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Multiparametric MRI as a Biomarker of Response to Neoadjuvant Therapy for Localized Prostate Cancer—A Pilot Study

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Abstract

Rationale and Objectives—To explore a role for multiparametric MRI (mpMRI) as a biomarker of response to neoadjuvant androgen deprivation therapy (ADT) for prostate cancer (PCa).

Materials and Methods—This prospective study was approved by the institutional review board and was HIPAA compliant. Eight patients with localized PCa had a baseline mpMRI, repeated after 6-months of ADT, followed by prostatectomy. mpMRI indices were extracted from tumor and normal regions of interest (TROI/NROI). Residual cancer burden (RCB) was measured on mpMRI and on the prostatectomy specimen. Paired t-tests compared TROI/NROI mpMRI indices and pre/post-treatment TROI mpMRI indices. Spearman's rank tested for correlations between MRI/pathology-based RCB, and between pathological RCB and mpMRI indices.

Results—At baseline, TROI apparent diffusion coefficient (ADC) was lower and dynamic contrast enhanced (DCE) metrics were higher, compared to NROI (ADC: $806 \pm 137 \times 10^{-6}$ vs. $1277 \pm 213 \times 10^{-6} \text{ mm}^2/\text{sec}$, $p = 0.0005$; K^{trans} : 0.346 ± 0.16 vs. $0.144 \pm 0.06 \text{ min}^{-1}$, $p = 0.002$; AUC_{90} : 0.213 ± 0.08 vs. 0.11 ± 0.03 , $p = 0.002$). Post-treatment, there was no change in TROI ADC, but a decrease in TROI K^{trans} (0.346 ± 0.16 to $0.188 \pm 0.08 \text{ min}$; $p = 0.02$) and AUC_{90} (0.213 ± 0.08 to 0.13 ± 0.06 ; $p = 0.02$). Tumor volume decreased with ADT. There was no difference between mpMRI-based and pathology-based RCB, which positively correlated ($\rho = 0.74\text{--}0.81$, $p < 0.05$). Pathology-based RCB positively correlated with post-treatment DCE metrics ($\rho = 0.76\text{--}0.70$, $p < 0.05$) and negatively with ADC ($\rho = -0.79$, $p = 0.03$).

Conclusion—Given the heterogeneity of PCa, an individualized approach to ADT may maximize potential benefit. This pilot study suggests that mpMRI may serve as a biomarker of ADT response and as a surrogate for RCB at prostatectomy.

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Keywords

Androgen deprivation therapy; Multiparametric MRI; Prostate; Biomarker

INTRODUCTION

Androgens have been shown to stimulate key angiogenic events in male cells in vitro, sex-specific proangiogenic effects which are mediated via the androgen receptor (AR) (1). Recently, clinical studies have confirmed that advanced castrate-resistant prostate cancer (PCa) remains driven in most cases by AR signaling (2–4), and that the AR is an important therapeutic target in castrate-resistant PCa as well as in hormone sensitive disease (5). Enzalutamide (Xtandi, Medivation Inc., San Francisco, CA, USA) is a novel second generation AR antagonist that is approved for treatment of metastatic castrate resistant PCa (6), based on improvements in progression-free and overall survival (7,8). In addition to palliation of advanced disease, enzalutamide is currently being evaluated for potentially curative benefit in patients with earlier stage PCa (9). While neoadjuvant systemic therapy combined with surgery is exploratory in PCa (the “neoadjuvant paradigm”), it has been shown to improve overall survival in other malignancies (10–14). Given that PCa is a very heterogeneous disease, an individualized approach may be required to maximize potential benefits from novel and combination therapies. A validated metric that measures the optimal length of an individual’s neoadjuvant androgen deprivation treatment (ADT) would be of great benefit in an era where current predictive biomarkers are lacking (15).

