ORIGINAL RESEARCH

Dynamic contrast enhanced MRI as a predictor of vascular-targeted photodynamic focal ablation therapy outcome in prostate cancer post-failed external beam radiation therapy

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Abstract

Introduction: Photodynamic therapy (PDT) can be employed as a focal therapy for prostate cancer. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) can potentially help identify tumour recurrence after failed external-beam radiotherapy (EBRT). The purpose of this study was to determine the ability of DCE-MRI to predict early response to PDT salvage treatment.

Methods: Patients with post-EBRT prostate cancer recurrence were prospectively enrolled into a Phase I/II trial of PDT using WST09. A 15-patient subgroup of this cohort undergoing 1.5T DCE-MRI at baseline and 1-week post-PDT was retrospectively analyzed. The reference standard was prostate biopsy obtained 6 months post-PDT. Analysis was performed on a patient-by-patient basis, by prostate gland halves, and by prostate sextants.

Results: Biopsy 6 months post-PDT identified cancer in 10/15 patients (66.7%), and in 24/90 sextants (26.7%). Residual cancer was identified in 22/37 sextants (59.5%) identified as being involved at baseline. DCE-MRI at 1 week correctly predicted recurrent disease with a sensitivity of 100% (10/10), specificity of 60% (3/5), positive predictive value of 83.3% (10/12), negative predictive value of 100% (3/3), and an overall accuracy of 86.7%, (13/15). When analysis was performed on prostate halves, the sensitivity and negative predictive value remained at 100%, with an improvement in specificity to 88.2% (15/17). The overall accuracy of DCE-MRI was similar regardless of analysis method: 86.7% on a patient-by-patient basis, 86.7% by prostate half and 83.3% by sextant. Changes in prostate-specific antigen (PSA) did not correlate to response.

Conclusion: DCE-MRI shows promise as a tool to predict successful outcome when performed 1 week post-PDT and could potentially be used to inform the need for re-treatment at an early time-point.

Introduction

External beam radiotherapy (EBRT) is an established radical treatment option for localized low-volume prostate cancer.[1,2] However, despite recent advances in delivery, the rate of biochemical failure remains significant. In a large series, Kuban and colleagues reported a biochemical failure in a third of patients treated with EBRT,[3] with published rates elsewhere ranging from 22% to 69%.[4,5] In patients with isolated local recurrence of prostate cancer, salvage therapy offers the only chance for cure. Salvage radical prostatectomy is able to offer long-term cancer control, with 30% to 40% of patients disease free at 10 years,[6,7] but the surgery is often technically challenging and associated with significant complications.[8,9] Androgen deprivation therapy is often used following ERBT failure, but it is not curative. Brachytherapy, although typically a first-line treatment, has started to be employed following EBRT failure. More recently there has been a trend to use less invasive approaches, such as cryotherapy and high intensity focused ultrasound (HIFU), to increase the efficacy/risk ratio in treating local recurrence after EBRT.[10]

Photodynamic therapy (PDT) is another minimally invasive technique, combining injection of an intravenous photosensitizing agent with exposure of the target to light, to produce reactive oxygen species and induce cell death. Palladium-bacteriopheophorbide (WST09, Steba-Biotech N.V., The Hague, Netherlands, and Negma, Toussus-le-Noble, France) is a PDT agent which has demonstrated promising results in Phase I and II trials for prostate cancer.[11-14] The agent induces vascular occlusion, with subsequent ischemic necrosis of the targeted area.[15,16] It is therefore intuitive that contrast-enhanced magnetic resonance imaging (MRI) could be used to monitor treatment response.

Indeed, several studies have shown that contrast-enhanced MRI can successful demonstrate the extent of necrosis from other ablative techniques, such as HIFU and cryotherapy.[17,18] Thus, DCE-MRI could theoretically determine efficacy of focal PDT earlier and predict longer-term response. This early knowledge could lead to early re-intervention in the appropriate setting. Therefore, the purpose of this study was to determine the feasibility of using DCE-MRI to predict the presence or absence of local residual tumour post-PDT in patients who have failed EBRT.

