Multiparametric MRI for the detection of local recurrence of prostate cancer in the setting of biochemical recurrence after low dose rate brachytherapy

Luca F. Valle
Matthew D. Greer
Joanna H. Shih
Tristan Barrett
Yan Mee Law
Andrew B. Rosenkrantz
Haytham Shebel
Akhil Muthigi
Daniel Su
Maria J. Merino
Bradford J. Wood
Peter A. Pinto
Andra V. Krauze
Aradhana Kaushal
Peter L. Choyke
Barış Türkbey
Deborah E. Citrin

PURPOSE
Prostate multiparametric magnetic resonance imaging (mpMRI) has utility in detecting post-radiotherapy local recurrence. We conducted a multireader study to evaluate the diagnostic performance of mpMRI for local recurrence after low dose rate (LDR) brachytherapy.

METHODS
A total of 19 patients with biochemical recurrence after LDR brachytherapy underwent 3T endorectal coil mpMRI with T2-weighted imaging, dynamic contrast-enhanced imaging (DCE) and diffusion-weighted imaging (DWI) with pathologic confirmation. Prospective reads by an experienced prostate radiologist were compared with reads from 4 radiologists of varying experience. Readers identified suspicious lesions and rated each MRI detection parameter. MRI-detected lesions were considered true-positive with ipsilateral pathologic confirmation. Inferences for sensitivity, specificity, positive predictive value (PPV), kappa, and index of specific agreement were made with the use of bootstrap resampling.

RESULTS
Pathologically confirmed recurrence was found in 15 of 19 patients. True positive recurrences identified by mpMRI were frequently located in the transition zone (46.7%) and seminal vesicles (30%). On patient-based analysis, average sensitivity of mpMRI was 88% (standard error [SE], 3.5%). For highly suspicious lesions, specificity of mpMRI was 75% (SE, 16.5%). On lesion-based analysis, the average PPV was 62% (SE, 6.7%) for all lesions and 78.7% (SE, 10.3%) for highly suspicious lesions. The average PPV for lesions invading the seminal vesicles was 88.8% (n=13). The average PPV was 66.6% (SE, 5.8%) for lesions identified with T2-weighted imaging, 64.9% (SE, 7.3%) for DCE, and 70% (SE, 7.3%) for DWI.

CONCLUSION
This series provides evidence that mpMRI after LDR brachytherapy is feasible with a high patient-based cancer detection rate. Radiologists of varying experience demonstrated moderate agreement in detecting recurrence.

The use of brachytherapy for prostate cancer has increased over the past several decades as technical improvements have led to enhanced efficacy (1). The rate of prostate cancer control with permanent low dose rate (LDR) brachytherapy alone or in combination with external beam radiation therapy (EBRT) is excellent, and may provide superior disease control compared with EBRT in some patient subsets (2, 3). As many as 30%–40% of prostate cancer patients will undergo LDR brachytherapy for treatment (4, 5).

Although most patients who receive LDR brachytherapy for prostate cancer will be cured of their disease, biochemical recurrence occurs in 3%–13% of men undergoing monotherapy (6–8). Although biochemical recurrence after radiotherapy for prostate cancer is often treated with immediate or delayed androgen deprivation therapy (ADT), documenting local recurrence after LDR brachytherapy may provide additional therapeutic options (9, 10). For brachytherapy practitioners, understanding the patterns of local recurrence after treatment may inform patient selection or alter implant techniques in certain cases to optimize dosimetry.

The use of magnetic resonance imaging (MRI) has enhanced the diagnosis and staging of localized prostate cancer (11). Multiparametric MRI (mpMRI) typically consists of T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCE) to provide anatomical and functional information about the prostate (11) and has been shown to improve prostate cancer detection and risk stratification (12). MRI has been used for detection of local recurrences after EBRT (13); however, MRI is often avoided in the setting of prior LDR brachytherapy due to concerns of post-treatment gland texture alterations and artifact from permanently implanted seeds.

We sought to determine the efficacy of mpMRI in identifying local recurrence of prostate cancer in patients with biochemical recurrence after LDR brachytherapy as a component of treatment. We hypothesized that mpMRI would be effective in identifying locally recurrent cancer in this setting. We compared prospective mpMRI reports with pathologic confirmation at biopsy following biochemical recurrence. We further evaluated mpMRI performance in the same patients using the retrospective interpretations of 4 additional blinded radiologists of varying experience. We compared the patient-based sensitivity and specificity and lesion-based positive predictive value (PPV) among these 5 radiologists.

