Implications of MRI contrast enhancement following focal prostate cancer cryoablation

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Introduction: *Local disease recurrence following focal therapy (FT) for prostate cancer may be due to failure to eradicate focal disease or development of disease in the untreated prostate (in- and out-of-field recurrences). Several studies suggest in-field contrast enhancement (CE) on post-treatment multi-parametric (mp) MRI between 6-12 months following FT indicates residual disease. The present study assesses the incidence and oncologic implications of early CE observed following primary partial gland cryoablation (PPGCA).*

Material and methods: *The surveillance protocol for men enrolled in our prospective outcomes study following PPGCA included mpMRI at 6-12 months, 2 years, 3.5 years, and 5 years. All cases of in-field early CE were re-reviewed retrospectively and graded using the previously described Prostate Imaging after Focal Ablation scoring system. All patients exhibiting early CE were re-evaluated by a single radiologist at 2-year mpMRI*

Results: *A total of 320 men enrolled in our PPGCA outcomes study had at least 6 months of follow up. Three hundred fifteen (98%) of these men had undergone post-PPGCA mpMRI at 6-12 months. Of these men, 9 were found to have early in-field CE and 8 underwent repeat MRI at 2 years. In all 8 cases, the CE resolved on the 2-year mpMRI. Of these 8 patients, seven underwent repeat protocol biopsy at 2 years and in-field significant disease was detected in only 1 case.*

Conclusions: *The most compelling evidence that early CE is not indicative of prostate cancer recurrence is that all lesions resolved within 24 months. While incidence of early CE is low, its consistent resolution calls into question the clinical significance of this finding after PPGCA.*

Key Words: contrast enhancement, mpMRI, prostate cancer focal therapy, cryoablation

Introduction

Prostate MRI and MRI-targeted biopsy facilitated a paradigm shift in the screening, diagnosis, and surveillance of prostate cancer by improving the ability to localize site(s) of clinically significant prostate cancer.[1] This paradigm shift has enabled focal therapy (FT) for men presenting with focal prostate cancer.[2]

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Local disease recurrence following focal therapy (FT) may be due to failure to eradicate the focal disease or the development of disease in the untreated prostate, often referred to as in- and out-of-field recurrence, respectively. Due to the multi-focality of prostate cancer and the lack of long term oncologic outcomes, accurate and timely detection of clinically significant prostate cancer recurrence is imperative. Consensus statements recommend surveillance PSA and multi-parametric prostate MRI (mpMRI) for monitoring disease recurrence following FT.[3,4] The timing of post-treatment mpMRI depends on the objective of the surveillance protocol. A mpMRI within the first week of treatment provides information about the gross extent of the ablation field. A mpMRI between 6-12 months provides an early indication of local disease

recurrence. mpMRI beyond 2 years is a proxy for both in- and out-of-field disease recurrence. Several studies suggest demonstration of in-field contrast enhancement (CE) on post-treatment mpMRI between 6-12 months following FT indicates residual in-field disease.[5-7] The present study assesses the incidence and oncologic implications of early CE observed in mpMRI obtained between 6-12 month following PPGCA.

Materials and methods

Subjects

Our prospective Institutional Review Board approved outcomes registry for primary partial gland cryoablation (PPGCA) was initiated in March 2017 (IRB No. 17-00354). Patient selection required pre-biopsy mpMRI. All observed regions of interest (ROI) categorized using Prostate Imaging Reporting and Data System (PI-RADS) v2 (from 2017-2019) and v2.1 (from 2019-2023) between 2 and 5 were segmented by radiologists in preparation for biopsy.[8] Both targeted biopsy (4 cores) of all segmented ROIs and 12-core systematic biopsy were performed using the Artemis biopsy platform as previously described.[9]

The study population included all subjects enrolled in the registry who underwent PPGCA with at least 6 months of follow up data at the time of database censure.