Methods

Patients

Patients with post-EBRT prostate cancer recurrence were prospectively enrolled into a Phase I/II trial of photodynamic therapy using WST09.[11] The current study involves a retrospective analysis performed on a subgroup from this cohort. Approval was obtained from the ethics review board and all patients signed informed consent forms. Patients with cystitis and proctitis (to avoid PDT effects on the hyperemic bladder/rectum), previous transurethral prostate resection, or concurrent hormone or chemotherapy were excluded from the study. Failed EBRT was defined on the basis of the ASTRO criteria of 3 consecutive elevations in serum prostate-specific antigen (PSA) level from a nadir value.

In total, 17 men (mean age 72.1, range: 61–83) underwent PDT with WST09. Prior to EBRT, 8 patients were classified as high risk for treatment failure (stage >T2c, PSA >20 ng/mL, or Gleason >7), 3 were low risk (stage <T2b, PSA <10, and Gleason <7), and 6 were intermediate risk (not high or low risk). Patients received EBRT at a mean dose of 75 Gy (range: 52.5–79.8). The mean PSA nadir was 3.8 ng/mL (range: 0–5.8), and the mean PSA value before MRI and biopsy was 5.4 ng/mL (range: 1.9–15.5). One patient was eliminated from analysis because he did not undergo a 6-month biopsy. Another patient was excluded due to microfocal disease and the fact that his tumour was not identified at baseline MRI. Therefore, in total, 15 men were included for image analysis.

Photodynamic therapy

A more detailed account of the procedure has been described previously.[12] Briefly, patients were anesthetized and placed in the lithotomy position, 2 to 6 closed-end catheters (15 gauge, 20 cm length) were guided transperineally into the prostate, using a modified brachytherapy insertion template. Based on previous work, WST09 was infused at 2 mg/kg, light delivery began 6 minutes post-infusion and lasted about 30 minutes, to achieve whole-gland ablation.[19] The site of fibre placement and the expected treatment effect were determined by in-house software.[12]

Biopsy and PSA follow-up

PSA was obtained at baseline, 1, 3, and 6 months post-PDT. To enable healing of potential rectal thermal damage, systematic transrectal ultrasound (TRUS) biopsy was not performed until 6 months postoperatively. All pathologic specimens were reviewed by a single pathologist specialized in genitourinary pathology and familiar with prostate post-radiation effects. Each specimen was classified as containing cancer, no cancer, or indeterminate (atypical cells, or marked radiation effect, with no Gleason grade determined). Indeterminate regions were considered negative, as these were not considered to represent significant cancer. Histology results were subsequently correlated to MRI findings.

Magnetic resonance imaging

MRI examinations were performed using a 1.5-T MRI system (Echospeed, Excite, or Excite-HD; GE Medical Systems, Milwaukee, WI) with an 8-channel phased array surface coil. T1-weighted, multiplanar T2-weighted (axial slice thickness 3 mm), and dynamic contrast-enhanced (DCE) T1-weighted were obtained in all patients prior to therapy, at 1 week (range 6–8 days), and 6 months post-treatment (mean 225 days, range: 178–465). For DCE-MRI, Gadopentate–diethylene triamine pentetic acid (Magnevist; Bayer Schering Pharma, Berlin, Germany) was injected at a dose of 0.1 mmol/kg, at 4 mL/s followed by a 20-mL saline flush using a power injector; 2 phases were acquired before contrast injection and 9 phases after.[20]

Image analysis

Tumour location was determined from the pre-treatment MRI by a radiologist (MAH), with 9 years prostate MRI reporting experience. The prostate was divided into 6 zones, three on each side (base, mid, and apex). On DCE-MRI, areas suspicious for tumour were identified as focal increased enhancement to background in the peripheral zone and increased nodular enhancement compared to background in the transition zone. This increased enhancement was determined on review of the first pass of contrast (48s after injection).[20]

On the 1 week MRI, necrosis was defined as nonenhancement on the dynamic contrast-enhanced images, allowing for areas of hemorrhage. Regions showing <10% enhancement on the last DCE phase were also considered necrotic.[11] The prostate volume was derived by contouring on axial T2-weighted images; a region-of-interest was drawn around the necrotic margin to calculate volume and derive the percentage volume of necrosis (Table 1).

