Evaluation of prostate gland hypoxia with quantified BOLD MRI: initial results from a correlated histological study

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Synopsis: A study investigating prostate cancer hypoxia was performed using BOLD-MRI in conjunction with DCE-MRI and verification using pimonidazole immunostaining of co-registered histological sections. $R_2^*$ alone best reflected the oxygenation status of tumours and incorporating blood volume reduced sensitivity and negative predictive value (NPV) without adding specificity. On average a positive MRI result is at least twice as likely to indicate tumour hypoxia as not. These early data provide evidence supporting the hypothesis that unstimulated BOLD-MRI can indicate the oxygenation status of human prostate cancer.

Introduction: Tumour hypoxia has important implications for patient prognosis at a number of anatomic sites including the prostate and on the efficacy of anti-cancer treatments, particularly resistance to radiotherapy (1-4). Prostate cancer hypoxia can be demonstrated by Eppendorf oxygen probes or by immunohistochemical staining with pimonidazole (5). Intensity modulated radiotherapy (IMRT) is being explored as a means of enabling selected areas of tumours to receive greater prescribed radiation doses in order to overcome radioresistance whilst maintaining normal tissue tolerances. If clinically relevant hypoxic regions in the prostate could be imaged non-invasively, then IMRT could be used to treat hypoxic regions as small as 5mm x 5mm. Previously, when attempting to understand $R_2^*$ image contrast in tumours we put forward the hypothesis that a measurable blood volume in conjunction with fast $R_2^*$ on BOLD-MRI may reflect underlying hypoxia (6). In this report we test this hypothesis in patients with prostate cancer who were given pimonidazole prior to radical prostatectomy for localised disease. We compare the spatial distribution of MRI parameters (unstimulated $R_2^*$ & relative blood volume) with pimonidazole stained histological sections obtained in the plane of imaging in order to assess the ability of MRI to predict clinically significant prostate cancer hypoxia.

Methods: Following local ethical approval, 5 patients (age 53-69 yrs old; Gleason score, 6-7; serum PSA, 5.9-15 µg/l) with localised prostate carcinoma were imaged prior to receiving 0.5g/m$^2$ pimonidazole intravenously 16-24 hours before radical prostatectomy. Patients were imaged in a Symphony 1.5T MRI scanner (Siemens, Germany) using a phased array pelvic coil. $T_2$-weighted images perpendicular to the urethra were used to stage tumours and to identify tumour slice locations (1 slice location per patient). Multiple gradient echo images were acquired with varying TE (5-75ms), TR=100ms, $\alpha=40^\circ$, slice thickness 8mm, FOV=200mm and 256$^2$ matrix from which $R_2^*$ maps were calculated (6). A dynamic series of 60 GRE $T_2^*$-weighted images was then acquired (TE=20ms, TR=34ms, 64x128 matrix, $\alpha=40^\circ$ and time resolution 2.01s) before, during and after an injection of 0.2mmol/kg body weight Gd-DTPA (Magnevist®, Schering Healthcare) given at 4ml/s after the 10$^\text{th}$ image using a power injector. A gamma variate fit function was applied to the data on a pixel-by-pixel basis and relative blood volume (rBV) maps were calculated. Images were empirically segmented for areas of fast $R_2^*$ (similar intensity to muscle) and areas of rBV greater than fat and mapped onto a prostate gland outline. Histological sections stained by H&E for tumour localisation and for pimonidazole (hypoxia detection) obtained in the imaging plane were inspected at low power (x4) and independently mapped on the same prostate gland outline. Correspondences between MRI metrics with histology were performed using 5x5mm grid overlays. The results were analysed using a 2x2 table analysis for regions predominantly containing tumour (>50% of a grid with tumour: 133 grid locations) and non-tumour prostatic tissues (165 grid locations).

Results: Hypoxia was found in benign prostatic hyperplasia. For tumour, 48/60 grids with fast $R_2^*$ stained positive for pimonidazole and 17/19 grids with slow $R_2^*$ stained negative. The results (Table) show that MRI is better able to identify hypoxia in tumours compared to non-tumour tissues. $R_2^*$ alone best reflects the oxygenation status of tumours and adding rBV information reduced the sensitivity (96% to 78%) and NPV (89% to 62%) without improving specificity. On average a positive MRI result including $R_2^*$ is twice as likely to indicate tumour hypoxia as not, but this does not hold true for normal tissues.

Discussion: Carbogen stimulated BOLD-MRI has been shown to reflect tissue hypoxia in preclinical models (7). Despite the limitations of this study (small patient sample, empirical image segmentation, partial volume averaging errors and fixation artefacts), these early patient data provide evidence to support the hypothesis that unstimulated BOLD-MRI may allow non-invasive mapping of significant hypoxia of human prostate cancer. A larger cohort of patient is currently being analysed to verify these findings. Preclinical verification is also needed before adopting unstimulated BOLD-MRI as a surrogate of tumour hypoxia.

References:

<table>
<thead>
<tr>
<th>Tissue type &amp; criteria for MRI</th>
<th>Hypoxia prevalence %</th>
<th>Sens %</th>
<th>Spec %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>LR+ve</th>
<th>LR-ve</th>
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</thead>
<tbody>
<tr>
<td>Non-tumour ($R_2^*$+rBV)</td>
<td>25</td>
<td>50</td>
<td>56</td>
<td>28</td>
<td>77</td>
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<td>Tumours ($R_2^*$+rBV)</td>
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<td>78</td>
<td>62</td>
<td>78</td>
<td>62</td>
<td>2.1</td>
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<td>Tumours ($R_2^*$ alone)</td>
<td>63</td>
<td>96</td>
<td>59</td>
<td>80</td>
<td>89</td>
<td>2.3</td>
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<tr>
<td>Tumours (rBV alone)</td>
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<td>80</td>
<td>80</td>
<td>59</td>
<td>9</td>
<td>0.8</td>
<td>5.8</td>
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Table: Sens=sensitivity; Spec = specificity; PPV & NPV = positive and negative predictive values; LR = likelihood ratios of a positive and negative test.