Multiparametric MRI (mpMRI) of the prostate is well-known to play an important role in PCa detection, localization, and staging (16–20). There have been a handful of studies that have investigated the effects of ADT and subsequent radiation therapy on parameters such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) (21,22), but none to date have prospectively evaluated the effect of ADT mpMRI parameters, with full pathological correlation. Detailed correlative pathology is necessary, however, as mpMRI may be an optimal tool for assessing ADT response, as it provides unique and complementary information regarding tumor pathophysiology, beyond the anatomical depiction of tumor. DWI and its derived apparent diffusion coefficient (ADC) reflect cell membrane integrity and hypercellularity, and have been demonstrated on multiple occasions to inversely correlate with Gleason score and serve as a biomarker for prostate tumor aggressiveness (19,23–27). DCE-MRI, which reflects local vascularity/perfusion, also has unique capabilities, as focal areas of PCa have been shown to demonstrate early arterial enhancement compared to normal prostate tissue (28). In these areas of PCa, the number of vessels in tumor foci increase and areas of neovascularity have higher permeability and more heterogeneous architecture than do normal vessels (29). Considering that androgens stimulate key angiogenic events mediated through the AR, and that strategies to effectively ablate AR activity are called for (9), mpMRI (in particular DCE-MRI) may be an appealing noninvasive biomarker to assess the properties of the local cellularity and microcirculation that capture the heterogeneity of tumor and its response to treatment with androgen blockade (Figs. 1–3).

This pilot study was therefore performed to explore a role for prostate mpMRI as a biomarker of response to treatment of localized PCa with the neoadjuvant second-generation AR inhibitor enzalutamide.

MATERIALS AND METHODS

Patients

This prospective study was approved by the institutional review board and was HIPAA compliant. Eight patients with surgically resectable, localized adenocarcinoma of the prostate (T1c–T3, N0/NX, M0) with either a PSA > 10 ng/mL or Gleason score 7 (4 + 3) on standard systemic prostate biopsy, for whom radical prostatectomy was indicated and who had consented to a prospective, randomized, open-label phase 2 study of neoadjuvant enzalutamide ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01547299) Identifier: NCT01547299) were included in this study. This was a multi-center trial, but only consecutive subjects from a single institution (XXXXXX) were approached for consent to be part of this ancillary mpMRI study. Intergroup comparison between treatment groups was not part of this study.

Consent for both a baseline prostate mpMRI and for a second post-treatment mpMRI at 3T after conclusion of neoadjuvant therapy was obtained at the time of enrollment into the parent clinical trial. The second prostate MR occurred within a two-week window prior to prostatectomy. Subjects were randomized into two arms, receiving enzalutamide alone or triple therapy (enzalutamide in combination with leuprolide (Lupron, Abbott Laboratories, Chicago, IL) and dutasteride (Avodart, GlaxoSmithKline Inc., London, United Kingdom) as neoadjuvant therapy for 6 months prior to prostatectomy. Exclusion criteria included prior ADT, chemotherapy, surgery, or radiation for PCa, any contraindication to MR imaging, and nonconsent to having both mpMRIs.

MR Imaging

All MR imaging exams were performed on a GE Signa HDx 3.0T magnet (GE Healthcare, Waukesha, WI) using a combination of an eight-channel abdominal array and endorectal coil (Medrad, Pittsburgh, PA). The multiparametric protocol (16) included T₁- and T₂-weighted imaging, DWI (b 0, 1400 s/mm²) and DCE MRI. DCE-MRI utilized a 3D SPGR sequence with TR/TE/α = 3.6 ms/1.3 ms/15°, FOV = 26 × 26 cm², with full gland coverage and an interpolated voxel size of 1 × 1 × 6 mm³. Frames were acquired at approximately 5-second intervals to achieve a clinically appropriate compromise between spatial and temporal resolution. Gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) was injected intravenously using a syringe pump (0.15 mmol/kg; rate 3 ml/sec). The protocol included ~5 baseline scans prior to contrast injection for estimation of baseline signal intensities.