The baseline tumour location was correlated to the necrotic region identified on the 1 week post-treatment MRI to determine if this completely encompassed the tumour. Necrosis fully encompassing tumour was classified as successful treatment by imaging (Fig. 1), otherwise it was classified as treatment failure (Fig. 2). Focal residual enhancement in a region where baseline MRI and initial biopsy did not identify tumour was due to benign glandular tissue (Fig. 3.). Histology remained the gold standard for outcome evaluation.

Statistics

Statistical analysis was performed by using SPSS v.11 software (SPSS, Chicago, IL). Sensitivity, specificity, accuracy, and positive and negative predictive values (PPV, NPV) were calculated for individual patients, by half-gland, and by sextant location. To account for multiple regions being assessed for each patient, we used generalized estimating equation models to calculate the corresponding variances and to test for differences between methods.[21] We calculated 95% confidence intervals using the Agresti-Coull interval and assuming a binomial distribution.[22]

Results

Baseline DCE-MRI identified prostate cancer in 15 men involving 37/90 (41%) sextants. Cancer was located in the apex in 14/37, mid-gland in 16/37, and base in 7/37.

Based on TRUS biopsy at 6 months, cancer was identified in 10/15 patients (66.7%) (Table 2). Two patients demonstrated bilateral disease, thus cancer was present in 12/30 half glands (40%); overall, cancer was present in 24/90
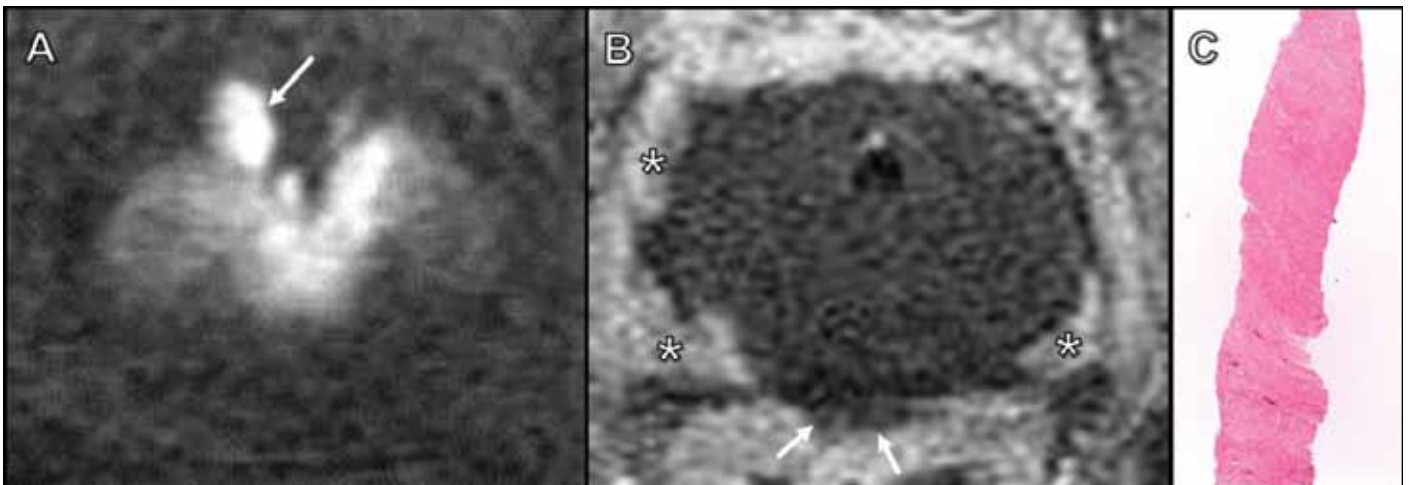
sextants (26.7%). Of the 10 patients with biopsy proven cancer, the average number of sextants involved was 2.4 (range: 1-4). Residual/ recurrent cancer was identified in 22/37 sextants (59.5%), which involved the baseline, prior to treatment. Cancer recurrence was in the apex in 8/22, mid-gland in 7/22, and base in 7/22. Based on 6-month biopsy results, cancer was contiguous, involving one set of adjacent sextants in 8/10 patients (80%), suggesting that most recurrences were unifocal. In the 10 patients with residual tumour after treatment, the Gleason score was 3+3 in 2 patients (20%), 3+4 in 6 (60%), and 4+4 in 2 (20%).

