

Predictors of prostate bed recurrence on magnetic resonance imaging in patients with rising prostate-specific antigen after radical prostatectomy

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Abstract

Introduction: Radical prostatectomy (RP) is a standard treatment modality for localized prostate cancer. Biochemical failure after RP is usually evaluated with whole body imaging to exclude distant metastatic disease, and pelvic magnetic resonance imaging (MRI) to detect local recurrence in the prostatectomy bed. The goal of this study is to correlate disease characteristics and demographic data in patients with rising prostate-specific antigen (PSA) after RP to determine association with MRI-detected cancer recurrence.

Methods: Sixty-four patients who underwent pelvic MRI for rising PSA after RP and had complete clinical and pathological data available were included. Using Chi-squared testing, we analyzed PSA levels, pathological disease characteristics (prostate cancer risk group, Gleason score, extracapsular extension, positive surgical margin, seminal vesicle involvement, perineural invasion, lymphovascular invasion, and PSA level before MRI), time from surgery to biochemical failure, and patient demographic characteristics as potential predictors of MR-detected local recurrence.

Results: Definite MRI-detected local recurrence was observed in 17/64 patients (27%). Eleven (17%) patients had a suspicious lesion with the differential of scarring, retained seminal vesicle, or recurrent cancer. Thirty-six (56%) patients had no evidence of tumor in the prostate bed or pelvis on MRI. Patient race was associated with likelihood of detecting a prostate nodule on MRI ($p=0.04$), with African-American patients having 82% lower odds of MRI-detected tumor

recurrence compared with White patients ($p=0.045$). No other tumor or patient characteristic was significantly associated with MRI-detected recurrence.

Conclusions: African-American patients with biochemical failure after RP are less likely to have MRI-detectable recurrence in the prostate bed compared with White patients.

Introduction

Prostate cancer is the most prevalent non-cutaneous malignancy among men¹. Primary treatment options for localized prostate cancer include radical prostatectomy (RP)² or radiation therapy (RT), which may involve external beam RT³ or brachytherapy^{4,5}.

Prostate Specific Antigen (PSA) is a human tissue kallikrein expressed in normal and malignant prostate tissues, which becomes undetectable after successful RP⁶. Elevated PSA in blood samples from undetectable levels after RP, termed biochemical failure, suggests recurrence of prostate cancer. Standard workup of a rising PSA after RP includes pelvic imaging, most commonly MRI, to detect local recurrence within the surgical bed and pelvic lymph nodes, and whole-body imaging to evaluate for distant metastatic bone disease. Whole-body imaging techniques include technetium-99m-MDP bone scan and positron emission tomography (PET) scan using prostate-specific membrane antigen (PSMA), C-11 choline, or F-18 fluciclovine^{7,8}.

Patients with biochemical failure and no evidence of distant metastatic disease are usually treated with salvage RT to the prostate bed with curative intent. Because RT targeted to the prostate bed does not eradicate distant metastatic disease⁹, a visible nodule in the prostate bed suggests localized recurrence and, thus, potentially increased chance of cure with salvage RT. Previous data suggest salvage RT is associated with a three-fold increase in prostate cancer-specific survival relative to patients who received no salvage treatment¹⁰. More than 60% of patients who are treated before the PSA level rises above 0.5 ng/mL will achieve an undetectable PSA level after salvage RT^{8,11}. Initiating RT when PSA is low (e.g. <0.5 ng/mL) has also been shown to improve overall survival¹².

Prostate bed RT doses of 64-72 Gy are commonly recommended^{13,14}, since a multi-institutional observational study demonstrated that a salvage radiation dose of ≥ 66.0 Gy was associated with reduced incidence of biochemical failure, but not of distant metastasis¹⁵. Biochemical control rates following salvage RT increase with higher RT dose and decrease with higher pre-treatment PSA¹⁶. Clinical practice guidelines¹⁴ also suggest treating prostate bed nodules that are visible on imaging at the time of recurrence with additional RT, either via simultaneous integrated boost or sequential boost techniques, although no randomized studies have been published demonstrating that boost RT improves control or survival rates¹⁷.