Methods

Patients

All patients were enrolled on institutional review board approved protocols for the evaluation and management of prostate cancer and provided informed consent. All patients who received LDR brachytherapy as a component of treatment, developed prostate specific antigen (PSA) recurrence, and subsequently underwent mpMRI and biopsy or surgical resection at our institution between January 2011 and March 2016 were analyzed. Patients with known metastatic disease were excluded. Prior treatment consisted of LDR brachytherapy alone or in combination with EBRT and/or ADT. Biochemical recurrence was defined by the Phoenix consensus definition of PSA nadir plus 2 ng/mL.

MRI protocol

Prostate mpMRI scans were acquired on a 3T scanner (Achieva 3T-TX, Philips Healthcare) using an endorectal coil (BPX-30, Medrad) filled with 45 mL fluorinert (3M) and anterior half of a 32-channel cardiac SENSE coil (InVivo). Table 1 contains MRI pulse sequence parameters used in this study.

Image interpretation

Patient images were examined prospectively by a prostate-dedicated radiologist (>3000 examinations evaluated over 8 years) as part of the clinical evaluation for biochemical recurrence. The intraprostatic level (apex, mid, and base) and zone (peripheral vs. transition) of visualized lesions, presence of seminal vesicle (SV) lesion, presence of detected abnormality on each sequence (T2-weighted, DWI, DCE), and overall likelihood of representing locally recurrent disease were included in clinical reports.

As part of the retrospective review, patient images were evaluated by 4 board certified radiologists at 4 separate institutions. Two of these readers were highly experienced in prostate mpMRI (>2000 cases evaluated), and two were moderately experienced (<2000 cases evaluated). All readers were blinded to clinical and pathologic outcomes at surgery or biopsy and were instructed to detect lesions suspicious for recurrent prostate cancer. The additional readers independently recorded screen-captures of each identified suspicious lesion, recorded the presence or absence of an abnormality on each sequence for each lesion, and scored the overall likelihood of representing recurrent disease using the same criteria as the initial reader. Further image interpretation details are included in the supplemental materials.

Pathologic correlation

Methods of pathologic confirmation of prostate cancer recurrence included transrectal ultrasonography (TRUS)-guided 12-core systematic biopsy, targeted mpMRI/TRUS fusion biopsy, radical prostatectomy (RP), or a combination of the above. Targeted mpMRI/TRUS fusion biopsy location was determined by the initial prospective reader and was directed at all suspicious lesions in the prostate and SV with two cores acquired from each target location. Biopsy and prostatectomy samples were evaluated for the presence of cancer and treatment effect by a genitourinary dedicated pathologist.

mpMRI interpretations were classified as: true positive in the presence of an identified mpMRI lesion with ipsilateral pathologic confirmation of disease within the prostate; false positive in the presence of an identified mpMRI lesion without ipsilateral pathologic confirmation of disease; and false negative in the presence of pathologic identification of disease without an identified ipsilateral mpMRI lesion. Because radiologists were only instructed to identify lesions suspicious for recurrent disease,

Main points

- Although artifact is observed, multiparametric MRI (mpMRI) can still be performed and may provide useful information following low dose rate (LDR) brachytherapy.

- At the patient level, mpMRI correctly detected pathologically confirmed lesions with a sensitivity of 88% (SE, 3.5%) for all lesions and a specificity of 75% (SE, 16.5%) for highly suspicious lesions.

- At the lesion level, mpMRI demonstrated a high cancer-detection rate of 78.7% (SE, 10.3%) for highly suspicious lesions.

- Radiologists of varying experience demonstrated 54.4% (SE, 11.9%) agreement when detecting recurrent cancers at the patient level.

- Pathologically confirmed LDR brachytherapy recurrences identified by mpMRI were frequently located in the transition zone (41%) and seminal vesicles (32.3%).

Table 1. Multiparametric MRI sequence parameters at 3 Tesla

Parameter	T2WI	DWI[a]	High b-value DWI[b]	DCE
Field of view (mm)	140×140	140×140	140×140	262×262
Acquisition matrix	304×234	112×109	76×78	188×96
Repetition time (ms)	4434	4986	6987	3.7
Echo time (ms)	120	54	52	2.3
Flip angle (°)	90	90	90	8.5
Section thickness (mm), no gaps	3	3	3	3
Image reconstruction matrix (pixels)	512×512	256×256	256×256	256×256
Reconstruction voxel imaging resolution (mm/pixel)	0.27×0.27×3.00	0.55×0.55×2.73	0.55×0.55×2.73	1.02×1.02×3.00
Time for acquisition (min:s)	2:48	4:54	3:50	5:16

[a]Five evenly spaced b values (0–750 s/mm^2) were used for ADC map calculation.
[b]b=2000 s/mm^2.
MRI, magnetic resonance imaging; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; DCE, dynamic contrast-enhanced imaging.

lesion-based true negative status was not assigned.

