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Award Number: DAMD17-00-1-0517

TITLE: A Quantitative MRI Study of Prostate Cancer Before and After Radiation Therapy

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REPORT DATE: May 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	May 2003	Annual (15 Apr 02 - 14 Apr 03)

4. TITLE AND SUBTITLE
A Quantitative MRI Study of Prostate Cancer Before and After Radiation Therapy

5. FUNDING NUMBERS
DAMD17-00-1-0517

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of the study is to examine the influence of external beam radiation on the prostate and prostate cancer using novel quantitative MRI techniques. Twenty-one men, previously diagnosed with prostate cancer, will be studied using T2 relaxation mapping and contrast agent kinetic methods before and after treatment by radiotherapy. The MRI findings will be correlated with biochemical (prostate specific antigen) progression and biopsy results.

At the end of year 3 all 21 patients have been recruited and studied pre-treatment. Two patients have returned for follow-up MRI. The data is both complete and of a high quality. Preliminary data analysis has provided important and novel information about the microvascular characteristics of prostate cancer. These results are shortly to be presented at a leading international scientific conference and will form the basis of a manuscript currently in preparation. Furthermore, these studies have generated a parallel line of novel research; the estimation of arterial input functions using MRI.

14. SUBJECT TERMS
magnetic resonance imaging, contrast agents, radiation therapy, angiogenesis, biological modeling

15. NUMBER OF PAGES
12

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

The following report details the results of year three of a quantitative magnetic resonance imaging (MRI) study of prostate cancer before and after radiation therapy. The study aims to examine the influence of external beam radiation on the prostate and prostate cancer using novel quantitative MRI techniques. Twenty-one men, previously diagnosed with prostate cancer, will be studied using T2 relaxation mapping and contrast agent kinetic methods before and after treatment by radiotherapy. The MRI findings will be correlated with biochemical (prostate specific antigen) and biopsy results.

BODY

The following section summarises the research accomplishments associated with the tasks outlined in the approved Statement of Work. Despite the delays experienced in transferring the grant funding from the University of Florida to the University of Manchester and the subsequent delay in obtaining Human Subjects approval (detailed in the Year 1 annual report), significant progress has been made with the Statement of Work. The research accomplishments associated with each of the tasks outlined are described below.

Task 1.

Months 1-6. To complete the imaging sequence design and testing. (specific aims 1 and 2).

a. The T1/T2 phantom will be constructed.
b. Calibration of the dynamic imaging sequences (proton density weighted + T1-weighted sequences)
c. Optimization of the FSE, T2 imaging sequence.
d. Selection of dynamic and T2 imaging sequences. Finalize imaging protocol.

As noted in the Year 1 report, with the cooperation of Drs. Steve Blackband, Amanda Barry (Post-Doctoral Research Assistant employed during the first year of the study) and Geoff Parker (Research Fellow working on related studies), all elements of *Task 1* were successfully completed.

Task 2.

Months 7-12. Dynamic data simulation and model development (specific aim 1). Software development (specific aims 1 and 2).

a. Compare simulated data with patient data (both existing and data being acquired in task 3).
b. Error propagation analysis of models under test.
c. Software development. T2 maps and dynamic data analysis.

a. &
b. All elements of *Task 2* have been completed but this work continues to provide the stimulus for further related developments. The model of St. Lawrence and Lee [1] has been implemented for the assessment of tissue perfusion, blood volume and Gd-DTPA extraction in regions of interest centred on cancer, normal prostate tissue and muscle. An extension to the model of Tofts and Kermode [2,3] has been selected for generating tissue uptake maps. The analysis of errors in the techniques employed led to work in the field of water exchange (detailed in the Year 1 and Year 2 reports and Appendix 1). Furthermore, Dr. Parker has developed automated techniques for identifying suitable arterial input functions for dynamic data analysis (Appendix 2):

    i. Appendix 1. A poster entitled, "The influence of transcapillary water exchange on the analysis of tracer kinetics in dynamic Gd-DTPA-enhanced T1-weighted MRI" was presented at the 10th Annual Meeting of the International Society for Magnetic Resonance in Medicine (Honolulu, May 2002). The poster described the effects of limited water exchange on the type of data generated in this and other studies.

ii. Appendix 2. An abstract entitled, "Automated arterial input function extraction for T1-weighted DCE-MRI" was accepted for presentation at the 11th Annual Meeting of the International Society for Magnetic Resonance in Medicine (Toronto, July 2003). The abstract describes the techniques used and their reproducibility including examples of the data obtained in this study.

c. Software for the analysis of the MR data is in place (largely due to the efforts of Dr. Geoff Parker and Mr. Caleb Roberts). Examples of the results obtained were presented in the Year 2 report (Figures 1, 2 and 3).

