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

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**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 boost doses to hypoxic regions as small as 5mm x 5mm. In this report we test the hypothesis that fast $R_2$* on BOLD MRI combined with low relative blood volume (rBV) on $T_2$*-weighted DCE-MRI informs on poor tissue oxygenation 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, 20 patients (age 53-76 yrs old; Gleason score, 6-7; serum PSA, 4.23-24.4 ng/ml) 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$^o$, 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$^o$ 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$^{th}$ image using a power injector. A gamma variate fit function was applied to the data on a pixel-by-pixel basis and rBV maps were calculated. Images were segmented for areas of fast $R_2$* (similar intensity to muscle) and areas of low rBV (≤ 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: 237 grid locations) and non-tumour prostatic tissues (861 grid locations).

**Results**: Hypoxia was found in benign prostatic hyperplasia (prevalence 34% of non-tumour grids). For tumours 146/166 grids with fast $R_2$* stained positive for pimonidazole and 25/70 grids with slow $R_2$* stained negative (Yates-corrected Chi² = 16.4 p<0.001). The table of results show that the presence of fast $R_2$* at a tumour grid location increase the likelihood of hypoxia being present by 1.37 (from a pre-test prevalence of 70% to 76%) and that a negative test decreases the likelihood of hypoxia being present by 26%. MRI is better able to identify hypoxia in tumours compared to non-tumour tissues. Adding rBV information increases sensitivity (88% to 95%) and NPV (56% to 70%) without improving specificity.

| Tissue type & criteria for MRI | Hypoxia prevalence % | Sens % | Spec % | PPV % | NPV % | 100-NPV | LR+ve |
|---|---|---|---|---|---|---|---|
| **Non-tumour** $R_2$* &/or low rBV | **34** | 65 | 20 | 30 | 52 | 48 | 0.81 |
| **Tumours** $R_2$*&/or low rBV | **71** | 95 | 29 | 77 | **70** | 30 | 1.34 |
| **Tumours** $R_2$* alone | 70 | **88** | **36** | **76** | **56** | 44 | **1.37** |
| **Tumours** low rBV | 69 | **24** | **91** | **86** | 34 | 65 | **2.65** |

**Table:**
Sens= sensitivity;
Spec = specificity;
PPV & NPV = positive and negative predictive values;
LR = likelihood ratios of a positive test.

**Discussion:**

Despite the limitations of this study (small patient sample, partial volume averaging errors and fixation artefacts), these patient data provide evidence that unstimulated BOLD-MRI with or without blood volume information allows non-invasive mapping of significant hypoxia of human prostate cancer. Preclinical verification is needed before adopting unstimulated BOLD-MRI as a surrogate of prostate tumour hypoxia.

**References:**

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