Statistical analysis

Patient-based sensitivity and specificity and lesion-based positive predictive value (PPV) were determined for each reader. A patient-based true positive identification was defined as any mpMRI detected lesion in a patient with pathologically verified recurrence. In patients with multiple lesions, the lesion with the highest likelihood of malignancy determined the overall patient likelihood score. PPV was defined as the proportion of true positive lesions among all lesions detected. The averaged sensitivity, specificity, and PPV were calculated from the average of reader-specific sensitivity, specificity, and PPVs. Sensitivity, specificity, and PPV were determined at low, moderate, and high overall suspicion levels for the single reader evaluation, for the duplicate four reader evaluation, and for all readers combined.

Interobserver agreement was examined with respect to (a) patient-based assignment, (b) lesion detection and (c) positivity scoring for each sequence (i.e., T2-weighted imaging, DWI, DCE). Agreement for (a) was determined by the kappa statistics, whereas agreement for (b) and (c) was determined by the index of specific agreement (ISA), which is defined as the conditional probability given that one reader, randomly selected, makes a specific rating which will be consistent with another randomly selected reader.

The bootstrap resampling procedure was used to calculate the standard error (SE) of sensitivity, specificity, kappa and ISA, where the bootstrap sampling unit was the patient. The number of bootstrap samples was 1000. SPSS was used to for statistical analyses.

Results

At the time of mpMRI, the average age of the cohort was 66.8 years (range, 57–85 years). The pretreatment mean PSA was 8.0 ng/mL (range, 3.4–31.1 ng/mL) and the median pretreatment Gleason score was 6 (range, 5–8). There was a mix of low (n=12), intermediate (n=4), high (n=2), and unknown (n=1) risk disease by D'Amico classification. Treatment with LDR brachytherapy was heterogeneous in terms of dose, radionuclide, adjuvant ADT, and combination with EBRT (Table 2). The mean time from implantation to recurrence was 5.25 years (range, 0.98–11.2 years) with a mean PSA of 4.37 ng/mL (range, 2.14–9.00 ng/mL) and a mean prostate volume of 19.0 cm^3 (range, 11.0–28.4 cm^3) at the time of recurrence. The mean time from implantation to mpMRI was 7.9 years (range, 1.1–15.8 years). Mean PSA at the time of mpMRI was 6.2 ng/mL (range, 0.17–22.6 ng/mL).

A total of 62 lesions were identified by 5 radiologists in 19 patients (mean, 3.26 lesions per patient; range, 1–6 lesions). Of these, 3 lesions identified in the SV did not have pathologic correlation and were therefore excluded from further analysis. Of the 59 remaining mpMRI lesions, 16 (27.1%) were identified in the peripheral zone (PZ), 33 (55.9%) in the transition zone (TZ), and 10 (16.9%) in the SV.

With regard to biopsy confirmation, 14 patients underwent systematic and MRI/TRUS fusion biopsy, 4 patients underwent systematic biopsy only, and 1 patient had a fusion biopsy alone (Table 2). Following biopsy, 4 patients underwent a radical prostatectomy and 1 underwent SV resection. Fifteen (78.9%) patients had at least one pathologically confirmed lesion on mpMRI. Among the 15 patients with local recurrence, there were 34 lesions confirmed as recurrent prostate cancer pathologically, 30 of which were identified by mpMRI, with a mean of 2.26 confirmed lesions per patient (range, 1–6 lesions).

Patient-based sensitivity and specificity of mpMRI, stratified by reader-designated cancer likelihood score, is shown in Table 3. Sensitivity and specificity were influenced by likelihood of malignancy groupings. With all lesions included, the average sensitivity was 88% (SE, 3.5%), and average specificity was 25% (SE, 13.3%). With a threshold of only high-likelihood lesions, specificity increased to 75% (SE, 16.5%).

Taking all readers in consensus, 30 of 34 pathologically detected lesions were detected by at least one reader (88.2%). Of the four lesions not detected, two were discovered at prostatectomy in the SV, and two were detected at random biopsy in the PZ. Of the two missed intraprostatic lesions, both were in patients with diffuse disease and all cores positive on systematic biopsy (Supplemental Fig. 1).