Information on predictors of MRI-detected local recurrence may be helpful to guide treatment decisions for patients with biochemical failure after RP. In this study, we investigated factors predictive of MRI-detectable prostate bed nodules among patients with rising PSA after RP.

Methods

Patient population

The Montefiore-Einstein Institutional Review Board (IRB) approved this retrospective, Health Insurance Portability and Accountability Act (HIPPA)-compliant analysis, and the need for informed consent was waived. All patients with biochemical failure who underwent MRI of the pelvis after having had a previous RP at a single tertiary care center between January 2013 and December 2017 were included in this study. Patients were identified using a commercial decision support tool (Looking Glass Clinical Analytics, Streamline Health), and the following data were collected for all eligible patients:

1. Demographics: Birthdate, race, ethnicity, and date of RP.
2. PSA blood levels: PSA values before and after RP, nadir PSA, time to nadir PSA, and PSA near the MRI scan.
3. Pathology reports (from RP): Gleason Score, resection margin involvement, seminal vesicle (SV) involvement, extracapsular extension (ECE), lymphovascular invasion (LVI) and perineural invasion (PNI).

MRI scans

Clinical MRI reports were reviewed, including the provided clinical indication. Exams are read by faculty radiologists (n = 5 during the study period) with fellowship training and expertise in abdominal imaging, each with 3 or more years of post-fellowship experience in MRI of the prostate. Each exam was read and approved by one of the five radiologists.

At our institution, prostate MRIs are performed on 1.5T or 3T scanners (Ingenia, Philips Healthcare, Best, Netherlands) using multiparametric techniques. During the study period, the examinations were performed in accordance to technical specifications proposed by the Prostate Imaging-Reporting and Data System (PI-RADS) manual. Multiparametric MRI included small field-of-view axial, coronal, sagittal T2-weighted images, axial diffusion-weighted sequences, dynamic contrast-enhanced sequences, and large field-of-view axial pre- and post-contrast T1-weighted images through the entire pelvis. Recurrence was identified as asymmetric area with differential signal intensity, detected on any of the obtained sequences. The examinations are performed with a surface coil, but without an endorectal coil.

Patients with suspected prostate cancer recurrence were included in the study. Included patients had not undergone RT to the prostate or pelvis prior to their MRI to investigate prostate cancer recurrence. Based on the radiology report, patients were classified as having definite

recurrent disease, no recurrent disease, or equivocal for recurrent disease. Patients with definite recurrent disease were those where MRI definitively demonstrated a recurrent tumor, patients with no recurrent disease were those with no detectable abnormality to suggest macroscopic recurrence, and patients with findings equivocal for recurrent disease were those with a reported asymmetric abnormality on MRI, with the differential of scarring, retained SV or recurrent cancer.

Patients were stratified into risk groups (low, favorable intermediate, unfavorable intermediate, high, and very high) according to the National Comprehensive Cancer Network (NCCN) guidelines based on preoperative PSA, Gleason score, ECE, and SV involvement ¹⁴.

Statistical analysis

Patients' clinical and demographic data were summarized numerically using descriptive statistics. Continuous scale variables that are normally distributed were summarized using mean and standard deviation, while median and range were used for variables that were not normally distributed. Three sets of sensitivity analyses were performed by categorizing those patients with equivocal MRI findings as (i) definite recurrence, (ii) no recurrence, and (iii) excluding them from the analysis entirely. Comparison of clinical characteristics between patients MRI confirmed recurrence and those with negative results were tested using student t-test; non-normal variables were tested using Wilcoxon rank-sum test. Categorical variables were tested either using chi-square test or Fisher's exact test as appropriate. A logistic regression model was fitted to examine the association between recurrence and covariates.