Treatment

Our treatment planning for PPGCA has been previously described.[10] Briefly, all PPGCA were performed under general anesthesia in the dorsal lithotomy position. The treatment plan was designed to achieve a 10-mm margin beyond the targeted ROI when technically feasible. Temperature probes were positioned to maximize safety and treatment margins. Cystoscopy was performed to confirm no aberrant probe placement and a urethral warming catheter was passed over a guidewire under ultrasound guidance prior to initiating the first freezing cycle. A minimum of 2 freeze/thaw cycles were carried out. PPGCA was performed using the Cryocare CS system. A Foley catheter was left indwelling for 3 to 5 days.

Surveillance protocol

The surveillance protocol for men enrolled in the study between March 2017 and August 2020 included PSA testing at 3 and 6 months following PPGCA and every 6 months thereafter; an mpMRI consisting of T2 weighted imaging, diffusion weighted imaging with high b-value (DWI), apparent diffusion coefficient (ADC) map, and dynamic contrast enhanced imaging (DCE) at 6-12 months, 2 years, 3.5 years, and 5 years, and a planned surveillance prostate biopsy at 6-12 months, 2 years, and 5 years. Additionally, men with suspicion of recurrence underwent additional mpMRI and prostate biopsy at the discretion of their provider. Surveillance biopsy between 6-12 months was abandoned following an interim analysis in August 2020 demonstrating in-field clinically significant prostate cancer recurrence rate of only 3%.[10] The 2-year surveillance prostate biopsy protocol included 4 cores directed into the ablation zone (AZ) even if the ablation cavity atrophied, 4 cores directed into any suspicious in- or out-of-field new MRI targets, and a 12-core systematic biopsy. A protocol 2-year biopsy was abandoned in 2022 following our in-field and out of field clinically significant prostate cancer detection rates of 3% and 13%, respectively.[11]

Board-certified and abdominal fellowship-trained radiologists reviewed the mpMRI following PPGCA. In-field CE was consistently reported. All reports were re-reviewed to ensure no under capturing of CE. All cases of in-field early CE were re-reviewed retrospectively by a single radiologist and graded using the previously described 3-point Prostate Imaging after Focal Ablation (PI-FAB) scoring system: 1; likely fibrosis; 2; equivocal for recurrence; 3; high suspicion for recurrence.[12] The natural history of all cases exhibiting early CE were re-evaluated retrospectively by a single radiologist on the 2-year mpMRI.

Statistical analyses

In-field and out-of-field recurrence of clinically significant prostate cancer was defined as any Gleason Grade Group (GGG) 2 or greater. The primary outcome of interest in this study was clinically significant prostate cancer associated with early in-field CE. Demographic and oncologic characteristics between patients with and without early CE were compared with Wilcoxon rank-sum tests.

Results

As of October 10, 2023, 320 men enrolled in our PPGCA registry had at least 6 months of follow up. Three hundred fifteen (98%) of these men had undergone a per-protocol post-PPGCA mpMRI at 6-12 months and were included in the analysis.

Of these men, nine were found to have early CE within the AZ. Baseline demographic and oncologic characteristics between those men with and without in field early CE are compared in Table 1 and 2. These cases were re-reviewed and assigned a PI-FAB score. Only 1 of 9 were classified as high risk for recurrence

TABLE 1. **Baseline patient characteristics**

Characteristic	CE on early MRI (n = 9)	No CE on early MRI (n = 306)	p value
Median age, y (IQR)	65.5 (62.8, 67.2)	65.1 (60.0, 70.5)	0.71
Median PSA, ng/mL (IQR)	5.8 (4.2, 10.8)	5.6 (4.4, 7.8)	0.63
PIRADS score, n (%)			0.97
1-2	1 (11.1)	30 (9.8)	
3	2 (22.2)	93 (30.4)	
4-5	6 (66.6)	179 (58.5)	
Median prostate volume, cc (IQR)	38 (31, 53)	42 (30, 58)	0.90
Gleason Grade group, n (%)			0.51
1	1 (11.1)	46 (15.0)	
2	7 (77.8)	165 (53.9)	
3	1 (11.1)	68 (22.2)	
4/5	0 (0)	27 (8.8)	

based on PI-FAB scoring system. Representative images of PI-FAB 1, 2 and 3 lesions are shown in Figure 1.