On lesion-based analysis, true positive and false positive interpretations were numerous and occurred in multiple locations throughout the gland (Supplemental Fig. 2). Lesion-based PPVs of mpMRI stratified by reader-designated cancer likelihood score are presented in Table 3. With enrichment of high-likelihood lesions, the duplicate readers demonstrated no significant increase in PPV ($P = 0.55$) compared with the initial radiologist that evaluated the mpMRI images as part of routine clinical practice. When the lesion identifications of all readers were considered together, mpMRI yielded a PPV of 62% (SE, 6.7%) for all lesions. The PPV improved to 78.7% (SE, 10.3%) for lesions designated as high-likelihood of malignancy by readers of multiple experience levels. When considering lesion identification based on mpMRI sequence, there was no evidence that DWI and T2-weighted imaging performed better than DCE in identifying biopsy-confirmed recurrent disease, with PPVs of 70% (SE, 7.3%), 66.6% (SE, 5.8%), and 64.9% (SE, 7.3%), respectively.

Table 2. Patient characteristics, treatment, and site of recurrence

Pt no	Age (yrs)	Race	Pre-BT Gleason score	Pre-BT PSA	D'Amico risk grouping	Total BT dose (Gy)	Radionuclide	Prostate D90 (Gy)	Prostate V100 (%)	EBRT dose (Gy)	ADT	Total lesions identified	mpMRI lesions identified	True positive mpMRI identifications	Pathology sample by
1	61	White	6	6.8	Low	145	I-125	173.9	99.7	N/A	No	4	3	3	SB, FB, RP
2	71	White	6	9.4	Low	145	I-125	176.6	99.9	N/A	No	2	2	0	SB, FB
3	57	Black	6	6.1	Low	125	Pd-103	NR	NR	N/A	No	4	4	0	SB, FB
4	62	White	6	4	Low	100	Pd-103	104.1	91.9	N/A	No	1	1	1	SB, FB
5	63	White	5	6	Low	115	Pd-103	NR	NR	N/A	No	2	2	0	SB
6	77	Asian	6	4.4	Low	145	I-125	171.5	97.2	N/A	No	4	3	3	SB
7	64	White	7	5.2	Intermediate	125	Pd-103	126.0	23.5	N/A	No	3	3	1	SB, FB
8	58	White	6	4.5	Low	125	Pd-103	NR	NR	N/A	No	3	3	0	SB
9	85	Black	8	12.99	High	100	I-125	85.0	90.0	52.5	No	4	3	3	SB, FB
10	64	White	7	7.4	Intermediate	125	Pd-103	127.0	91.1	N/A	No	4	4	1	SB, FB
11	62	White	7	4.9	Intermediate	145	I-125	160	100.0	N/A	No	6	6	1	SB, FB
12	65	White	6	3.6	Low	125	Pd-103	170.2	99.9	N/A	No	2	2	1	SB
13	73	White	7	31.1	Intermediate	80	Pd-103	NR	NR	46.8	Yes	3	3	2	SB, FB, RP
14	67	White	5	5.3	Low	115	Pd-103	100.0	76.0	N/A	No	2	2	1	SB, FB, SV
15	61	Black	6	3.4	Low	125	Pd-103	119.7	87.95	N/A	No	6	6	6	SB, FB, RP
16	67	Black	8	23	High	100	Pd-103	129.3	98.7	45	Yes	4	3	3	FB, RP
17	68	White	6	4.6	Low	125	Pd-103	113.9	83.6	N/A	No	4	4	1	SB, FB
18	75	White	6	5.8	Low	125	Pd-103	NR	NR	N/A	No	5	5	2	SB, FB
19	69	White	6	3.78	Low	125	Pd-103	162.9	98.5	N/A	No	3	3	1	SB, FB