Results

Initially, 76 patients were identified by CLG software. Eleven patients were excluded from analysis: seven patients did not have previous prostate cancer, one patient had an intact prostate visible on MRI, one patient received hormonal therapy before radical prostatectomy, and for two patients the pathology was not available. One patient was found to have low-risk disease and was excluded from analysis. Figure 1 shows a Consolidated Standards of Reporting Trials (CONSORT) diagram describing patient inclusion in this study. Sixty-four patients had pelvic MRI after RP for evaluation of prostate cancer recurrence and had complete data available. Clinical and demographic characteristics are presented in Table 1. The average age of patients at the time of RP was 59.6 years (range 40-76). Median PSA prior to surgery was 9.8 ng/ml (range: 0.46 - 114). Two-thirds of the patient had high or very high-risk disease (per NCCN criteria) at the time of RP.

MRI recurrence results

Definite local recurrence of prostate cancer on MRI was found in 17 (27%) of 64 patients (Table 2). Representative images of these tumor recurrences are presented in Figure 2. Thirty-six (56%) had no evidence of recurrence on MRI. Eleven (17%) had MRI report with findings equivocal

for recurrence (Table 2).

For the primary analysis, we considered patients with equivocal MRI findings as definite recurrence (Table 3, Sample 1). In this analysis, MRI-confirmed local disease was observed more often among white patients compared with African American patients (70% vs 30%). Compared with white race, the estimated odds of MR-detected local disease were 82% less among African American patients (OR = 0.18, 95% CI: 0.04-0.96, $p = 0.045$), and 77% less among Hispanic patients (OR = 0.23, 95% CI: 0.05-1.10, $p = 0.065$).

Two secondary sensitivity analyses were performed. In the first sensitivity analysis, patients with equivocal MRI results were considered as negative (Table 3, Sample 2). MRI-confirmed local disease was observed more often among white patients compared with African American patients (50% vs 15%). Compared with white patients, the estimated odds of MR-detected local disease were 82% less among African American patients (OR = 0.176, 95% CI: 0.03-1.01, $p = 0.0513$), and 76% less among Hispanic patients (OR = 0.238, 95% CI: 0.05-1.15, $p = 0.0745$).

In the second sensitivity analysis, patients with equivocal MRI results were not included (Table 3, Sample 3). MRI-confirmed local disease was observed more often among white patients compared with African American patients (63% vs 18%). Compared with white patients, the estimated odds of MR-detected local disease were 87% less among African American patients (OR = 0.129, 95% CI: 0.02-0.86, $p = 0.0342$), and 82% less among Hispanic patients (OR = 0.176, 95% CI: 0.03-1.15, $p = 0.0513$).

None of the other examined characteristics including prostate cancer risk group, Gleason score, ECE, positive surgical margin (defined as tumor present at the inked margin), SV involvement, PNI, LVI, and PSA level before MRI were significantly associated with MRI-detected recurrence in any of our three analyses. Results of all three analyses are shown in Table 3.

Discussion

In this retrospective cohort of patients with rising PSA after radical prostatectomy, 27% of patients were found to have MRI-detectable prostate bed recurrence, while 17% had a radiologically-apparent nodule equivocal for disease recurrence. Logistic regression modelling found that patients' self-declared race and ethnicity was the only significant predictor of MRI-detected local recurrence, with African-American patients having 82% lower odds of MRI-detected tumor recurrence compared with white patients. A trend toward lower MRI-detected recurrence rates among Hispanic patients was also seen, although did not reach statistical significance. Other factors which are predictive of outcomes in prostate cancer such as PSA level, Gleason score, surgical margin status, and prostate cancer risk group did not predict MRI-detectable local recurrence in our cohort. This finding may be due to the relatively small number of patients, the retrospective nature of our study or due to different tumor biology presenting

among different patient populations (e.g. higher propensity for African American patients to develop aggressive prostate cancer and recur distantly).