Image Processing

ADC maps were obtained from the DWI images, and subtraction DCE images (calculated as the difference between the early arterial contrast bolus arrival phase and the baseline phase) were generated by the MR scanner software. Quantitative pharmacokinetic parameters from the high temporal resolution DCE images were obtained based on the Generalized Kinetic

Model (30), and were performed using OncoQuant research software (GE Global Research, Niskayuna, NY), as described elsewhere (31,32). These parameters included the area under the plasma concentration time curve for the first 90 seconds after injection of the contrast agent (AUC_{90}) and forward volume transfer constant (K^{trans} , min^{-1}).

Lesion Localization on mpMRI

Tumor Regions of Interest (TROIs) and Normal Regions of Interest (NROIs) were contoured using 3D Slicer, an open source image processing software (www.slicer.org) (33). TROIs were confirmed on all mpMRI maps and contoured separately by a radiologist with more than 15 years of experience with prostate MR imaging (XX) on each of the following sequences: T2WI, ADC, and subtraction DCE-MRI. NROIs were also delineated based upon all mpMRI maps, on the same or closest adjacent axial image to the TROI.

Histopathology Analysis

After radical retro-pubic prostatectomy, the intact specimens were inked for laterality and fixed in formalin overnight at room temperature. Care was taken in each case to maintain orientations of each slice of the prostate so that the same sides of each slice was routinely cut (ie, the superior or inferior edge for each prostate cross section), thus allowing for relatively equal spaces between Hematoxylin and Eosin (H&E) sections. Subsequently, 4-micron tissue sections were cut, glass-mounted, and stained with H&E. Residual cancer burden (RCB) and % tumor cellularity were recorded from entirely submitted prostates, as previously reported (9), by a dedicated central pathology genitourinary pathologist (XX) with more than 16 years of experience in genitourinary pathology. Pathology-based RCB was calculated using three-dimensional volume estimation based upon the largest cross-sectional tumor dimensions and the number of cross-sections involved by tumor, corrected for tumor cellularity (34), where RCB represents tumor cellularity x tumor volume.

Clinical Data

Serum prostate specific antigen (PSA) levels were obtained prior to starting neoadjuvant ADT, and at 30, 90, 150, and 175 days after starting neoadjuvant ADT, to determine PSA nadir and time to PSA nadir.

STATISTICAL ANALYSIS

At baseline, a paired two-tailed t-test was used to compare quantitative mpMRI indices between TROI and NROI within each patient, and to compare pre-and post-treatment mpMRI parameters and tumor volumes.

To evaluate for correlations between RCB on prostatectomy specimens and post-treatment MR-based RCB, and to evaluate for correlations between mean quantitative post-treatment mpMRI parameters and pathological RCB and cellularity, a Spearman's rank correlation was used. Wilcoxon test was used to test for differences in volume.

Institutional Review Board Approval

Our institutional review board approved this HIPAA-compliant prospective study. Written informed consent was obtained from all patients.

RESULTS

Baseline Patient and Tumor Characteristics

The average age at enrollment was 58.8 ± 7.4 years of age. Median serum PSA in seven out of eight cases (one case was a non-PSA producing tumor) was 9.34 ± 4.3 ng/ml. Six patients received triple therapy and two received enzalutamide alone.

Pretreatment diagnostic prostate biopsy revealed primary Gleason grade 4 in all patients, with secondary components of Gleason grade 4 in four patients, Gleason grade 3 in two patients and Gleason grade 5 in two patients. The epicenter of all tumors were in the peripheral zone. On MRI, tumor was seen extending into both sides of the prostate in five cases, was present only on the right side in two cases and only on the left side in one case. At pathology, extra-prostatic extension was identified in four patients and extension into the seminal vesicles in three patients. None of the eight patients were noted to have lymph node involvement on pathology. All tumor characteristics at pathology for each patient are outlined in Table 1.

Baseline MRI Characteristics

Baseline MR-based tumor volumes were 4964 ± 4430 mm³ (mean $\pm$ SD) on T2WI, 3613 ± 3042 mm³ on ADC and 3477 ± 2778 mm³ on subtraction DCE-MRI. (The baseline ADC imaging was missing for one patient). There was no significant difference in baseline MR-contoured tumor volume between all three MRI sequences.