Pt, patient; yrs, years; BT, brachytherapy; PSA, prostate-specific antigen; Gy, Gray; EBRT, external beam radiation therapy; ADT, androgen deprivation therapy; mpMRI, multiparametric magnetic resonance imaging; I-125, iodine-125; Pd-103, palladium-103; NR, no record (i.e., records from outside facilities not retained); N/A, not applicable; SB, standard of care biopsy; FB, MRI-ultrasound fusion biopsy; RP, radical prostatectomy; SV, seminal vesiculectomy.
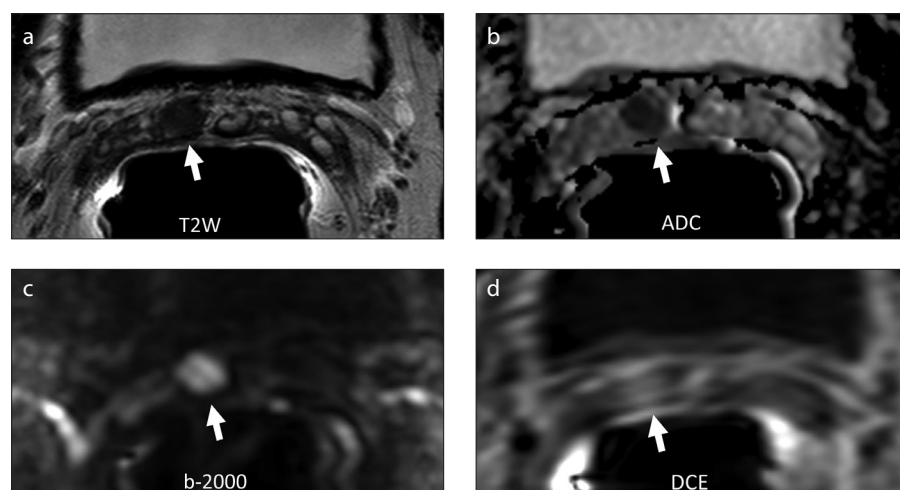

Figure 1. a–d. Multiparametric magnetic resonance imaging (mpMRI) of seminal vesicle recurrence after low dose rate brachytherapy. Axial T2-weighted MRI (**a**), apparent diffusion coefficient (ADC) map (**b**), b-2000 diffusion-weighted imaging (DWI) (**c**), dynamic contrast-enhanced imaging (DCE) (**d**) show a lesion in the right seminal vesicle *(arrow)* in a 67-year-old man with serum PSA=3.25 ng/mL. Findings are consistent with recurrent prostate cancer within the right seminal vesicle. This lesion was pathologically confirmed as recurrent prostate cancer.

Agreement between all readers is shown in Supplemental Table 1. On a per patient basis, readers demonstrated an agreement of 54.4% (SE, 11.9%) for the presence or absence of disease. For scoring each parameter, all readers demonstrated good agreement ranging from 71.9% to 81.1% with agreement on DCE reaching 81.1% (SE, 5.7%). Readers exhibited greater variation for the location of a detected lesion, with only moderate agreement at 48.2% (SE, 5.4%). On a per patient basis, moderately experienced readers had higher agreement than highly experienced readers (69.8% [SE, 16.1%] vs. 43.5% [SE, 13.1%], *P* = 0.121). Nevertheless, on the lesion basis, highly experienced readers tend to agree more often than moderately experienced readers (53.6% [SE, 8.5%] vs. 38.6% [SE, 8.5%], *P* = 0.234).

In terms of patterns of recurrence, of 30 true positive mpMRI lesions, 7 (23.3%) were located in the PZ, 14 (46.7%) were located in the TZ, and 9 (30%) were located in the SV (Table 4). Within the SV, there was a high prevalence of true positive lesions relative to false positive lesions (77.8% and 11.1%, respectively, Supplemental Fig. 2), with a representative SV lesion shown in Fig. 1. Accordingly, the average PPV for SV invasion was 88.5% compared with 57.1% PPV for PZ

Table 3. Performance of multiparametric MRI

	Initial reader	Average of independent readers	Average of initial and independent readers
Patient-based sensitivity (SE)			
Low, intermediate, & high likelihood lesions	93.3 (6.3)	86.7 (4.3)	88 (3.5)
Intermediate & high likelihood lesions	66.7 (12.0)	76.7 (4.9)	74.7 (5.6)
High likelihood lesions	13.3 (8.6)	43.3 (8.7)	37.3 (7.9)
Patient-based specificity (SE)			
Low, intermediate, & high likelihood lesions	25 (21.2)	25 (12.8)	25 (13.3)
Intermediate & high likelihood lesions	25 (21.2)	56.2 (18.7)	50 (16.8)
High likelihood lesions	75 (21.8)	75 (15.4)	75 (16.5)
Lesion-based positive predictive value (SE)			
Low, intermediate, & high likelihood lesions	66.7 (8.5)	60.8 (7.6)	62.0 (6.7)
T2WI	60.0 (9.2)	68.3 (6.7)	66.6 (5.8)
DCE	62.5 (9.7)	65.5 (8.3)	64.9 (7.3)
DWI	52.4 (10.0)	74.4 (8.6)	70.0 (7.3)
Intermediate & high likelihood lesions	57.9 (10.9)	68.9 (8.0)	66.7 (6.9)
High likelihood lesions	66.7 (29.2)	81.7 (7.3)	78.7 (10.3)

Data are presented as percentage.
SE, standard error; T2WI, T2-weighted imaging; DCE, dynamic contrast-enhanced imaging; DWI, diffusion-weighted imaging.