Known risk factors for biochemical failure after RP include PSA level before surgery, Gleason score, seminal vesicle involvement, extracapsular extension, positive surgical margins, and perineural involvement¹⁸⁻²². Anscher et al.²³ found that positive surgical margins, poorly differentiated histology, and elevated acid phosphatase were significant predictors of local recurrence after prostatectomy. Stephenson et al.⁹ found that positive surgical margins, long PSA doubling time (>10 months), and PSA level <2 ng/mL at the time of salvage treatment were positive predictive factors for survival after salvage RT following BF. Because RT acts only locally in the prostate bed, in the case of salvage RT, improved salvage rates among patients with these risk factors suggests higher likelihood of local recurrence (compared to metastatic spread) in patients with these factors.

Previous studies have investigated recurrence patterns and risk factors for local compared with distant recurrence after BF. Giovacchini et al.²⁴ used C-11 choline PET to investigate patterns of recurrence in patients with biochemical failure after RP. Prostate bed recurrence was observed in 55/368 patients (15%) compared with 107 (29%) patients with lymph node recurrence and 46 (13%) with recurrence in the bones. PET/CT or PET/MRI with C-11 choline could provide more data with regard to recurrences in the prostate bed by correlating anatomic and metabolic data. A retrospective study that investigated the clinical impact of C-11 choline PET/CT on treatment management decisions in patients with recurrent prostate cancer after radical therapy, showed that it led to an overall treatment change in 46.7% of patients, with a major clinical change implemented in 18% of patients (such as changing the decision of palliative androgen deprivation therapy, before C-11 choline PET/CT to salvage therapy after PET/CT)²⁵.

Hernandez et al.²⁶ reported on a cohort of 70 patients from Spain imaged with multiparametric MRI. Mean PSA before MRI was 0.38 ng/mL. Local recurrence was identified in 33 patients (47%). No factors predicted for detectable prostate bed nodules including PSA, pathologic cancer stage, lymph node positivity, Gleason score, bladder neck involvement, LVI, location of surgical margin or whether pelvic lymph node dissection was performed²⁶. Our results, from a cohort with similar characteristics to this study, also suggested a similar lack of predictive ability of pathologic and PSA markers for predicting MRI-detectable local recurrence.

Endorectal MRI (eMRI) has been suggested as an improved method for detecting local recurrence after RP, with reported sensitivity and specificity ranging from 84-97% and 74-100%, respectively²⁷⁻³⁰. Using a variety of sequences obtained with 3T eMRI including T2-weighted imaging, dynamic contrast-enhanced (DCE), and diffusion-weighted imaging (DWI), Kitajima et al.³¹ studied a cohort of 80 patients with evidence of recurrence based on biopsy, PSA reduction after salvage treatment (e.g. RT), or MRI finding of a growing suspicious pelvic lesion. In this cohort of patients with high suspicion of local recurrence, eMRI detected recurrence in 57/80

patients (71%). The PSA value at the time of MRI in this cohort was higher than in our cohort (mean 1.17 ng/mL and median 0.43 ng/mL versus 0.8 ng/mL and 0.3 ng/mL in our cohort, respectively). Liauw et al.³² studied 88 men with detectable PSA after RP without clinically palpable disease who agreed to undergo eMRI. The mean PSA value before MRI was 0.3 ng/mL. Using eMRI, 24% of patients had detectable local recurrence. Univariate analysis suggested that the highest post-operative PSA value was a significant predictor of local recurrence, with 0.3 ng/mL acting as the most predictive cut-off. Age, Gleason score, T stage, N stage, positive surgical margins, and MRI magnet strength (1.5 vs 3 T) were not predictive. Race/ethnicity was not studied.

In our cohort, eMRI was not used. Mean PSA prior to MRI was 0.3 ng/mL in our cohort, similar to that measured in Hernandez et al.²⁶ (without eMRI) and Liauw et al.³² (with eMRI). Definite evidence of recurrence was seen in 27% of patients in our cohort, similar to the 24% detected by Liauw et al.³² but lower than the 47% reported by Hernandez et al.²⁶. The difference between the rates reported by Hernandez et al. and our study could be that 17% of our patients had equivocal disease recurrence which may have been reported as positive in that cohort.

