growth were obtained. Notably, in the single patient with a mixture of tumour growth and shrinkage had the highest R-value (0.402) signifying that the FDOPA has some ability to predict future growth locally within individual patients. Local analysis of tumours could help realize ambitions for tailoring treatment not only to the individual, but at an intra-tumour level.

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