Of the initial 70 men enrolled in the registry prior to 2020, 6 exhibited in-field early CE. Four of these 6 men underwent protocol biopsy and none showed in-field clinically significant prostate cancer. Due to low early detection rates of clinically significant prostate cancer, protocol biopsies were not mandated within the first year post-treatment. Therefore, an additional 3 men subsequently exhibiting in-field early CE and did not undergo a protocol biopsy.

Of the 9 patients exhibiting in-field early CE, 8 underwent repeat MRI at 2 years post-PPGCA. In all 8 cases, the CE resolved on the 2-year protocol mpMRI. Of these 8 patients, seven underwent repeat protocol biopsy at 2 years and in-field clinically significant prostate cancer was detected in only 1 case.

Discussion

Local disease recurrence following FT develops due to failure to eradicate the "focal disease" or development of disease in the untreated prostate. There is an emerging consensus that mpMRI should be performed following FT in order to detect both in and out-of-field clinically significant prostate cancer recurrences.[2,3] There is no consensus regarding timing of post-treatment mpMRI and imaging characteristics indicative of in-field clinically significant prostate

TABLE 2. **MRI contrast enhancement characteristics**

PI-FAB score early MRI	Max length CE on early MRI	Early in-field biopsy	Resolution of early CE on 2-year mpMRI	2-year in-field biopsy
1	9 mm	N/A	Yes	Negative
2	4 mm	Negative	Yes	Negative
2	7 mm	N/A	Yes	Negative
1	13 mm	Negative	Yes	GGG3
2	11 mm	Negative	Yes	Negative
2	4 mm	N/A	Yes	N/A
2	7 mm	Negative	Yes	Negative
1	5 mm	N/A	Yes	Negative
3	3 mm	N/A	N/A	N/A

cancer recurrence. Energy directed at the prostate generates fibrotic and/or inflammatory signal changes which can obscure detection of in-field clinically significant prostate cancer recurrences.[5] Specifically, the post-ablation fibrotic and/or inflammatory changes obscures T2 and diffusion-based sequences, which drives the PI-RADS scoring system. The variability in tissue changes associated with different FT modalities is controversial and may further confound interpretation of post-treatment mpMRI.[7] It has been suggested, but not validated, that CE represents the most relevant predictor of clinically significant prostate cancer recurrence after FT.[5] The objective of the present study was to provide insights into the incidence of