Task 3.

Months 7-18. Patient recruitment (21 patients) and examination for pretreatment phase of specific aim 3.

a. In collaboration with Pathology, examine recent biopsy data for potential patients.
b. Select patients (in collaboration with Mr. Clarke) for the study. Obtain written, informed consent.
c. Acquire data from the 1.5 T system. Backup (optical disks) and transfer data to laboratory.
d. Stain and reanalyze biopsy specimens.

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a. &
b. Despite the early problems with recruitment, all 21 patients were successfully identified, recruited and consented by the end of 2002.
Data were successfully acquired from all patients. Ten patients (described in the Year 2 report) were scanned between July 2001 and March 2002; the remaining 11 patients were scanned between May 2002 and January 2003. All data were backed-up on both optical disk and CD.
c. As noted in last year's report, Dr. West and Mr. Clarke decided that the most efficient and appropriate means of analysing the biopsy specimens was to process them as a batch. Analysis of the pre-treatment specimens will therefore begin as follow-up biopsies are performed.

Task 4.

Months 13-24. Data analysis, pretreatment phase.

a. Generation of Gd-DTPA concentration maps, uptake rate/max uptake maps and T2 maps.
b. Image review with biopsy results. Preliminary identification of cancer/BPH/normal tissue.
c. Region of interest analysis. Model fitting (dynamic data).

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a. In collaboration with Dr. Parker and Mr. Roberts, maps of the following parameters were generated for each study: Baseline T1 and T2, contrast agent volume transfer constant, rate constant and interstitial volume fraction [4]. Examples of these were presented in the Year 2 report (Figs. 1, 2 and 3).
b. Dr. Charles Hutchinson, with the help of Mr. Roberts and Dr. Buckley, employed the biopsy results and high quality T2-weighted images to identify regions of suspected tumour, normal peripheral zone and muscle (internal obturator, chosen as a reference tissue). These regions were defined (where possible) in each patient. An example of the regions chosen in tumour and normal peripheral zone was presented in poster form and can be seen in Appendix 3 (Figure 1).
c. Data from each region drawn, plus data from internal iliac or femoral artery, were converted to concentration-time courses then analysed by Dr. Buckley using the model of St. Lawrence and Lee [1]. Examples are presented in Figure 2 of the poster in Appendix 3 and again in the abstract presented in Appendix 4.

i. Appendix 3. A poster entitled, "*In vivo* determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI" was presented at a Cancer Workshop organised by the International Society for Magnetic Resonance in Medicine (Santa Cruz, Ca; October 2002). This represents the first public presentation of the clinical results obtained in the study. At the time of the meeting data from 15 patients was available for analysis.
ii. Appendix 4. An abstract entitled, "*In vivo* determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI" was accepted

for oral presentation, in a clinical science focus session, at the 11th Annual Meeting of the International Society for Magnetic Resonance in Medicine (Toronto, July 2003). The abstract details the same results presented in the poster above but provides an opportunity for the complete 21-patient data set to be presented at the leading international meeting for MR scientists in July.

Since the poster and abstracts detailed above were written the full 21-patient data set has been analysed. Since the earlier work was presented the method of analysis has undergone some minor modifications to improve the accuracy of parameter estimates. The results are detailed in table 1.

Table 1.
Analysis of the data from each region provided estimates (mean ± SD) of blood flow (F), blood volume (V_b) and microvascular permeability-surface area product (PS).