Tumor diffusion metrics were significantly lower compared to normal tissue (ADC value of $806 \pm 137 \times 10^{-6}$ mm²/sec in TROIs vs. $1278 \pm 213 \times 10^{-6}$ mm²/sec in NROIs, $p = 0.0005$), with a mean calculated ADC ratio (tumor/normal ADC) of 0.64. Likewise, the quantitative DCE-MRI parameters K^{trans} and AUC_{90} were significantly higher in TROI compared to NROI (K^{trans} : 0.346 ± 0.16 min⁻¹ in TROIs vs. 0.145 ± 0.06 min⁻¹ in NROIs, $p = 0.003$; AUC_{90} : 0.214 ± 0.21 in TROIs vs. 0.113 ± 0.11 in NROIs, $p = 0.002$).

Response to Therapy Assessment

Mean PSA nadir was 0.16 ± 0.08 ng/ml. Mean time to PSA nadir was 203.9 ± 25.8 days. Mean time to surgery from post-treatment MR was 7 ± 6.6 days, ranging from 1 to 18 days. Overall prostate volume based upon T2 WIs decreased from 29254 ± 15032 mm³ at baseline to 15032 ± 6037 mm³ post-treatment, $p < 0.005$.

After prostatectomy, mean pathology-based RCB was 963 ± 1218 mm³, ranging from 30 to 3770 mm³. Mean RCB on all post-treatment mpMRI sequences had significantly decreased from baseline ($p = 0.04$ for all, see Table 2). Using Wilcoxon means for differences in volumes, there was no significant difference between RCB on whole gland histopathology and visible tumor on post-treatment mpMRI.

Post-treatment, while diffusion ADC ratios (tumor/normal) increased from 0.64 ± 0.163 to 0.73 ± 0.12 , diffusion ADC values remained significantly lower ($p = 0.003$) and the DCE-MRI metrics K^{trans} and AUC_{90} remained significantly higher ($p = 0.009$ and $p = 0.004$, respectively) in the TROIs compared to NROIs. In response to neoadjuvant ADT there was a significant decrease in DCE-MRI metrics in areas of tumor ($p = 0.02$ for both K^{trans} and AUC_{90}) and in normal tissue ($p = 0.02$ and $p = 0.0003$ for K^{trans} and AUC_{90} , respectively; see Table 3). There was no significant change in ADC of tumor or normal tissue in response to neoadjuvant therapy.

Correlation Between Pathology-Based RCB and MRI-Based RCB

There was a strong positive correlation between pathology-based RCB after prostatectomy and mpMRI-derived RCB outlined on all post-treatment mpMRI sequences as follows: T2WI ($\rho = 0.74$, $p = 0.045$); ADC ($\rho = 0.81$, $p = 0.02$); DCE-MRI ($\rho = 0.81$, $p = 0.02$).

Correlation Between Pathology-Based RCB and Cellularity with Quantitative mpMRI Indices

There was no significant correlation between baseline quantitative post-treatment mpMRI parameters and pathology-based RCB. However, pathology-based RCB was noted to have a strong positive correlation with post-treatment DCE metrics (AUC_{90} , $\rho = 0.79$, $p = 0.03$; K^{trans} $\rho = 0.76$, $p = 0.04$) and a strong negative correlation with post-treatment ADC metrics (Mean ADC 1400 $\rho = -0.74$, $p = 0.045$; min ADC 1400 $\rho = -0.79$, $p = 0.03$), as outlined in Table 4. Mean tumor cellularity of the prostatectomy specimen was $43.1 \pm 23\%$, ranging from 5% to 70%. Tumor cellularity did not have a significant correlation with baseline or post-treatment quantitative mpMRI parameters.

DISCUSSION

To date, the value of mpMRI in the setting of ADT treatment of advanced PCa has been evaluated in a small number of predominantly retrospective studies in those undergoing combined ADT and radiation therapy (21,22,35,36), but to our knowledge a role for quantitative mpMRI in assessing response in the neoadjuvant setting prior to prostatectomy has never been investigated. As such, this study is novel in that it is prospective and provides detailed pathology for correlation with mpMRI, to allow determination of mpMRI as a surrogate for residual tumor.