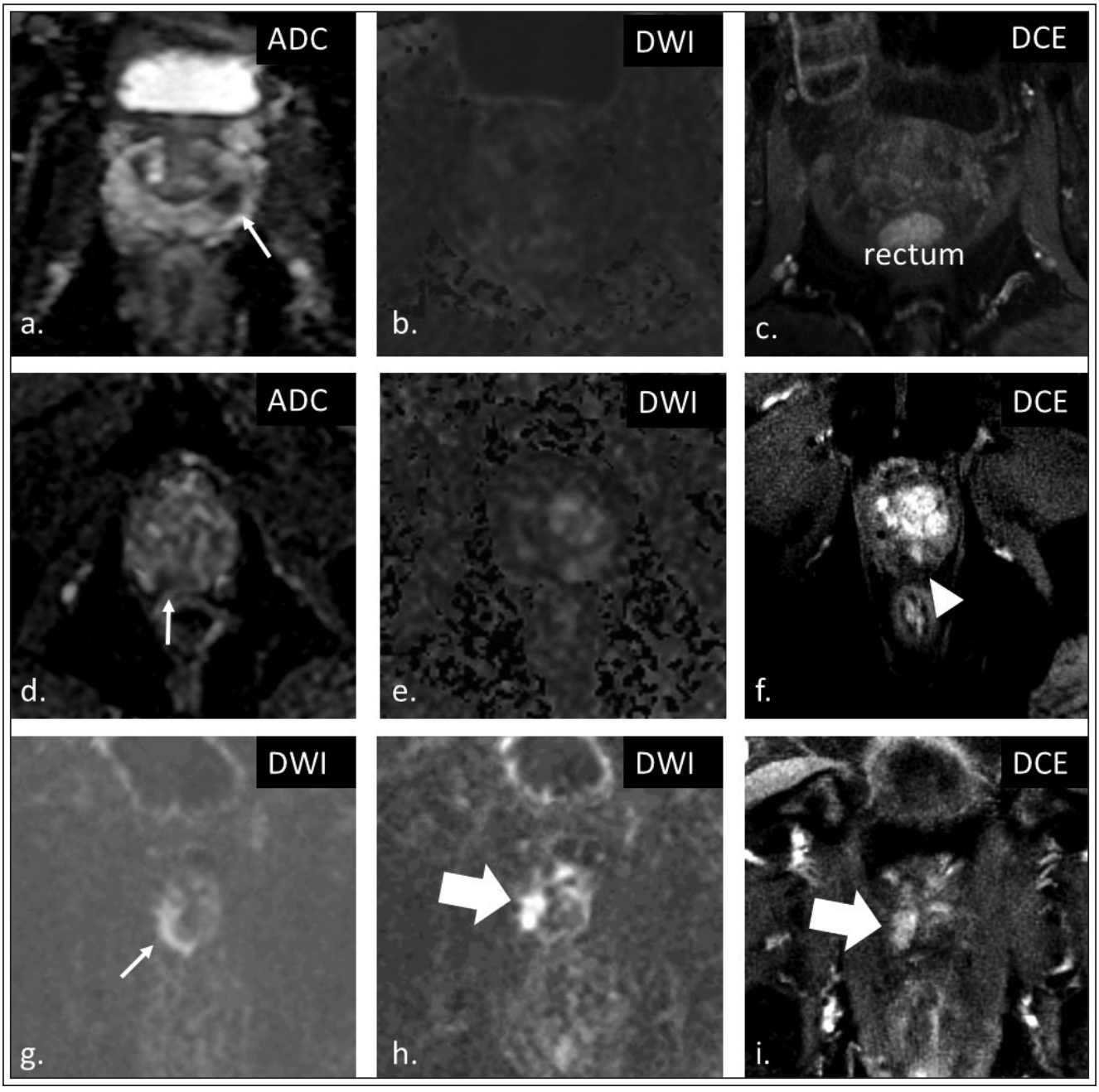

Figure 1. Representative pre-treatment prostate MRIs **(Fig 1a, d, g)**. Post-treatment MRI **(Fig 1 b/c)** showing no signal on DWI and DCE (PI-FAB 1). **Fig 1 e/f** shows no signal on DWI but signal on DCE (PI-FAB 2). **Fig 1 h/f** shows signal in DWI and DCE (PI-FAB 3).

early in-field CE following PPGCA, and if this finding is a reliable indicator of in-field clinically significant prostate cancer recurrence.

Our post-PPGCA protocol includes mpMRI at 6-12, 24, 42 and 60 months. Our compliance rate for obtaining a protocol mpMRI at 6-12 months was 98%, indicating the lack of selection bias for early imaging. Of the 315 men undergoing a 6-12 month protocol mpMRI, in-field early CE suspicious for malignancy was observed in only 9 (2.8%). The mean greatest dimension of the lesion exhibiting CE was 6 mm (range 3 mm-13 mm). There were no specific preoperative demographic, imaging or disease predictors of early post-treatment CE. We also found no relationship between early CE and clinically significant prostate cancer recurrence at 2 years. Prior to 2020, we biopsied 4 of the 6 men exhibiting CE on the 6-12 months mpMRI and none were found to have in-field clinically significant prostate cancer. The 3 subsequent cases of CE did not undergo early protocol biopsy since we revised criteria for performing surveillance biopsy.