The relationship between race and prostate cancer has been previously studied. One previous report found that African Americans have higher rates of recurrence following RP³³. Another recent study found that, after adjustment for nonbiological differences (notably access to care and standardized treatment), African-American patients did not have different stage-for-stage prostate cancer specific mortality³⁴. Steele et al.³⁵ reported that among 1,527,602 prostate cancers diagnosed between 2001 and 2009 in the USA, the proportion of localized cases increased from 73% to 77% in black males and from 77% to 79% in white males, compared to the years 1990-1994³⁶, and net survival exceeded 99% for localized stage in both racial groups.

The differences in prostate cancer rates by race, ethnicity, and geography may be explained by variation in access to screening and treatment as well as variation in the underlying biology of prostate carcinogenesis. Some groups have a genomic propensity to develop biologically aggressive disease, with men of African descent having higher prostate cancer incidence and poorer prognosis due to more aggressive disease at diagnosis³⁷. These factors could account for the differences in the patterns of recurrence with relation to race reported in our study, since African-American patients may be more likely to harbor micrometastatic disease at initial diagnosis, leading to higher rates of distant failure rather than local failure when disease recurs.

Our results suggest that African-American patients with biochemical failure after RP may be less likely to have MRI-detectable recurrence in the prostate bed compared with white patients. Analysis of subsequent survival data can help us understand if patients with an imaging-detected prostate bed nodule have a higher chance of cure than those without a detectable nodule. Lack of a radiologically-detected macroscopic disease after biochemical failure suggests

microscopic disease recurrence, which may be associated with either local (and salvageable) recurrence or distant (non-salvageable) recurrence.

Serum PSA levels should be undetectable after successful prostate cancer cure via radical prostatectomy. Any detectable PSA levels with currently available commercial essays should prompt investigatory imaging including pelvic MRI. Ultrasensitive PSA assays could be beneficial in detecting persistent PSA after radical prostatectomy^{38,39}.

We expect that patterns of local and systemic failure after prostate brachytherapy or external beam radiation therapy for prostate cancer would be similar to those observed in the cohort presented here. Proving this, however, would be more challenging as prostate biopsies (likely multiple) would be needed in addition to MRI to accurately detect and characterize local recurrence in the setting of an intact prostate.

The main limitations of our study are its retrospective nature and a relatively small cohort size, although our sample was similar in number to previous similar publications. We used the MRI clinical report to discriminate between patients with or without local recurrence, rather than reviewing the scans again. This method was used to reflect and be applicable to real-world clinical practice patterns. Larger prospective cohorts and longer follow-up will help further refine the factors predictive local recurrence and the significance of these predictions in personalizing treatments and improving outcomes for all prostate cancer patients.

Conclusions

African-American patients with biochemical failure after RP are less likely to have MRI-detectable recurrence in the prostate bed compared with white patients.

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Figures and Tables

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart. ADT: androgen deprivation therapy.