Table 4. Patterns of recurrence

	True positive lesions n (%)
Lesion laterality	
Left	12 (40)
Right	12 (40)
Midline	6 (20)
Lesion zone	
TZ	14 (46.7)
PZ	7 (23.3)
Lesion level	
Apex	10 (33.3)
Mid	18 (60)
Base	9 (30)
Lesion location	
Anterior	8 (26.7)
Posterior	13 (43.3)
Seminal vesicle invasion	
Yes	9 (30)

TZ, transition zone; PZ, peripheral zone.

and 52.2% PPV for TZ. Additionally, of the 14 true positive lesions localized in the TZ, 8 were located anterior to the urethra (Table 4, Fig. 2). True positive lesions in the apex accounted for 33.3% of the lesions (representative image in Fig. 3).

Discussion

MRI has an increasing role in the diagnosis and management of prostate cancer (14). Because of concern for MRI artifact caused by brachytherapy seeds, mpMRI is rarely used in the setting of biochemical re-

currence following this treatment. We present evidence of the feasibility and efficacy of prostate mpMRI in the setting of biochemical recurrence after LDR brachytherapy.

In this cohort, we found an average patient-based sensitivity of 88% (SE, 3.5%) for 5 radiologists of varying experience with 54.4% agreement between readers. This observation suggests mpMRI is moderately effective in detecting local recurrence in patients after LDR brachytherapy. Detected lesions were likely to represent recurrent cancer, especially at high suspicion levels, reaching a PPV of 78.7%. However, mpMRI was not highly specific for patients without evidence of local recurrence (25% for all lesions, 75% for high likelihood lesions). This finding is limited by the fact that our cohort included only 4 patients without biopsy confirmed recurrence. Furthermore, as readers were only asked to detect positive lesions, no lesion-based negative identifications were included in this study design.