Tissue	F (ml/100 ml/min)	V_b (ml/100 ml)	PS (ml/100 ml/min)
Tumour (n=21)	61 ± 34	1.5 ± 3.1	30 ± 23
Normal (n=19)	26 ± 17	1.5 ± 2.4	19 ± 25
Muscle (n=21)	12 ± 10	1.6 ± 1.8	6 ± 5

The full results support the findings reported in the poster and abstract and confirm previous studies. Blood flow to tumour exceeds that to normal prostatic tissue (paired t-test, $p = 0.0002$) [5] but blood volume and capillary permeability are not significantly different ($p = 0.84$ and 0.58, respectively). In line with previous MR studies [6,7], K^{trans} (the product of extraction and flow) was significantly higher in tumour than normal peripheral zone ($p < 0.0001$). The additional statistical power of the full data set has also highlighted a difference between the values of V_e, the interstitial distribution volume, in tumour and normal prostatic tissue (41 ± 19 ml/100 ml and 25 ± 11 ml/100 ml, respectively). This difference is significant ($p = 0.002$). These results form the basis of a manuscript that is currently in preparation. It is anticipated that this paper will be submitted to a leading journal in the field of Urology.

Task 5.

Months 19-30. Patient follow-up (21 patients) and examination for post-treatment phase of specific aim 3.

a. Request 2nd examination for each of the patients studied in task 3.
b. Acquire data from the 1.5 T system. Backup (optical disks) and transfer data to laboratory.

a. &
b. To date two patients have undergone their follow-up MR examinations and, as previously, all their data was backed-up to both optical disk and CD. A further two patients have been lined up for scanning. Dr. Logue and his staff continue to coordinate the follow-up of all the other patients.

Task 6.

Months 19-30. Data analysis, post-treatment phase.

a. Generation of Gd-DTPA concentration maps, uptake rate/max uptake maps and T2 maps.
b. Image review with previous MRI and biopsy results. Identification of cancer/BPH/normal tissue.
c. Region of interest analysis. Model fitting (dynamic data).

As further follow-up data is obtained work will begin in earnest on *Task 6*. With only two follow-up data sets the most effective approach to analysing these data it is not yet entirely clear. We anticipate that the first group of results will be generated during the summer.

Task 7.

Months 31-36. Review of results, patient follow-up and publication.

a. Obtain follow-up biopsies on each patient (18 months after treatment).
b. Stain and analyze biopsy specimens.
c. Review each patients clinical and biochemical data.
d. Compare and correlate MRI data and clinical data.
e. Publication of significant findings/experience.

Dr. John Logue (Clinical Oncologist) and Mr. Noel Clarke (Urologist) have put in place procedures for biopsy of the patients at the Christie Hospital. The first two patients are now approaching 18 months post-radiotherapy and will undergo biopsy imminently.

KEY RESEARCH ACCOMPLISHMENTS

- Data analysis techniques in place incorporating a novel technique for the automated identification of an arterial input function.
- High quality data from 21 patients with confirmed prostate cancer successfully acquired.
- Data analysis complete. Blood flow, blood volume, interstitial volume and capillary permeability in tumour, normal peripheral zone and muscle estimated for the first time ever using cross-sectional imaging.
- Data successfully acquired in the first two patients post-treatment.

REPORTABLE OUTCOMES:

The outcomes are listed in chronological order:

1. May 2002.
Poster, "D.L. Buckley, The influence of transcapillary water exchange on the analysis of tracer kinetics in dynamic Gd-DTPA-enhanced T1-weighted MRI", presented at the 10th Annual Meeting of the International Society for Magnetic Resonance in Medicine.

2. June 2002.
Invited lecture, "D.L. Buckley, Quantitative MR imaging of the prostate gland". Presented to delegates at the 1st Philips Body MRI Users Meeting in Sint-Michielsgestel, the Netherlands.

3. August 2002.
Abstract, "D.L. Buckley, C. Roberts, G.J. Parker, J.P. Logue, C.E. Hutchinson, *In vivo* determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI", accepted for presentation at the ISMRM Cancer Workshop, Santa Cruz, Ca.

4. October 2002.
Poster, "D.L. Buckley, C. Roberts, G.J. Parker, J.P. Logue, C.E. Hutchinson, *In vivo* determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI", presented at the ISMRM Cancer Workshop, Santa Cruz, Ca.

5. November 2002.
Abstract, "G.J. Parker, A. Jackson, J.C. Waterton, D.L. Buckley, Automated arterial input function extraction for T1-weighted DCE-MRI", accepted for presentation at the 11th Annual Meeting of the International Society for Magnetic Resonance in Medicine, Toronto, Canada.