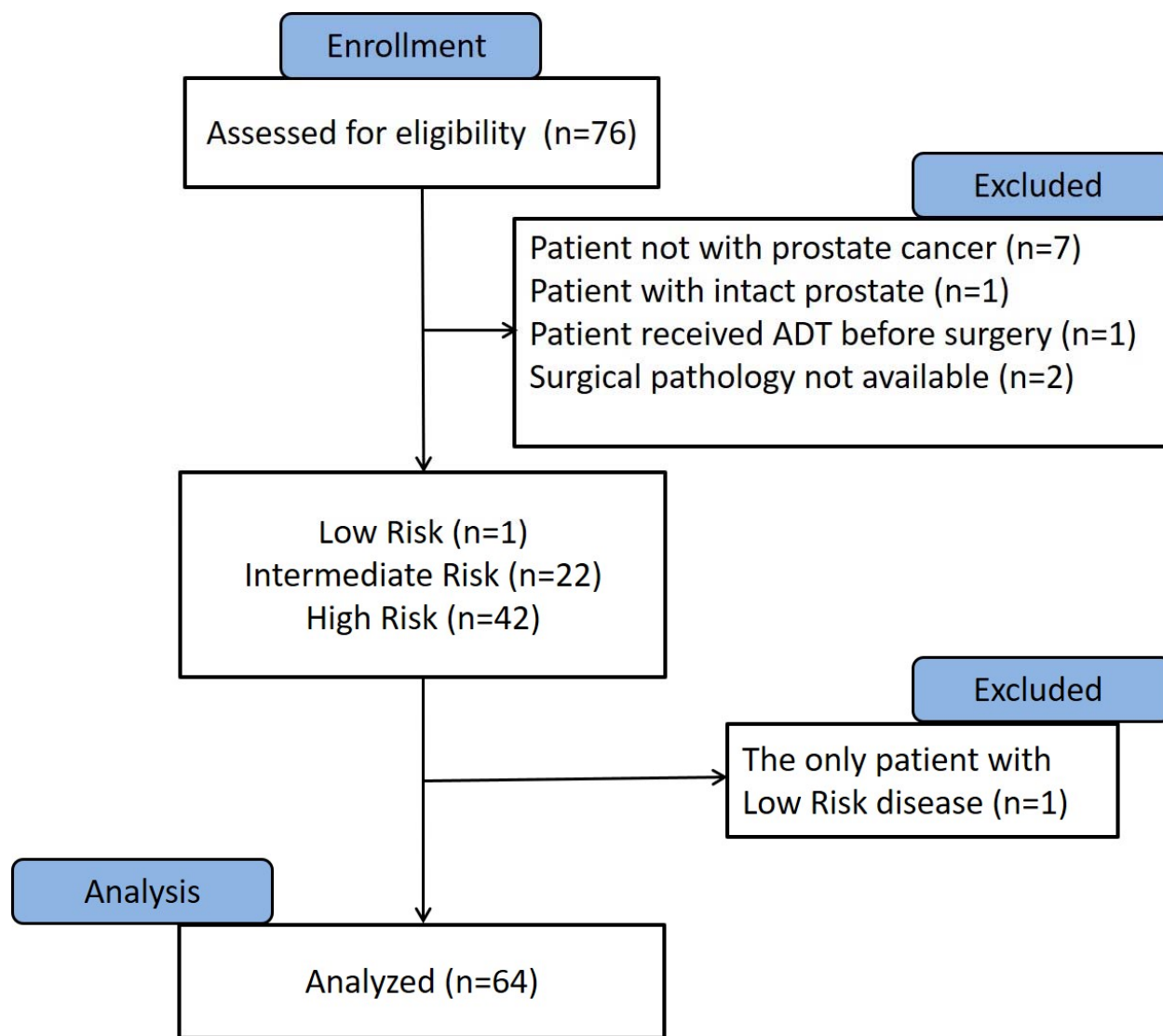


Fig. 2. Prostate bed nodule compatible with local recurrence of prostate cancer (white arrows) was found in 17 patients (27%). Representative images from 16 patients are presented.