Our results demonstrate that mpMRI is somewhat less effective in the post-LDR brachytherapy setting compared with after high dose rate (HDR) brachytherapy and EBRT. In a series of 16 patients who underwent HDR brachytherapy, the consensus sensitivity of 2 readers for detecting recurrence was 77%, and the PPV was 68% (15).
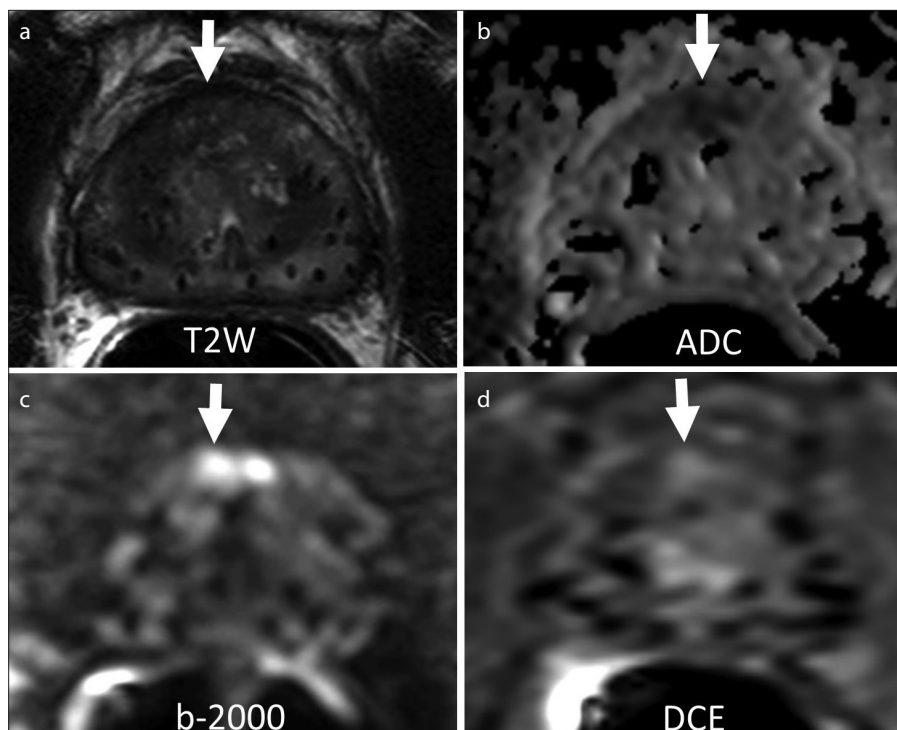
Figure 2. a–d. mpMRI images of recurrence after prostate LDR brachytherapy. **(a)** Axial T2-weighted MRI, **(b)** ADC map, **(c)** b-2000 DWI, and **(d)** DCE show an intraprostatic lesion within the midline mid anterior transition zone *(arrows)*, consistent with recurrence, in a 69-year-old man with serum PSA=2.56 ng/mL. The lesion was pathologically confirmed as recurrent prostate cancer.
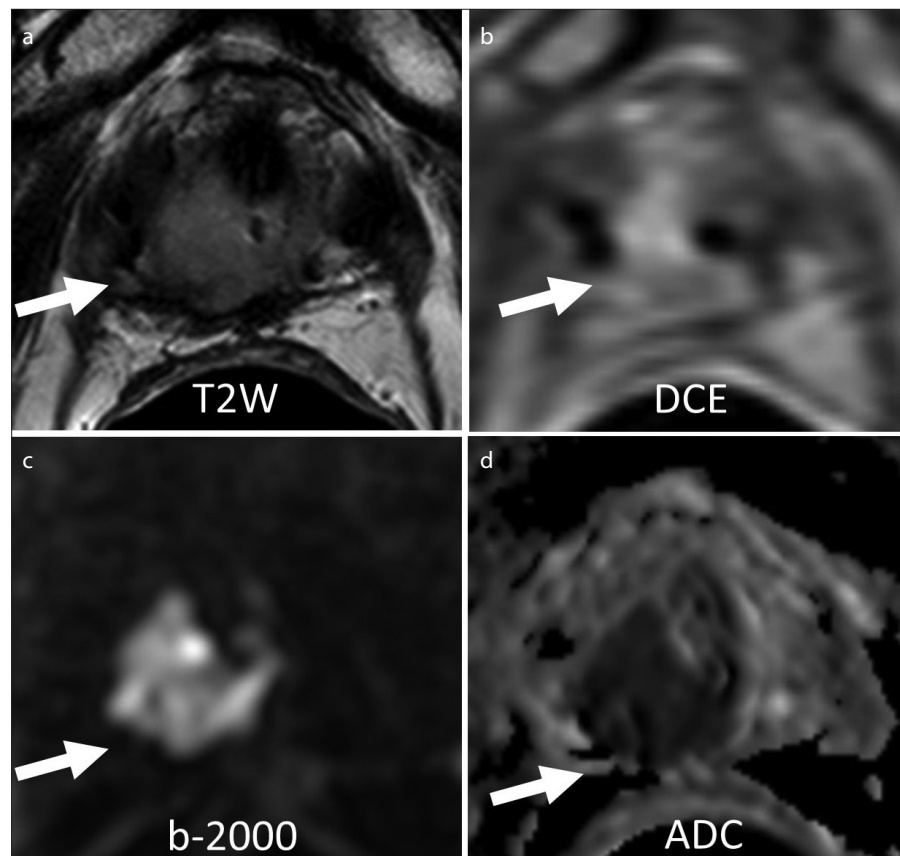

Figure 3. a–d. mpMRI images of recurrence after prostate LDR brachytherapy. **(a)** Axial T2-weighted MRI, **(b)** DCE, **(c)** b-2000 DWI, and **(d)** ADC map show an intraprostatic lesion *(arrows)* within the apex in a 78-year-old man with serum PSA=11.97 ng/mL. The lesion was pathologically confirmed as recurrent prostate cancer.

Our consensus sensitivity was comparable at 88.2%. Average PPV was also comparable at 62%. In mpMRI after EBRT, a series of 37 men with biochemical recurrence demonstrated a sensitivity of 76%–80%, a PPV of 68%–72%, and a kappa of 0.722 between two readers (16). Importantly, when examining only lesions at high likelihood to represent recurrence, our PPV improved substantially to 78.7%, suggesting that careful risk-stratification of lesions at initial interpretation can help overcome the effects of seed distortion on the cancer detection rate. Our reported PPV also compares favorably to that observed in the setting of untreated prostate cancer (17), despite artifacts from permanently implanted seeds.