The MRI performed 1 week post-therapy identified residual tumour in all 10 patients with subsequent recurrence. In the remaining 5 patients, DCE-MRI correctly predicted no residual disease in 3 patients, but incorrectly identified areas suspicious for residual disease in 2 patients. The ability of DCE-MRI to predict PDT outcome in terms of the individual patient by patient, prostate half and sextant core were comparable (Table 3). On a patient-by-patient basis, DCE-MRI predicted recurrent disease with a sensitivity of 100% (10/10), specificity of 60% (3/5), PPV of 83.3% (10/12), NPV of 100% (3/3), and an overall accuracy of 86.7%, (13/15). The sensitivity and NPV remained at 100% when analysis was performed on the basis of prostate halves, with an improvement in specificity to 88.2%. The overall accuracy of DCE-MRI was similar regardless of analysis method, being 86.7% by patient, 86.7% by prostate half and 83.3% by sextant, thus both the presence and location of residual disease was demonstrated with reasonable accuracy.

Changes in PSA values did not correlate well with clinical response (Fig. 4), with 13/15 patients (86.7%) showing a PSA drop. The average baseline PSA value in patients with residual disease was 6.2 ng/mL (range: 2.5–15.5), reducing

Table 1. Operative factors and effects on prostate gland and surrounding tissue

Patient	Baseline prostate volume (cm³)	1 week prostate volume (cm³)	Percent increase in volume	Total drug injected (mL)	No. fibres used	Necrosis volume at 1 week	Percent necrosis at 1 week	Extra-prostatic necrosis
1	29.53	35.24	19.3	64.3	5	0.3	0.85	No
2	29.47	31.28	6.14	63.5	5	2.08	6.64	No
3	27.72	34.24	23.5	47.8	5	2.79	8.14	yes
4	27.13	31.9	17.6	62.0	5	2.49	8.11	Yes
5	25.65	26.64	3.86	78.6	4	2.59	9.72	Yes
6	22.66	29.76	31.3	74.0	5	6.42	21.6	Yes
7	27.50	32.53	18.3	60.0	5	4.99	15.3	Yes
8	33.28	42.79	28.6	61.2	6	10.21	23.9	Yes
9	6.63	9.36	41.2	62.7	2	4.1	43.8	Yes
10	21.15	25.85	22.2	79.0	4	9.84	38.1	Yes
11	31.50	36.88	17.1	74.8	6	15.1	40.9	Yes
12	34.14	40.19	17.7	84.0	5	19.34	50.1	Yes
13	30.42	38.17	25.5	63.6	6	23.35	61.2	Yes
14	23.60	25.33	7.33	64.6	5	19.57	78.0	Yes
15	36.75	37.57	2.23	66.0	5	31.52	83.9	Yes

Fig. 1. Successful photodynamic therapy. A. Baseline dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) shows early enhancement in the right anterior mid gland (arrow). B. 10 minute post contrast DCE-MRI at day 7 post-treatment showing widespread non-enhancing areas of necrosis, with only small residual areas of enhancement peripherally (*), overall gland necrosis = 80%; note an area of necrosis within the outer wall of the rectum (arrows). C. Core biopsy from the right mid gland 6 months post treatment shows complete fibrosis, with no preserved prostate stroma or tumour. Scattered small vascular channels lined by reactive endothelial cells are seen consistent with late stage reparative fibrosis following coagulative necrosis and granulation tissue formation (25× original magnification).