6. November 2002.
Abstract, "D.L. Buckley, C. Roberts, G.J. Parker, J.P. Logue, C.E. Hutchinson, *In vivo* determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI", accepted for presentation at the 11th Annual Meeting of the International Society for Magnetic Resonance in Medicine, Toronto, Canada.

CONCLUSIONS

The preparatory work of Years 1 and 2 has proved successful with excellent results obtained in all 21 pre-treatment studies. The patients themselves have all undergone the imaging protocol without reporting any serious concerns and the first two patients studied (back in mid-2001) have returned for equally successful follow-up scans. Most encouragingly, the results of the data analysis have been both consistent and exciting. For the first time in a meaningful group of patients, the physiological basis (blood flow, volume and capillary permeability) of contrast enhancement in prostate tumours and normal prostatic tissue has been measured *in vivo*.

As noted in the conclusions of last years report, the only similar quantitative work (and limited to whole prostate analysis) elsewhere in the world had been undertaken using PET [5] and CT [8]. A recent study of just six patients compared a semi-quantitative MR technique with PET [9]. Though extremely preliminary, those findings support our approach. We anticipate considerable interest in our work from both the MR community (when the study is presented in Toronto later this year) and the Urological community once we publish our data (and a manuscript is in preparation). Moreover, we are extremely encouraged by the quality of the data obtained in the first two post-treatment studies and look forward to the coming year as the remaining patients return following radiotherapy.

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The influence of transcapillary water exchange on the analysis of tracer kinetics in dynamic Gd-DTPA-enhanced T_1-weighted MRI

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Introduction

- Water exchange plays a major role in determining the signal changes measured in contrast-enhanced MRI [1,2].
- Transcytolemmal exchange assumed to be fast (? [3]) but transcapillary exchange more difficult to characterize.
- How significant an effect is it?

Simulation study undertaken to examine the influence of slow transcapillary water exchange on estimates of tracer kinetic parameters obtained from dynamic Gd-DTPA-enhanced T_1-weighted MRI of the brain [4, 5].

Methods

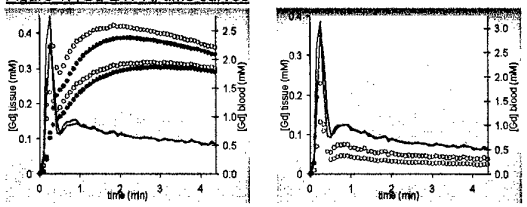
Concentration-time data representing the interstitial and vascular spaces of four different tissue types were simulated using an input function previously measured in the brain [4] and a distributed pathway model of tracer kinetics (MMID4, made available by the National Simulation Resource [6]).

Four tissue types:

Glioma1 (high extraction)
Glioma2 (low extraction)
Normal gray matter
Normal white matter

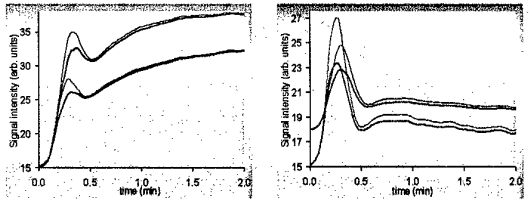
Each tissue had associated with it representative values of blood flow (F), blood volume (V_b), vessel permeability-surface area product (PS) and interstitial volume (V_e). The simulated data were subsequently used to generate tissue signal-time curves using an equation describing a FLASH sequence (TR, 4.3 ms; flip angle, 35° [4]) and assuming either fast or slow water exchange (i.e., mono- or biexponential T1 recovery, respectively). Finally, each whole tissue signal-time curve was converted back to a concentration-time curve using the standard assumption of fast water exchange [7]. A tracer kinetic model [8] was then fitted to these processed data to arrive at exchange-mediated estimates of F, V_b, PS and V_e.

Figure 1: [Gd-DTPA]-time curves



Simulated Gd-DTPA concentration-time curves for the gliomas (left panel, glioma1 red and glioma2 blue) and normal gray (red symbols) and white (blue symbols) matter (right panel). For each tissue type separate curves are shown for the whole tissue (open circles), intravascular space (lines) and interstitial space (filled circles). The blood-brain barrier prevents extravasation of Gd-DTPA in the normal gray and white matter

Figure 2: Signal intensity-time curves



Signal-time curves for the gliomas (left panel, glioma1 red and glioma2 blue) and normal gray (red lines) and white (blue lines) matter (right panel). The curves are representative of data obtained in a FLASH acquisition (TR, 4.3 ms, flip 35°) when transcapillary water exchange is either fast (faint lines) or slow (bold lines).