In this pilot study with both baseline and post-treatment mpMRI, we found that quantitative DCE and ADC metrics differ between outlined TROIs and NROIs, and this difference remains after neoadjuvant therapy, despite a significant decrease in the DCE metrics K^{trans} and AUC_{90} in both TROIs and NROIs. In addition, quantitative DCE metrics and tumor volume measurements from the post-treatment mpMRI strongly correlate with RCB at subsequent prostatectomy.

Our cohort of patients had intermediate to high risk PCa. At baseline, they all had large tumors, often bilateral and extending into the extra-prostatic tissue or seminal vesicles. All biopsies showed a dominant Gleason pattern 4 but with secondary patterns ranging from 3 to 5. As expected, at baseline we found TROI to have lower mean ADC values compared to

NROI, with mean ADC values of $806 \pm 137 \times 10^{-6} \text{ mm}^2/\text{sec}$ within the range reported elsewhere (19,23,37,38). The ADC ratios obtained are also in agreement with others (19,39). Likewise the DCE parameters K^{trans} and AUC_{90} were higher in TROIs, as previously reported (32,40,41).

In this study, we found that tumor volumes decreased significantly with neoadjuvant ADT, and there was no significant difference between RCB measured on histopathology after prostatectomy compared with that measured on post-therapy mpMRI. It could be argued that a reduction in volume in response to neoadjuvant ADT would be expected by the contouring radiologist and as such there is inherent bias during annotation. However, we have previously demonstrated the repeatability of mpMRI-based prostate tumor volume measurements (42), and the changes in tumor volume in this current study exceed the values of the repeatability coefficient previously reported, underscoring the significance for our findings. Residual tumor post treatment was detected on mpMRI for all patients, except for patient #7, in which a small volume of tumor was outlined on all sequences except T2WI, and indeed the true RCB at pathology in this case was very small (30 mm^3). Turkbey et al have previously demonstrated that MR-based tumor volume accurately estimates index tumor volume, once $>0.5\text{cc}$'s, based upon comparison with histologically confirmed tumor volumes (43). Both baseline and post-therapy mean tumor volumes in our study were $>0.5\text{cc}$'s, and our findings are in agreement with this paper, although we also found a strong correlation for all RCB estimates from all post-treatment mpMRI sequences (T2WI, ADC, DCE-MRI), whereas Turkbey et al investigated the role of T2WI only. Our findings are in contrast to a study that investigated 6 months of the ADT agent dutasteride (Avodart, GlaxoSmithKline Inc., London, United Kingdom) alone in reducing tumor volume, where no significant change in tumor volume was found (44). However, in addition to using different ADT agents, our patient cohort had higher-risk disease, and tumor volume was measured on routine mpMRI sequences, not magnetic resonance spectroscopic imaging voxels. As the field of urology continues to define potential roles for mpMRI in detection of PCa and in guidance for minimally invasive diagnostic and therapeutic procedures, our study would suggest that we should also consider a role for mpMRI as a biomarker to neoadjuvant therapy response, and also as a guide for duration of therapy.

Neoadjuvant ADT resulted in a significant reduction in the quantitative metrics K^{trans} and AUC_{90} in both areas of tumor and normal appearing tissue. However, DCE metrics and ADC parameters remained significantly different between TROI and NROI on the post-treatment study. This may be explained by the fact that neoadjuvant ADT has an effect on all prostate tissue, and the observed changes in DCE parameters are likely reflective of the antivasular effects of ADT (36). This has been previously demonstrated in advanced PCa managed with standard ADT (21,22). However, while Barrett et al demonstrated a decrease in K^{trans} and AUC_{90} in areas of tumor (22), their observed decrease in DCE parameters within normal tissue did not reach statistical significance. The treatment in Barrett et al was with standard ADT (AR antagonist treatment and gonadotropin releasing hormone analogue), and treatment length was less (three months compared to our 6-month treatment period). In addition, normal tissue was contoured based on T2WI in just over one-third of cases, whereas in our study NROIs were contoured based on the benign appearance of that tissue on all mpMRI sequences for each patient. A similar study by Hotker et al found a

decrease in K^{trans} in both tumor and benign tissue, the decrease only being significant for tumors (21), but subjects in this study also received standard ADT for a varied length of time.

