# Sensitivity and specificity of functional MRI to map tumour hypoxia in the human prostate gland

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**Aim:** To determine the sensitivity, specificity and predictive values for Blood Oxygen Level Dependent (BOLD) and Dynamic Susceptibility Contrast (DSC) MRI in the detection of tumour hypoxia in the human prostate gland.

**Introduction:** Tumour hypoxia is a known cause of radiotherapy treatment failure and is associated with poor local tumour control rates and relapse in a variety of tumour types. The lack of a reliable, non-invasive method for measuring and mapping hypoxia in intact human tumours has hampered the development of strategies to combat hypoxia. BOLD MRI capitalizes on the differing magnetic properties of oxygenated and deoxygenated haemoglobin. Microscopic field inhomogeneity gradients in the vicinity of perfused vessels are caused by changes in the paramagnetic deoxyhaemoglobin concentration, leading to signal changes in susceptibility-weighted MRI sequences ($T_2$*). Validation of the technique has been achieved by correlation with direct microelectrode measurements [1,2], intravital microscopy [3] and immunohistochemistry [4]. For BOLD-MRI to be able to depict tissue oxygenation status it is necessary to know that tissues are perfused by red blood cells. Combining Dynamic Susceptibility Contrast (DSC) MRI based blood volume measurements with BOLD imaging may therefore reflect tissue oxygenation more accurately [5].

**Patients and Methods:** 17 patients with histologically confirmed prostate cancer (age 56-76 years, Gleason grade 6-8, PSA 1.9-32.0 ng/ml) that were due to be treated by radical prostatectomy were recruited. Each patient was examined with MRI the day before surgery. An intravenous pimonidazole infusion (0.5g/m$^2$ bsa) was administered 16 – 24 hours before surgery. The excised prostate specimen was cut in the same plane as the imaging slice (figure 1). Whole mount sections of the prostate were stained for pimonidazole and compared with the BOLD and DSC imaging slices using grid based analysis as previously described [5] (figure 2).

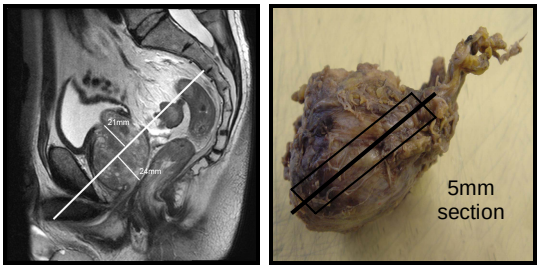


**Figure 1** Imaging and Cutting the prostate

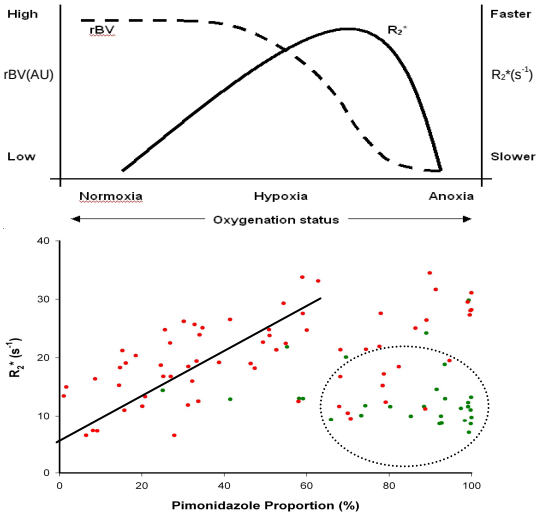


**Figure 3** Above: Theoretical change in $R_2$* and rBV with oxygenation. Below: experimental data supporting this hypothesis

**References:**

1. Al-Hallaq et. al. *Int J Radiat Oncol Biol Phys* (41) 1998. 2. Maxwell et. al. *proc. ISMRM* (abst. 495) 1999. 3. Neeman et. al. *Magn Reson Med* (45) 2001. 4. Robinson et. al. *Magn Reson Imaging* (17) 2003. 5. Hoskin et al. *Int J Radiat Oncol Biol Phys* (68) 2007

BOLD-MRI: Five spoiled gradient-echo images were acquired for three 8mm thick slices through the prostate with varying TE (5-60ms), TR=100ms, flip angle=40°, FOV=200mm, 256$^2$ matrix, from which $R_2$* (min$^{-1}$) maps were calculated.
DSC-MRI: Following pre-dosing with 0.1 mmol/kg b.w. of Gd-DTPA, a $T_2$*-weighted sequence was used to acquire data every 2 seconds over 2 minutes (TE 20ms, TR 30ms, flip angle = 40°, one slice of 8mm thickness). A bolus of 0.2 mmol/kg b.w. of Gd-DTPA was administered at 4ml/s after 20 seconds. rBV (AU) maps were calculated.

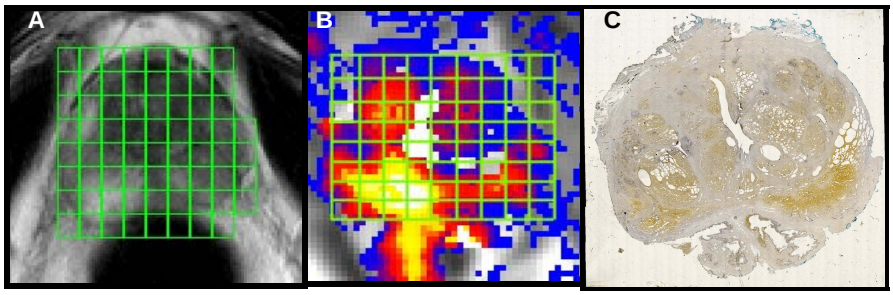


**Figure 2** Grid comparison between (a) R2*, (b) rBV and (c) pimonidazole staining

**Results and discussion**: Graph figure 3 (top) depicts the theoretical change in BOLD-MRI signal ($R_2$*) that would be expected as tissue oxygenation reduces, from reference [5]. Note how in the absence of red blood cell delivery, $R_2$* levels fall despite the presence of hypoxia indicating that in order to correctly interpret $R_2$* images to infer oxygenation status, it is necessary to know whether blood is being delivered to tissues. Figure 3 (bottom) confirms that in the presence of blood volume (red dots; >42AU), $R_2$* correlates with tissue pimonidazole staining and by inference with oxygenation status. For data points that represent tumour grids with low blood volume (green dots within circle) $R_2$* correlation with oxygenation status is lost.

A combined test to exclude hypoxia, using the algorithm: *rBV greater than 42 a.u.* ***AND*** *$R_2$* less than 21.3s$^{-1}$*, gives the following test statistics using pimonidazole staining as a 'gold-standard' for hypoxia detection:

| | |
|---|---|
| **Sensitivity** | **80.00% (95% CI 68.23% to 88.90%)** |
| **Specificity** | **77.42% (95% CI 58.90% to 90.41%)** |
| **Positive Predictive Value** | **88.14% (95% CI 77.07% to 95.09%)** |
| **Negative Predictive Value** | **64.86% (95% CI 47.46% to 79.79%)** |