Table 1: Exchange-mediated kinetic parameter estimates

Estimates of the kinetic model parameters as a function of tissue type and water exchange regime. The first line of each tissue type shows the parameters used for the simulations. Lines labelled fast and slow show the estimates obtained from data analysed assuming fast and slow water exchange. Hence, the difference between the actual and fast lines highlights errors associated with tracer kinetic modelling. The difference between fast and slow lines highlights the errors associated with restricted water exchange.

	EF (ml/min/g)	V_e (ml/g)	V_b (ml/g)	F (ml/min/g)	PS (ml/min/g)
	0.18	0.15	0.06	0.43	0.13
Glioma1	0.19	0.16	0.04	0.32	0.16
	0.20	0.16	0.02	0.24	0.24
	0.12	0.14	0.03	0.52	0.08
Glioma2	0.13	0.15	0.02	0.59	0.08
	0.13	0.15	0.01	0.43	0.09
	0.00	0.20	0.04	0.50	0.00
Gray	0.00	-	0.04	0.62	0.00
	0.02	0.01	0.02	0.53	
	0.00	0.15	0.03	0.15	0.00
White	0.00	-	0.02	0.16	0.00
	0.01	0.01	0.02	0.12	

Results & Discussion

As previously reported [2,7], the effect of slow exchange was to flatten the first pass response of the signal-time curves (Fig. 2). This tends to influence estimates of F and V_b directly while leading to overestimates of PS (and thus E) due to the mismatch between the first pass and equilibrium phases. Effects on the estimates of the EF product (K^{trans}) and V_e were slight [7]. Disturbingly, the non-linear effect of slow exchange on the normal gray and white matter signal-time curves was to erroneously imply mild blood-brain barrier breakdown (see yellow highlights in Table 1).

These findings support previous studies and highlight the importance of exchange in contrast enhanced T_1-weighted imaging. It is important to note that many of the errors associated with slow exchange compound those already associated with the use of kinetic modeling [5] and suggest that estimates of blood volume using such approaches are appreciably error prone.

Summary

- Slow transcapillary water exchange flattens the first pass peak of signal-time curves.
- Effects on estimates of EF (K^{trans}) and V_e are small.
- Effects on estimates of F and PS may be significant.
- Estimates of V_b severely compromised.

Acknowledgments

Supported by the U.S. DoD Prostate Cancer Research Program (PC991154). The National Simulation Resource is supported by the NIH (RR-01243). Thanks to Hamied Haroon and Alan Jackson, University of Manchester, for the original clinical data.

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Automated Arterial Input Function Extraction for T1-Weighted DCE-MRI

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Synopsis
We present a method for the automatic identification of an arterial input function (AIF) for T_1-weighted dynamic contrast-enhanced MRI (DCE-MRI). The method uses a set of heuristics to identify voxels within the DCE-MRI dataset in which the time course of contrast agent concentration changes indicates the presence of voxels containing arteries with minimal partial volume contamination. We demonstrate applicability in a range of body areas, including the brain, lung, and prostate, and investigate the reproducibility of the technique in the brain.

Introduction DCE-MRI studies require that the concentration of contrast agent in the blood supply (the AIF) is identified in order to allow the application a kinetic model that allows the change in tissue contrast agent concentration to be interpreted in terms of physiological variables such as vascular volume, v_b, and transfer coefficient, K^{trans} [1]. Measurement of an AIF is in general difficult, due to problems including flow artefacts, inflow effects, and partial volume effects. Data acquisition strategies have previously been described that allow signals from arteries to be converted into an AIF[2,3]. Most measurements of the AIF have to date been made using manual selection of an artery of interest – an approach that is susceptible to user bias and partial volume effects. Automation of AIF identification has been investigated[4]. Here, we introduce a modified method for automated AIF identification, demonstrate its applicability in a range of clinically relevant sites in the body, and investigate the reproducibility of the technique.