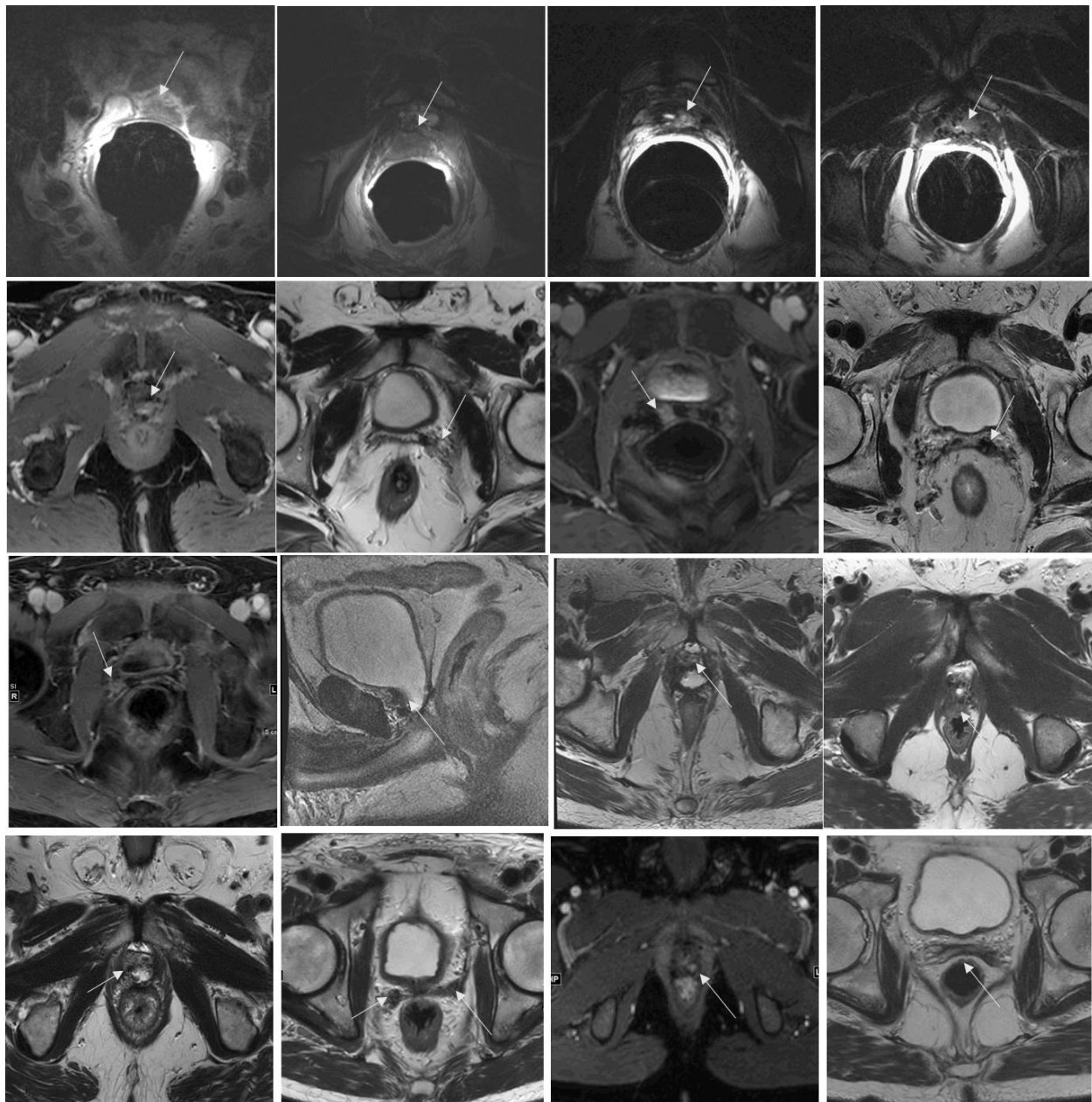


Table 1. Patient characteristics (n=64)		
Age at surgery mean(SD) years		59.6 (7.35)
Race	Hispanic	26 (41%)
	African-American	20 (31%)
	White/Other	10 (16%)
	Unknown	8 (12%)
Median PSA before surgery (ng/mL)		9.8 (range 0.46–114)
Gleason score at surgery	7	54 (84%)
	8	4 (6%)
	9	6 (10%)
ECE present		32 (50%)
Positive margin*		40 (63%)
SV involvement		14 (22%)
PNI		53 (83%)
LVI		14 (22%)
Risk group	Favorable-intermediate	9 (14%)
	Unfavorable-intermediate	13 (20%)
	High-risk	32 (50%)
	Very high-risk	10 (16%)
Median nadir PSA (ng/mL)		0.04 (range 0–1.4)
Median time to nadir PSA (days)		110 (range 25–1830)
Median time from surgery to prostate MRI (days)		653 (range 13–3638)
Highest PSA before MRI (ng/mL), median		0.3 (range 0–9.1)
Prostate MRI results	No local disease	36 (56%)
	Local disease present	17 (27%)
	Equivocal local disease	11 (17%)

*Defined as tumor at the inked surgical margin. ECE: extracapsular extension; LVI: lymphovascular invasion; MRI: magnetic resonance imaging; PNI: perineural invasion; PSA: prostate-specific antigen; SV: seminal vesicles.