to 2.9 ng/mL at 6 months (range: 0.8–3.8), and 5.3 ng/mL (range: 1.9–13.4), reducing to 4.6 ng/mL at 6 months (range: 0-17.9) in patients without disease.
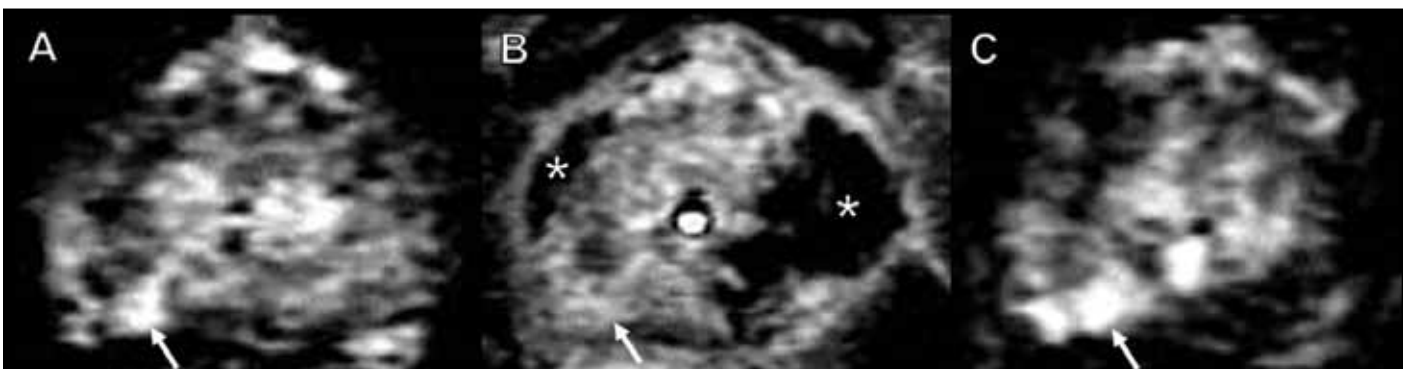
Discussion

DCE-MRI can localize prostate cancer after failed EBRT with an accuracy as high as 83%,[20,23] and can assess response to focal therapies with HIFU and cryotherapy.[24] We have demonstrated the ability of DCE-MRI to successfully predict early outcome of photodynamic therapy with a sensitivity and NPV of 100%.

The sensitivity and NPV of DCE-MRI dropped from 100% to 75% and 90.5%, respectively when the analysis was performed on a sextant-by sextant basis. Possible explanations include under-estimation of tumour volume by DCE-MRI,
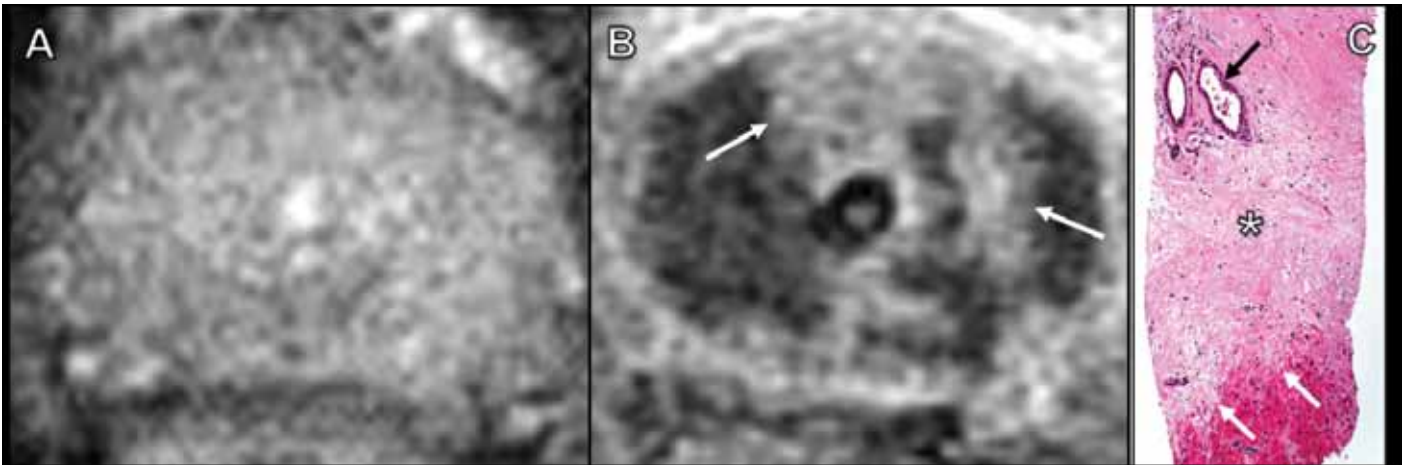
interval tumour growth to 6-month biopsy, or sextant registration differences between the MRI reader and the person performing the biopsy. These factors would not affect analysis on prostate half or a patient-by-patient basis. From a clinical stand-point, a decision to re-treat will be based on the prediction of recurrence on a patient-by-patient basis. Even if a more focal form of therapy is considered, this would still likely involve at least half of the gland. DCE-MRI incorrectly identified areas suspicious for residual disease in 2 patients. This may relate to enhancing benign glandular tissue, or possibly that the 6-month biopsy missed a site of recurrence.