Methods All data were acquired on a Philips 1.5 T system. For the reproducibility study six patients with glioma were scanned on two occasions with a mean inter-scan interval of 1.5 days. A previously published DCE-MRI acquisition protocol[2], consisting of 3-D gradient echo acquisitions acquired over a period of approximately 3.5 minutes, with a temporal resolution of 5-8.5 s was used. Baseline T_1 was calculated using 3 acquisitions with different flip angles. Concentration of contrast agent was estimated from the change in T_1 during the dynamic series. An intravenous contrast agent bolus of less than 10 s duration was manually injected. Acquisitions in the lung and prostate utilised similar protocols, but with 4 s and 2.3 s temporal resolution, respectively, and with the bolus administered using a power injector.

AIF estimation: **1.** Manually identify a slice that contains a suitable artery, and does not suffer in-flow effects (note that the use of 3-D acquisition allows significantly reduced in-flow effects compared with multi-slice techniques when a slice in the centre of the volume is selected); **2.** Extract the time course for every voxel in slice and identify those that show a maximum in concentration within 20 s of the arrival time (*early max voxels*); **3.** Identify the early max voxels within the top 5% of peak concentrations; **4.** Average the resultant time courses together to create a mean AIF.

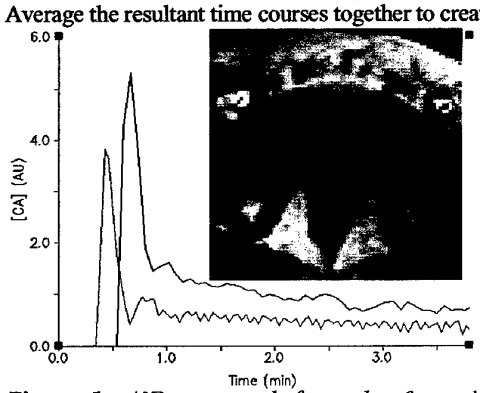

Figure 1. *AIFs extracted from the femoral arteries and the* ***aorta****. Image shows position of identified arteries in prostate study*

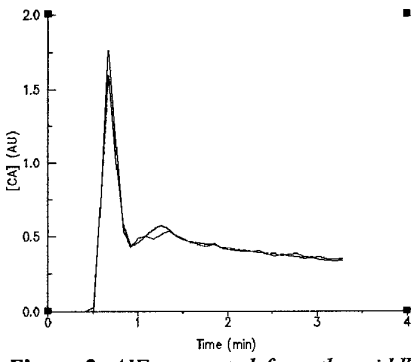

Figure 2. *AIFs extracted from the middle cerebral artery on two separate scanning sessions.*

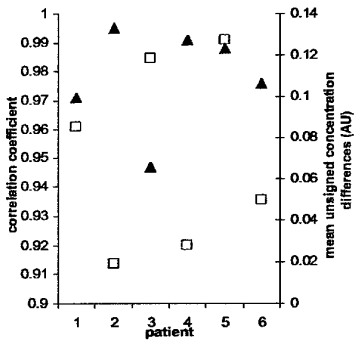

Figure 3. *Inter-visit time series correlation coefficient and mean unsigned AIF [CA] differences.*

Results and Conclusion The AIF identification method proved to extract plausible AIFs from a range of regions of the body, including the lung and prostate (Fig. 1). The positions of the voxels that contribute to the AIF may be determined and mapped onto an anatomical image, showing that the mean AIF is extracted from voxels positioned in arteries. The selection of the top 5 % of early max voxels ensures that partial volume effects are minimised. Figure 2 shows the results of the technique in a glioma patient scanned twice, showing qualitatively good reproducibility. Figure 3 shows measures of the repeatability of the method across all 6 glioma patients. The method provides an AIF estimate with a minimum of user input and is applicable to any area of the body with a suitable artery. The method shows good scan-rescan reproducibility, even in the case shown using manual bolus administration.

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Acknowledgements

This work was supported by AstraZeneca Pharmaceuticals and the U.S. DoD Prostate Cancer Research Program (PC991154).

