Hypoxia modification during prostate radiotherapy: an evaluation of changes in the tumour microenvironment using multi-parametric MRI (mpMRI)

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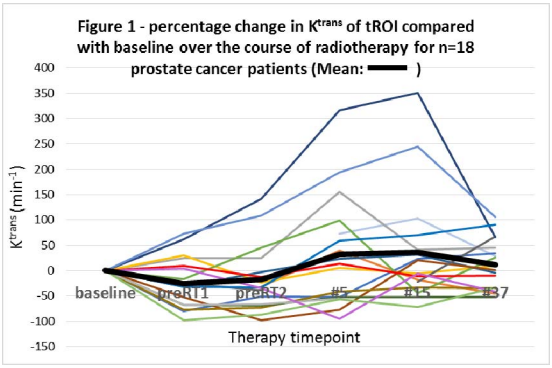
Introduction: Lack of oxygen in the tumour microenvironment is known to reduce the effectiveness of radiotherapy (RT)[1]. Correction of hypoxia has been shown to improve survival in patients treated with RT for bladder and head and neck cancer[2,3]. Previous studies have demonstrated the existence of hypoxia in untreated prostate cancer (PCa) and an improvement in prostate tumour oxygenation following carbogen gas breathing (98% O_2 + 2% CO_2)[4]. It is standard practice to administer androgen deprivation therapy (ADT) prior to the commencement of RT. ADT is anti-angiogenic and causes vascular disruption in prostate tumours within weeks of androgen withdrawal[5]. It is currently not known whether the application of carbogen gas post-ADT and during RT will still be effective in correcting hypoxia. The purpose of our study was to address this question, and to evaluate the changes in the tumour micro-environment during a course of conventionally fractionated RT.

Methods: 50 patients with high risk PCa (PSA ≥ 20ng/ml or Gleason score ≥ 8 or stage T3) took part in a phase II clinical trial of prostate radiotherapy in conjunction with hypoxia modification using carbogen gas and nicotinamide. The primary objective was to evaluate the toxicity associated with the addition of daily carbogen and nicotinamide to standard RT (74Gy/37#). 20 patients also underwent serial mpMRI examination during their treatment. Six scans were carried out in total at the following time points: 1st: immediately prior to ADT (three months pre-RT); 2nd and 3rd (reproducibility pair) one week pre-RT and three months into ADT; 4th, 5th & 6th – at week 1, 3 & 7 of RT. The following sequences were carried out: DCE-MRI (3D-VIBE, TE 1.24ms TR 6.6ms, flip angles 3° and 21°, acquisition matrix 256x74, 20 slices of 5mm thickness, field of view [FOV] 260mm); ISC-MRI pre- & post-carbogen (Multi-gradient-echo, TE 4.76-62ms, TR 100ms, flip angle 25°, acquisition matrix 128^2, 16 slices of 5mm, FOV 260mm); DW-MRI (TE 74ms, TR 3500ms, acquisition matrix 102 x128, recon matrix 256^2, slice thickness 3.6mm & b-values 0, 50, 100, 400, 800, 1100, 1500 s/mm^2). Tumours were identified on the scans obtained at baseline (three month pre-RT and pre-ADT) on the basis of their morphological appearances on T_2W & DW-MRI images. A standard tumour region of interest (tROI) was outlined around each tumour. For scans at subsequent time points the tROIs were delineated with reference to the baseline scans. Voxel based calculations were performed using in-house analysis programmes: MRIW[6] for DCE data and DiffusionView for ISW-MRI data (both ©Institute of Cancer Research, London). The following kinetic parameters were derived (units in parenthesis): K^{trans} (min^{-1}), $IAUGC_{60}$ (mmol.s), R_2* (s^{-1}). The extended Kety Model[7] was used for data fitting to calculate K^{trans} using a population arterial input function[8]. Changes in kinetic parameters compared with baseline values for each day were calculated.



Results: Basal tumour R_2* increased by 17% after 3 months of ADT compared with baseline (**Table 1**). Carbogen inhalation resulted in decreased R_2* at all time points, by as much as 10%. K^{trans} and $IAUGC_{60}$ of whole prostate and tROIs reduced after 3 months of ADT but recovered during the course of RT (**Table 1**). Response to radiotherapy as evaluated by changes in K^{trans} and $IAUGC_{60}$ at the end of RT compared with baseline was more variable among tROIs than whole prostate (**Table 1**). At midpoints in the RT, response was highly heterogeneous (**Figure 1**).

Conclusion: Reductions in K^{trans} and increases in R_2* are consistent with worsening in tumour oxygenation after the 3 month period of ADT. Despite the changes in K^{trans}, tumours remained responsive to carbogen gas breathing with reductions in R_2* consistent with improved oxygenation. The increases in blood flow and/or tissue permeability induced by RT may help to maintain the response to hypoxic modification during RT.

Table 1

	% change compared with baseline (mean, 95% Confidence Interval in brackets) [R_2* during carbogen: % change is relative to pre-carbogen values on same day]				
	Post 3mo ADT: Repro 1	Post 3mo ADT: Repro 2	Post 5# RT	Post 15# RT	End RT
Tumour ROI (tROI)					
R_2* (pre-carbogen)	17% (-2 to 35%)	21% (-3% to 45%)	19% (-8% to 45%)	21% (-5% to 46%)	-4% (-22% to 13%)
R_2* (during carbogen)	-6% (-15% to 2%)	-10% (-21% to 2%)	0.5% (-16% to 17%)	-10% (-22% to 3%)	-9% (-2% to -16%)
K^{trans}	-25% (-0.1 to -50%)	-18% (-49% to 14%)	32% (-20% to 85%)	37% (15% to 89%)	11% (-12% to 34%)
$IAUGC_{60}$	-40 % (-24% to -56%)	-37% (-18% to -56%)	-10% (-38% to 17%)	4% (-25% to 33%)	-16% (-4.4% to -29%)
Whole prostate ROI					
K^{trans}	-25% (-8% to -41%)	-27% (-14% to -40%)	22% (-3% to 46%)	25% (1.8% to 48%)	28% (13% to 43%)
$IAUGC_{60}$	-23% (-10% to -48%)	-29% (-7% to -34%)	21% (0.3% to 41%)	22% (3% to 41%)	38% (16% to 50%)

1 Gray et al., *Brit. J. Radiol.* 1953; **26:** 638-48 2 Hoskin et al., *J Clin Oncol* 2010; **28:** 4912-4918 3 Overgaard, *Radiother Oncol.* 2011; **100:** 22-32
4 Yip and Alonzi, *Ther Adv Urol.* 2013; **5:** 25-34 5 Alonzi et al., *Int. J. Rad. Oncol. Biol. Phys.* 2011; **80:** 721-727 6 d'Arcy et al. *Radiographics* 2006; **26:** 621-32
7 Tofts et al. *J. Mag. Reson. Imag* 1999; **10:** 223-232 8 Parker et al. *Magn. Reson. Med.* 2006; **56**: 993-1000