PSA levels did not appear to correlate well with the presence of residual disease. Unless 100% of the gland is ablated, any residual prostatic tissue, even if it is disease-free, will produce PSA, thus PSA levels are unlikely to be a

Fig. 2. Failure of photodynamic therapy predicted by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) at day 7. A. Baseline DCE-MRI shows enhancement in the right mid gland PZ at an early time point post-contrast (arrow). B. 10 minute post contrast DCE-MRI at day 7 post-treatment showing non-enhancing areas of necrosis (*) that do not encompass tumour location from baseline (arrow) indicates treatment failure; overall gland necrosis = 22%. C. DCE-MRI performed at 6 months shows area of early enhancement corresponding to location of the tumour at baseline (arrow), histology shows Gleason 3+3 disease in the right mid, involving 20% of the core.

Fig. 3. Entrapped benign atrophic glands within an area of photodynamic therapy (PDT)-induced fibrosis. A. Baseline post-contrast T1-weighted imaging shows homogeneous enhancement at the level of the mid gland with no obvious tumour focus. B. 10-minute post-contrast dynamic contrast-enhanced magnetic resonance imaging at day 7 post-treatment shows non-enhancing areas of necrosis, with spared areas demonstrating enhancement (arrows), representing residual benign prostatic tissue. C. Core biopsy at 6 months post-treatment shows PDT-induced fibrosis (*), with entrapped atrophic glands (black arrow). Note also the characteristically sharp interface between the partial PDT effect and preserved fibromuscular prostate stroma at the bottom of the figure (white arrows); (100× original magnification).

reliable discriminator of treatment failure, as demonstrated in our cohort.

PDT is less invasive than prostatectomy; therapy can usually be performed in an outpatient setting,[25] and multiple therapies can be performed without the dose limitations associated with radiotherapy. Furthermore, following therapy, tumour can be readily identified by histology, showing no cytonuclear or architectural modification, in contradistinction to such treatment effects of hormonal or radiation therapy which can hinder interpretation.[18] It should be noted that that WST09 has now been superseded by a

more hydrophilic generation of the compound for clinical use (WST11); however, the agents retain similar pharmacodynamic properties and tissue treatment effects,[26] and thus the imaging results reported are valid and would be expected to be equivalent.

Our study has some limitations, including its retrospective nature. Whole-mount histology was not used for validation; however, the nature of the study cohort precluded this. A 6-core TRUS biopsy was employed, which has potential to under-sample and miss small foci of residual tumour. This core number was due to the small gland size post-radiation

Table 2. Patient demographics and clinico-pathological features at baseline and follow-up