In vivo determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI

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Introduction

- **Regional blood flow and capillary permeability have not been measured in the prostate gland.**
- **Baseline estimates of these microvascular characteristics are required before treatment response can be assessed.**

The purpose of this study was to assess the microvascular characteristics of the pathological prostate gland prior to treatment with external beam radiotherapy using dynamic contrast-enhanced MRI and a distributed parameter tracer kinetic model [1]. The hypothesis to be tested is that these characteristics will be sensitive indicators of tissue response to treatment and thereby provide a useful prognostic tool

Methods

After obtaining written informed consent, data were acquired from 15 patients with biopsy confirmed stage T2 or T3 carcinoma of the prostate gland. These patients all selected external beam radiotherapy for subsequent treatment of their disease. The patients were scanned on a 1.5 T Philips MR system using a pelvic phased-array coil and a 3D T_1-weighted gradient echo pulse sequence. Images were acquired using flip angles of 2, 10 and 30 degrees to estimate baseline T_1 [2]. This was followed by a dynamic series in which volumes were acquired every 2.3 s for approximately 4 minutes. Early in this series 0.1 mmol/kg Gd-DTPA-BMA was injected at 3 ml/s using a power injector.

The image data were subsequently analysed off-line. For each patient regions of interest were drawn in the external iliac or femoral arteries (to provide a vascular input function). With the aid of T_2-weighted images a radiologist (CEH) drew further regions in prostate tumour, muscle (internal obturator) and, where possible, normal contralateral peripheral zone. Signal intensity variations in these regions were converted to temporal changes in Gd-DTPA-BMA concentration [2] and a distributed parameter model [1] was fitted to the data. Parameters estimates in each region were compared using a paired t-test.

Figure 1.
T_2-weighted fast spin echo image showing a tumour-bearing prostate gland. Regions of interest have been drawn over tumour and normal contralateral peripheral zone.

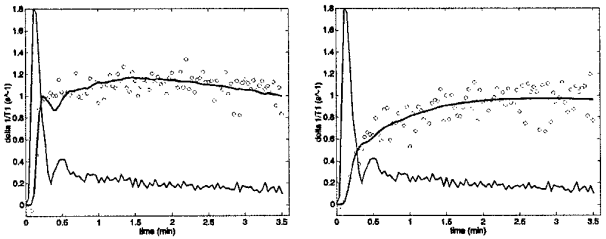

Figure 2.
Changes in $1/T_1$ measured over time in the regions outlined in Fig. 1, tumour (left) and normal peripheral zone (right). Blue lines show the vascular input function (scaled down by a factor of 10) measured in the external iliac artery and the red lines represent model fits to the data.

Table 1: MR data, both vascular input and tissue residue curves, were successfully acquired in 14 patients. Analysis of the data from each region of interest provided mean (± SD) estimates of blood flow (F), blood volume (V_b) and microvascular permeability-surface area product (PS) [3].

Tissue	F (ml/100ml/min)	V_b (ml/100ml)	PS (ml/100ml/min)
	81 (± 66)	2.1 (± 3.7)	24 (± 11)[a]
	30 (± 16)	1.6 (± 2.6)	15 (± 12)[b]
	11 (± 8)	1.7 (± 2.1)	5.2 (± 3.5)[c]

a. Unable to determine PS when E = 1, mean ± SD quoted for n = 12.
b. Unable to determine PS when E = 1, mean ± SD quoted for n = 9.
c. Unable to determine PS when E = 1, mean ± SD quoted for n = 11.

Discussion

These findings highlight the capabilities of MR imaging to estimate parameters only previously measured using PET [4] or CT [5]. The preliminary results confirm that blood flow to tumour tissue exceeds that to normal prostatic tissue ($p = 0.02$) [4] but suggests that blood volume and capillary permeability may not be significantly different ($p = 0.51$ and 0.37, respectively). In line with previous MR studies [6,7], K^{trans} was significantly higher in tumour than normal peripheral zone ($p<0.0005$). Further studies are ongoing and the patients will all be rescanned 12 months after treatment. These initial findings show considerable promise for isolating the physiological basis for contrast enhancement in the prostate.

Summary

- **Regional estimates of blood flow, volume and PS product were obtained in the prostate using dynamic contrast-enhanced MRI.**
- **Blood flow and K^{trans} higher in tumours than normal contralateral peripheral zone.**
- **PS product not significantly raised in tumours.**

Acknowledgments

Funded by the U.S. DoD Prostate Cancer Research Program (PC991154). Jeanette Lyons, Yvonne Watson and David Clark kindly helped with the patient studies.