Table 2. Location of definitive and equivocal recurrences detected on MRI		
	Definite recurrence, n=17 (%)	Equivocal recurrence, n=11 (%)
Prostatectomy bed	7 (41%)	5 (45%)
Adjacent to the urinary bladder	6 (35%)	1 (9%)
Urethral anastomosis	3 (18%)	2 (18%)
Superior aspect of urogenital diaphragm	1 (6%)	0
Perivesical space	0	3 (27%)

MRI: magnetic resonance imaging.

Table 3. Multivariate logistic regression MRI detection of local recurrence, and its association with race/ethnicity, risk group, Gleason score, ECE, surgical margin status, SV involvement, PNI, LVI, and PSA level before MRI						
	Sample 1*		Sample 2**		Sample 3***	
Covariates	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Race/ethnicity						
African American	0.18 (0.04, 0.96)	0.045	0.18 (0.03, 1.01)	0.051	0.13 (0.02, 0.89)	0.034
Hispanic	0.23 (0.05, 1.10)	0.065	0.24 (0.05, 1.15)	0.075	0.18 (0.03, 1.01)	0.051
Unknown	1.28 (0.16, 10.45)	0.814	1.00 (0.16, 6.42)	1.00	1.20 (0.13, 11.05)	0.872
White/Other	Reference		Reference		Reference	
High vs. low						
H/VH	2.14 (0.73, 6.32)	0.168	1.36 (0.41, 4.52)	0.616	1.71 (0.50, 5.90)	0.393
FI/UI	Reference		Reference		Reference	
Gleason score						
7	1.20 (0.30, 4.74)	0.795	0.48 (0.12, 1.95)	0.302	0.65 (0.16, 2.70)	0.553
>7	Reference		Reference		Reference	
ECE present						
Yes	1.82 (0.66, 4.99)	0.246	1.34 (0.43, 4.20)	0.613	1.61 (0.49, 5.26)	0.433
No	Reference		Reference		Reference	
Positive margins						
Yes	1.15 (0.41, 3.19)	0.795	2.41 (0.68, 8.49)	0.172	2.07 (0.56, 7.63)	0.275
No	Reference		Reference		Reference	

SV involvement						
Yes	1.45 (0.44, 4.78)	0.541	0.76 (0.18, 3.14)	0.699	0.96 (0.21, 4.29)	0.954
No	Reference		Reference		Reference	
PNI						
Yes	6.25 (0.72, 54.39)	0.097	2.76 (0.31, 24.41)	0.360	3.75 (0.42, 33.39)	0.236
No	Reference		Reference		Reference	
LVI						
Yes	0.48 (0.13, 1.74)	0.262	0.77 (0.18, 3.25)	0.725	0.63 (0.15, 2.69)	0.529
No	Reference		Reference		Reference	
PSA near MRI						
>0.3	0.52 (0.19, 1.41)	0.198	0.67 (0.22, 2.06)	0.485	0.56 (0.17, 1.80)	0.331
≤0.3	Reference		Reference		Reference	

OR, 95% CI, and p are provided for each parameter. Sample 1: equivocal MRI results counted as positives; sample 2: equivocal results counted as negatives; sample 3: equivocal results excluded from the analysis. *Equivocal MRI results counted as positives. **Equivocal results counted as negatives.

***Equivocal results excluded from the analysis. CI: confidence interval; ECE: extracapsular extension; LVI: lymphovascular invasion; MRI: magnetic resonance imaging; OR: odds ratio; PNI: perineural invasion; PSA: prostate-specific antigen; SV: seminal vesicle.