# Intrinsic Susceptibility-Weighted MRI to assess the response of Combretastatin-A4-Phosphate during radiotherapy for prostate cancer

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Aim: To demonstrate prostate gland oxygenation changes induced by the vascular disrupting agent Combretastatin-A4-Phosphate (CA4P) during a course of radiotherapy, using Intrinsic Susceptibility-Weighted MRI (ISW-MRI).

Introduction: Radiotherapy is increasingly being delivered in combination with novel pharmaceuticals in order to improve efficacy. The performance of imaging biomarkers for response assessment may be compromised by the differing or conflicting effects between drug and radiation on tumor tissues. Preclinical studies have shown a potential therapeutic benefit from the addition of the vascular disruptive agent CA4P to radiotherapy, which produces marked vascular shutdown in tumors.[1] We have previously shown that the Dynamic Contrast MRI (DCE-MRI) derived parameter K^{trans} has the potential to demonstrate changes in prostate vascularity following CA4P administration.[2] However, K^{trans} was not capable of fully describing the acute consequences of CA4P-mediated vascular shutdown during radiotherapy. In particular, it was not possible to show significant decreases in K^{trans} following vascular recovery after CA4P delivery, contrary to previously published K^{trans} data on CA4P used alone. This is likely to be due to the well established acute hyperemia caused by radiotherapy, which appears to mask CA4P mediated tumor vascular disruption. This study evaluated whether R_2^*, calculated from ISW-MRI data, may be a more suitable biomarker to assess vascular response during radiotherapy.

Patients and Methods: 18 patients due to undergo radical radiotherapy (57Gy in 19 fractions) following neoadjuvant hormonal therapy for prostate cancer (Gleason >6, PSA >20ng/ml or T3/4) were recruited prospectively in 3 cohorts as part of a Phase Ib toxicity determining study. Cohort 1 received CA4P ($50mg/m^2$) on radiotherapy day 5 only. Cohort 2 received weekly CA4P ($50mg/m^2$) on radiotherapy days 5, 12 and 19. Cohort 3 received weekly CA4P ($63mg/m^2$) on radiotherapy days 5, 12 and 19. A matched control group of 10 patients received the same radiotherapy schedule without CA4P. Imaging was performed on eight occasions: two baseline scans prior to radiotherapy (1&2); three scans at the end of the first week of radiotherapy: before CA4P, 4hrs and 72hrs after CA4P (3,4&5); three more scans at the end of the third week of radiotherapy: before CA4P, 4hrs and 72hrs after CA4P (6,7&8). The control group only received 5 scans (scans 2,6& 7 were omitted). At each time point anatomical images were acquired followed by five spoiled gradient-echo images 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^* (s^{-1}) maps were calculated using previously described methods.[3]

Figure 1
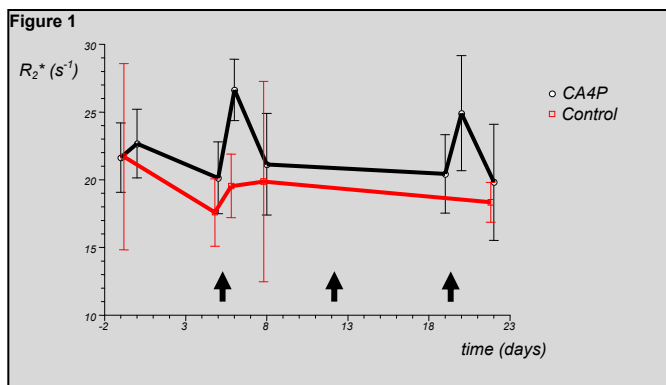
Results and Discussion: 18 CA4P and 10 control patients were recruited. One patient in cohort 3 discontinued vascular disruptive therapy because of toxicity and was removed. There were significant reductions in R_2^* in both treatment and control groups at the end of the first week, in keeping with the reactive hyperemia and the known reoxygenation effects of radiotherapy (see table). R_2^* increased significantly in response to CA4P at both 1 and 3 weeks (figure 1). No such effect was seen in the control group. This effect was significant for the CA4P group as a whole and for each cohort separately (apart from cohort 3 at 3 weeks due to the small number of patients evaluable). R_2^* returned to baseline within 72 hours of CA4P infusion. We conclude that R_2^* has the potential to be an alternative, clinically useable, response biomarker for assessment of vascular disruptive therapy in combination with radiotherapy in prostate cancer. In contrast to DCE-MRI, R_2^* is able to reveal therapeutic effects even after radiotherapy has begun.