Patient	Age	Baseline Gleason	TNM Stage	PSA baseline (ng/mL)	PSA at 1 month (ng/mL)	PSA at 6 months (ng/mL)	No. positive sextants	Post-PDT Gleason
1	68	3 + 3	T2A	3.8	2.1	3.4	2	3 + 4
2	72	3 + 4	T1C	6.8	1.4	1.8	2	4 + 4
3	63	3 + 3	T2A	3.8	8.0	3.7	4	3 + 4
4	70	3 + 3	T2B	3.0	1.2	2.0	2	3 + 4
5	62	3 + 4	T2C	5.2	1.0	1.8	2	3 + 3
6	72	3 + 3	T2B	2.5	2.8	1.7	2	3 + 3
7	76	3 + 4	T2C	6.4	1.7	2.2	2	3 + 4
8	74	3 + 3	T2A	2.1	1.0	0.6	Negative	Negative
9	83	3 + 4	T1A	15.5	1.7	3.8	3	3 + 4
10	71	3 + 3	T2B	4.8	4.6	4.5	Negative	Negative
11	74	3 + 4	T2A	5.5	3.9	8.0	4	4 + 4
12	70	3 + 4	T2A	9.6	0.4	0.8	1	3 + 4
13	75	3 + 3	T1C	1.9	0.3	0.1	Negative	Negative
14	75	3 + 4	T2B	4.5	0.1	0.0	Negative	Negative
15	75	3 + 4	T1C	13.4	6.2	17.90	Negative	Negative

PSA: prostate-specific antigen; PDT: photodynamic therapy.

Table 3. Accuracy of DCE MRI performed 1 week post-photodynamic for predicting therapy failure

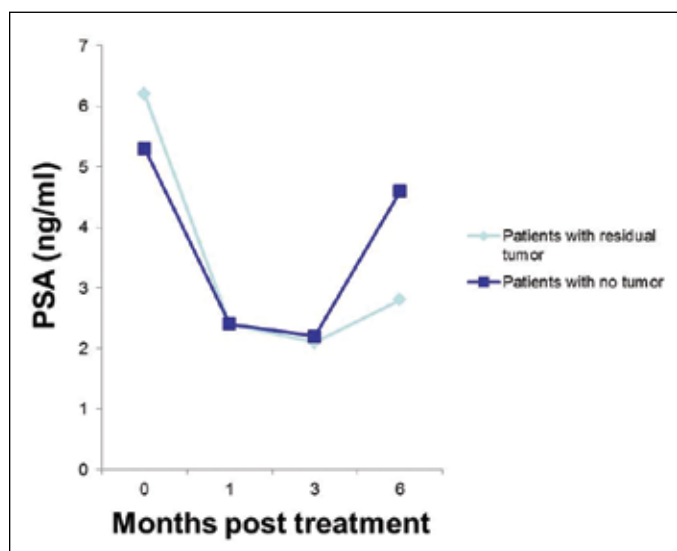|	DCE MRI by Patient	95% CI	DCE MRI by prostate halves	95% CI	DCE MRI by Prostate sextant	95% CI
Sensitivity	100% (10/10)	72.2–100	100% (11/11)	74.1–100	75% (18/24)	55.1–88.0
Specificity	60% (3/5)	23.1–88.2	88.2% (15/17)	65.7–96.7	86.4% (57/66)	80–95.8
PPV	83.3% (10/12)	55.2–95.3	73.3% (11/15)	48.0–89.1	66.7% (18/27)	40.1–93.3
NPV	100% (3/3)	43.9–100	100% (15/15)	79.6–100	90.5% (57/63)	80.7–95.6
Accuracy	86.7% (13/15)	62.1–96.3	86.7% (26/30)	70.3–94.7	83.3% (75/90)	74.3–89.6

DCE: dynamic contrast-enhanced; MRI: magnetic resonance imaging; PPV: positive predictive value: NPV: negative predictive value; CI: confidence interval.

therapy and PDT, and to minimize the risks of inducing a recto-prostatic fistula. An average gland ablation of only 34.95% suggested a degree of under-treatment in the cohort, however, this is not unexpected in a Phase I/II trial. Although this is a limitation of the Phase I/II trial, this is less relevant to the current study which aims to assess the ability of MRI to predict treatment response at an early time-point. The small number of patients included has the potential to limit the statistical significance of the results, and our limited early experience in this cohort will require further validation.

Conclusion

DCE-MRI shows promise as a tool to predict successful outcome when performed 1 week post-PDT and could potentially be used to inform the need for re-treatment at an early time-point.

Fig. 4. Average prostate-specific antigen level at baseline, and at 1, 3, and 6 months post-therapy for patients with recurrence and no residual disease on follow-up biopsy.

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