We have previously reported that 40% of PI-RADS 4 lesions with negative targeted biopsy resolve on a follow up mpMRI.[9] Resolution of a mpMRI lesion is indicative of a true negative biopsy or absence of clinically significant prostate cancer. In the present study, all early CE lesions resolved on the 2-year mpMRI. The resolution of the early CE is definitive evidence CE in our study does not indicate clinically significant prostate cancer recurrence. Interestingly, for the one case showing in-field clinically significant prostate cancer at 2 years, CE also resolved on the 2-year mpMRI.

The rate of in-field recurrence following FT is influenced by patient selection and treatment planning. The overwhelming majority of our study cohort were GGG 2 and 3 and by consensus are optimal candidates for FT.[13]

Giganti et al recently proposed a three-point mpMRI scoring system, PI-FAB, for evaluating disease recurrence following prostate FT. PI-FAB weights DCE and high b-value DWI over other imaging sequences to suggest likelihood of recurrence. Biopsy is recommended for PI-FAB 3, which is described as abnormal signal on both high b-value DWI and DCE. Of the 9 patients reported to have early in-field CE described on the 6-12 month mpMRI report, upon re-review, 3, 5 and 1 were PI-FAB 1 PI-FAB 2 and PI-FAB 3, respectively. All of these lesions resolved on subsequent mpMRI, emphasizing the need to prospectively validate the proposed PI-FAB scoring system.

One notable difference between the Giganti series and the current study is the different energy sources utilized and the post-treatment recurrence rate. Our study reported 3 year in-field and out of field clinically significant prostate cancer recurrence rates were 3% and 12%, respectively.[13] Giganti et al reported a 31% rate of clinically significant prostate cancer and did not stratify in versus out of field recurrences. Nuances in recommendations in interpretation of mpMRI acquired at various time points post treatment is also necessary as post-treatment inflammation and granulation tissue may mimic disease recurrence. Our early CE rate may have been even lower if all mpMRI were performed at one year. The resolution of early CE suggests that this finding in our cohort is likely indicative of residual granulation tissue.

Further studies may also consider the potential role of Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) imaging. PSMA PET has emerged as a highly sensitive modality for the detection of prostate cancer.[14] The specificity of PSMA PET for prostate cancer tissue may afford earlier detection of recurrence. This could be particularly beneficial in cases where MRI findings are ambiguous or where the PI-RADS or PI-FAB scoring systems provide indeterminate results.

The present study is not without limitations. To our knowledge, we report the lowest rate of local disease recurrence following any modality for FT.[10,13] Our low rate of in-field recurrence was achieved in men exclusively with intermediate risk disease. We aggressively treat the index lesion without significant compromise of functional outcomes.[11] It is possible that early CE may be indicative of residual disease using energy sources other than cryoablation or in cohorts with higher rates of clinically significant prostate cancer recurrence.

Another limitation is the small number of men exhibiting early CE. While the incidence of early CE is low, the number of men undergoing a 6-12 month mpMRI was over 300 and our compliance with protocol mMRI was 98%. In addition, not all men with early CE underwent a biopsy at 6 months. The most compelling evidence that the early CE is not indicative of in-field recurrence is that all the lesions resolved within 24 months. While the incidence of early CE is low, its consistent resolution calls into question the clinical significance of this finding in our cohort of men undergoing PPGCA.

Identifying validated MRI criteria to inform decisions who should undergo a prostate biopsy following FT will minimize the burden of surveillance while also enabling early detection of clinically significant prostate cancer. The present study questions whether CE is a reliable predictor of clinically

significant prostate cancer. Our study suggests that mpMRI scoring systems developed to inform biopsy decisions post FT must be rigorously validated by target biopsy of the site(s) of CE and observing the natural history of those negative biopsies. □

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