Another possible explanation for our finding of a change in DCE quantitative indices within the NROIs may be that in this population of patients with significant localized disease, the background prostate tissue, while demonstrating quantifiable differences from tumor on mpMRI, may itself not be entirely normal to begin with. Many molecular markers are now recognized to be in accordance with the definition of prostate field cancerization (45,46), and as such a change in NROIs in response to ADT may not be surprising.

While ADC trended towards an increase in TROI and a decrease in NROI in response to neoadjuvant therapy, these changes were not significant, consistent with findings in other studies (22). We also previously evaluated the repeatability of ADC measurements in the prostate (42), and reported that changes in mean ADC may be considered significant at 95% level if they exceed 40%, or about $400 \text{ mm}^2/\text{s}$ in absolute value. The changes in ADC after neoadjuvant treatment in the present study are of much smaller magnitude. As ADC reflects cellularity in PCa (37,47), these findings are not surprising as ADT does not cause changes in cellular density (48) or necrosis in tumor cells (49), and an induced change in tumor neovascularity and perfusion does not have a significant impact on ADC metrics.

We also correlated quantitative post-treatment mpMRI metrics with pathology-based RCB after prostatectomy and found there to be a strong positive correlation between post-treatment DCE-MRI metrics K^{trans} and AUC_{90} and pathology-based RCB, and a strong negative correlation between post-treatment ADC and pathology-based RCB. We postulate that the correlation of post-treatment ADC metrics with pathology based RCB may be due to a sufficient post-treatment increase in ADC, although this increase was not statistically significant compared to pre-treatment values, possibly a reflection of the small sample size. Nonetheless, these findings raise the possibility that abnormal quantitative metrics may have a role in predicting the extent of residual functioning tumor. This information could be important in terms of early detection of nonresponders, but perhaps also in terms of identifying those who are responding but may benefit from a longer period of treatment, prior to prostatectomy.

While the focus of this pilot study was to explore a role for mpMRI as a biomarker of response to treatment of localized PCa with neoadjuvant second-generation ADT, there are notable limitations. First, we do not have whole mount pathological correlation to confirm TROIs and NROIs, although quantitative metrics from the contoured NROIs were significantly different to those of TROIs, and our metrics were similar to those reported elsewhere (19,23,32,37,38,40,41,50). Second, all TROIs were contoured on all mpMRI maps by a single radiologist, which may have introduced bias in lesion selection. Thirdly, the overall goal of the parent clinical trial, of which this mpMRI study was a subset, was to evaluate whether optimal AR blockade can occur with either AR antagonism alone (enzalutamide) or with more intense AR signaling suppression using enzalutamide, the LHRHa agonist leuprolide and dutasteride to block the conversion of testosterone to the more active metabolite dihydrotestosterone. As the number of participants who

prospectively consented to the ancillary mpMRI preprostatectomy was small, no intergroup comparison can be made. However, we do not consider this a major limitation as the focus of this imaging study was to explore a biomarker role for mpMRI, without comparing treatment arms.

In conclusion, this study demonstrates that quantitative mpMRI assessment of PCa may be useful as a biomarker in assessing response to neoadjuvant ADT, and that 3D MR volumetric assessment may also be a useful tool in predicting RCB at pathology. Our findings are very promising for an integral role for mpMRI in the neoadjuvant setting and these results should be validated and extended to larger clinical trials in high risk localized prostate cancer.