mpMRI includes a number of sequences, and it is possible that the artifact introduced by brachytherapy seeds may further alter the performance of certain sequences while minimally impacting others. Radiation-induced changes have been demonstrated to cause diffuse T2-weighted signal hypointensity, limiting the diagnostic capability of T2-weighted imaging (18). Indeed, in our study T2-weighted imaging did not perform as well as other parameters, but interestingly, DWI trended towards a higher cancer detection rate at 70% compared with 66.6% for T2-weighted imaging and 64.9% for DCE. Although the differences between PPVs of sequences were not significant, this trend suggests true positivity relied on DWI, which depends on minimal gland distortion from metallic artifact. As the anterior prostate and SV are the most visible after seed implant, and under-sampled by systematic biopsies, DWI may play an important role in detecting recurrent cancer after mpMRI. Regardless, these data support that interpretation relying on multiple sequences may optimize interpretation.

Prior reports have suggested that DCE may be superior for detecting recurrent cancer after radiation therapy, given that the enhancement of post-radiation fibrosis is "slow and low", which offers a good contrast with the usually hypervascular recurrent cancer (14). Other studies have examined mpMRI efficacy after EBRT (19–22), and observed DCE to be a valuable sequence. Our results suggest that DCE may be easy for radiologists to interpret (81.1% agreement), though its relative low PPV (64.9%) suggests that metallic seed distortion may limit its interpretation. It is possible that the discrepancy between our findings and others resulted from a more heterogeneous decrease

in prostate vascularization after brachytherapy compared with EBRT, making it more difficult to interpret post-brachytherapy DCE (22).

Importantly, mpMRI was also likely to correctly identify lesions in locations that are not typically sampled by systematic biopsy, such as SV, TZ, and other locations anterior to the urethra. These findings highlight the potential utility of mpMRI as a diagnostic strategy to guide biopsy if local salvage options are considered. The increasing interest in the use of focal therapies or focal salvage approaches (23–26) necessitates a clear understanding of sites of recurrence to maximize efficacy. Further, the patterns of recurrence may have implications for the treatment of patients with brachytherapy.

A finding of particular interest in our study is the pattern of recurrence. Of the 30 true positive lesions in our cohort, 23.3% were in the PZ, 46.7% in the TZ, and 30% in the SVs. This finding may be due to a higher proportion of seeds deployed in the PZ with resultant artifact and glandular atrophy that complicate interpretation. Alternatively, the recurrence pattern may be related to the brachytherapy technique. The portion of the prostate anterior to the urethra may be relatively under-dosed with traditional transperineal approaches due to the need to avoid the course of the urethra (23). Loading patterns that spare the urethra may also unintentionally under-dose tumor in the TZ. The use of preimplant MRI may assist in the identification of lesions that may not be adequately treated with an implant or that may require a modified loading to enhance treatment efficacy.

Another concerning finding in this small patient subset is the frequency of SV recurrence. Pathologically confirmed SV invasion was found frequently, despite the majority of patients being classified as low-risk at the time of treatment. As few patients underwent MRI before treatment, the incidence of occult SV invasion pretreatment cannot be determined. It is possible that SV invasion occurred as a result of direct extension of an intraprostatic recurrence. Regardless, the frequency of SV recurrence in this study raises a concern that the SVs were undertreated. Even in the combined EBRT and brachytherapy setting, the doses delivered to the majority of the SVs is below 50 Gy. Although this dose may be sufficient in the vast majority of patients based on the low rate of recurrence after brachytherapy, it is possible that pretreatment MRI may

identify patients at highest risk of occult SV invasion for which alternative treatment approaches may be preferred.

This study has some limitations. The conclusions are based upon a small number of patients and thus our results require validation in larger series. Additionally, pathologic confirmation of disease relied predominantly on systematic and targeted biopsies, as not all patients underwent radical prostatectomy. Biopsy results alone likely underestimate true positive identifications, and this may have contributed to the false positive identifications we report. Although including multiple readers adds complexity to our analysis, we felt it important to include a broad range of readers with varying experience to decrease subjectivity and to increase applicability of our findings. Finally, our patient population was heterogeneous in terms of initial treatment characteristics and method of confirmatory biopsy.

In conclusion, we demonstrate that mpMRI after LDR brachytherapy recurrence is feasible and effective in our small series. Seed distortion cannot be discounted, but in areas not influenced by metallic artifact, DWI can be a valuable sequence for identifying true positive lesions. Patterns of recurrence suggest anterior prostate as well as the SV should be areas of focus for optimizing initial diagnosis and treatment as well as detecting recurrence.

Funding

Conflict of interest disclosure

The authors declared no conflicts of interest.

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