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In vivo determination of the microvascular characteristics of prostate cancer using dynamic contrast-enhanced MRI

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Synopsis.
Tumour angiogenesis is a recognised prognostic indicator in patients with prostate cancer treated with external beam radiotherapy. Using rapid dynamic contrast-enhanced 3D MRI and a distributed parameter tracer kinetic model the microvascular characteristics of prostate cancer were assessed in a group of patients prior to treatment with radiotherapy. Blood flow was higher in the tumours than in normal peripheral zone but there were no significant differences in PS product or blood volume. This novel approach may prove valuable as a prognostic tool and the patients will be studied post-treatment to assess tissue response.

Introduction.
Baseline estimates of blood flow and capillary permeability are required to assess response of the prostate to treatment. The purpose of this study was to assess the microvascular characteristics of the pathological prostate gland prior to treatment with external beam radiotherapy using dynamic contrast-enhanced MRI and a distributed parameter tracer kinetic model [1]. The hypothesis to be tested is that these characteristics will be sensitive indicators of tissue response to treatment and thereby provide a useful prognostic tool.

Methods.
After obtaining written informed consent, data were acquired from 15 patients with biopsy confirmed stage T2 or T3 carcinoma of the prostate gland. These patients all selected external beam radiotherapy for subsequent treatment of their disease. The patients were scanned on a 1.5 T Philips MR system using a pelvic phased-array coil and a 3D T_1-weighted gradient echo pulse sequence. Images were acquired using flip angles of 2°, 10°, 20° and 30° to estimate baseline T_1 [2]. This was followed by a dynamic series in which volumes (flip angle 30°) were acquired every 2.3 s for approximately 4 minutes. Early in this series 0.1 mmol/kg Gd-DTPA-BMA was injected at 3 ml/s using a power injector.

The image data were subsequently analysed off-line. For each patient regions of interest were drawn in the external iliac or femoral arteries (to provide a vascular input function). With the aid of T_2-weighted images a radiologist (CEH) drew further regions in prostate tumour, muscle (internal obturator) and, where possible, normal contralateral peripheral zone. Signal intensity variations in these regions were converted to temporal changes in Gd-DTPA-BMA concentration [2] and a distributed parameter model [1] was fitted to the data. Parameters estimates in each region were compared using a paired t-test.

Results.
Analysis of the data from each region provided estimates (mean ± SD) of blood flow (F), blood volume (V_b) and microvascular permeability-surface area product (PS) [3].

Tissue	F (ml/100 ml/min)	V_b (ml/100 ml)	PS (ml/100 ml/min)
Tumour (n=14)	81 ± 66	2.1 ± 3.7	24 ± 11
Normal (n=12)	30 ± 16	1.6 ± 2.6	15 ± 12

Discussion.
These findings highlight the capabilities of MR imaging to estimate parameters only previously measured using PET [4] or CT [5]. The preliminary results confirm that blood flow to tumour tissue exceeds that to normal prostatic tissue ($p = 0.02$) [4] but suggests that blood volume and capillary permeability may not be significantly different ($p = 0.51$ and 0.37, respectively). In line with previous MR studies [6,7], K^{trans} was significantly higher in tumour than normal peripheral zone ($p<0.0005$). Further studies are ongoing and the patients will all be rescanned 12 months after treatment. These initial findings show considerable promise for isolating the physiological basis for contrast enhancement in the prostate.

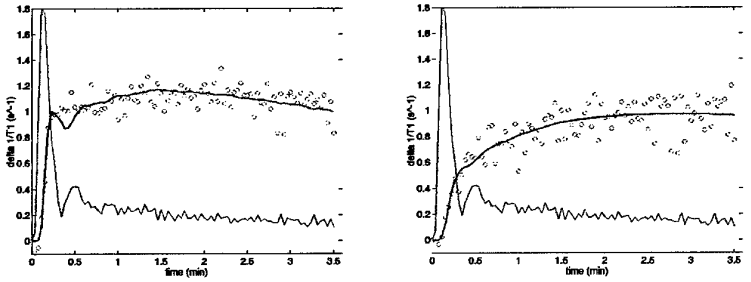

Figure 1. Changes in $1/T_1$ measured over time in tumour (left) and normal peripheral zone (right) of the same patient. Blue lines show the vascular input function (scaled down by a factor of 10) measured in the external iliac artery and the red lines represent model fits to the data.

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