Figure 1: Graph of R_2^* versus time during radiotherapy for prostate cancer. Arrows indicate the times of CA4P administration. The three treatment cohorts have been combined (black) and compared with the control group (red). Significant increases in R_2^* were clearly seen to occur following CA4P administration at both 1 and 3 weeks of radiotherapy. No such effect was seen in the control group.
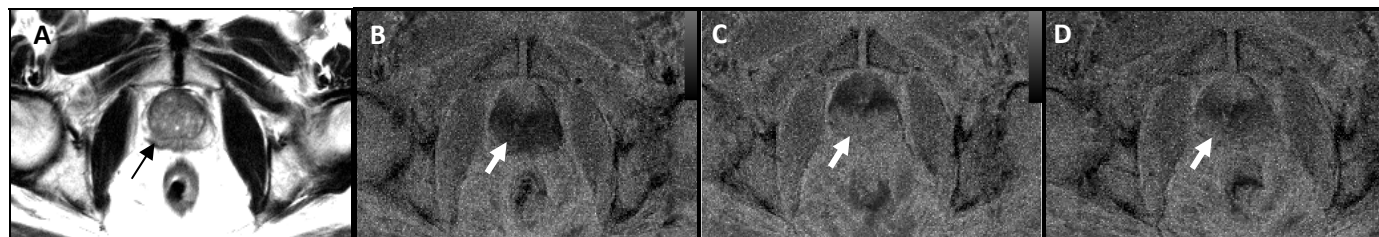

Figure 2: Example of the changes in R_2^* following CA4P administration. Panel A shows the anatomical T_2-weighted image with tumour in the posterior peripheral gland (arrow). Panel B is the R_2^* map immediately prior to CA4P administration. Panel C shows the induction of hypoxia 4 hours after CA4P infusion with partial resolution by 72 hours (panel D).

	Number of patients		Baseline R_2^* (s^{-1})	$\Delta R2^*$ Baseline to Day 5 pre-CA4P (s^{-1})	ΔR_2^* Week 1 pre – 4 hrs post CA4P (s^{-1})	ΔR_2^* Baseline to 72 hours post CA4P (s^{-1})	ΔR_2^* Week 3 pre – 4 hrs post CA4P (s^{-1})
CA4P group (Cohorts 1-3)	16	Value	22.08	-1.93	+6.49	-1.55	n/a
		Significance	n/a	p = 0.02	p < 0.001	p = 0.24	n/a
Cohort 1	6	Value	23.76	-2.04	+7.43	+0.07	n/a
		Significance	n/a	p = 0.04	p = 0.019	p = 0.98	n/a
Cohort 2	6	Value	22.36	-0.18	+5.36	-2.40	+8.96
		Significance	n/a	p = 0.9	p = 0.006	p = 0.12	p = 0.002
Cohort 3	5	Value	18.83	-4.40	+6.79	-0.05	+5.21
		Significance	n/a	p = 0.03	P = 0.018	p = 0.97	p = 0.09
Control Group	10	Value	21.70	-4.11	+1.95	-1.16	n/a
		Significance	n/a	p = 0.05	p = 0.14	p = 0.4	n/a

References: [1]Chaplin DJ, *Anticancer Res*. 1999; **19**: p189. [2]Mandeville H, *proc. ISMRM.* 2007, program no.565. [3]Alonzi R, BJC. 2009; **100**: p644