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Abbreviations

mpMRI	multiparametric MRI
ADT	androgen deprivation therapy
PCa	prostate cancer
TROI	tumor regions of interest
NROI	normal regions of interest
RCB	residual cancer burden
ADC	apparent diffusion coefficient
DCE-MRI	dynamic contrast enhanced MRI

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Figure 1. Axial subtraction (calculated as the difference between the early arterial contrast bolus arrival phase and the baseline precontrast phase) DCE-MRI images pre-ADT (A) and post-ADT. Enhancing tumor is seen in the left anterolateral gland in A, but no longer apparent in B.

Figure 2. Axial diffusion weighted imaging (DWI) ($b\ 0,1400\ \text{s/mm}^2$) pre (A) and post (C) ADT treatment, and their derived ADC maps pre (B) and post-ADT (D) treatment. Tumor on the left anterolateral prostate is seen as high signal intensity on DWI and low signal intensity on ADC maps, both pre and post ADT.

Figure 3. Axial T2 WIs on the prostate demonstrate well-defined tumor (A) pre-ADT, which is less well-defined post-ADT (B).

TABLE 1.

Patient Tumor Characteristics

	Tumor Margins	EPE	LVI	SVI	Lymph Node +	TNM Stage
Patient 1	abuts	pos	neg	pos	0/17	ypT3bN0
Patient 2	neg	neg	neg	pos	0/3	ypT3bN0
Patient 3	neg	neg	neg	neg	0/7	ypT2aN0
Patient 4	neg	pos	neg	neg	0/4	ypT3aN0
Patient 5	abuts	pos	neg	neg	0/2	ypT3aN0
Patient 6	pos	pos	neg	pos	0/15	ypT3bN0
Patient 7	neg	pos	neg	neg	0/6	ypT3aN0
Patient 8	neg	neg	neg	neg	0/2	ypT2aN0

EPE, extraprostatic extension; LN +, number of positive lymph nodes; LVI, lymphovascular invasion; neg, negative; pos, positive; SVI, seminal vesicle invasion.

TNM stage “y,” signifies preoperatively treated tissue.

TABLE 2.

Tumor Volume Changes in Response to Androgen Deprivation Therapy

	TV on T2WI	TV on ADC	TV on Subtract DCE
Pre-ADT	4964 ± 4430 mm ³	3613 ± 3042 mm ³	3477 ± 2778 mm ³
Post-ADT	1537 ± 1569 mm ³	1194 ± 1511 mm ³	1533 ± 999 mm ³
% volume change	67 ± 16%	73.3 ± 16%	48.4 ± 31%
<i>p</i> value	0.01	0.04	0.03

ADC, apparent diffusion coefficient; ADT, Androgen Deprivation Therapy; Subtract DCE, the difference between the early arterial (corresponding to the contrast bolus arrival) and the baseline phase of dynamic contrast-enhanced imaging; TV, tumor volume.

% volume change represents change from baseline.

TABLE 3.
Quantitative mpMRI Indices at Baseline and in Response to Androgen Deprivation Therapy

	Pre-ADT TROI	Post-ADT	*p Value	Pre-ADT NROI	Post-ADT **p Value
ADC	806 ± 137	883 ± 121	NS	1278 ± 213	1180 ± 245 NS
K ^{trans}	0.346 ± 0.16	0.188 ± 0.1	0.02	0.145 ± 0.06	0.086 ± 0.03 0.02
AUC ₉₀	0.214 ± 0.21	0.13 ± 0.05	0.02	0.113 ± 0.11	0.07 ± 0.07 0.0003

ADC, apparent diffusion coefficient ($\times 10^{-6}$ mm²/sec); ADT, Androgen Deprivation Therapy; AUC₉₀, area under the plasma concentration time curve for the first 90 seconds after injection of the contrast agent (AUC₉₀); NROI, normal region of interest; NS, not significant; TROI, tumor region of interest.

TABLE 4.
Correlations Between Post-ADT mpMRI Quantitative Parameters and Histological Parameters of Prostatectomy Specimen

Quantitative mpMRI Parameter	RCB	*p Value	Tumor Cellularity	**p Value
Mean AUC ₉₀	$\rho = 0.79$	0.03	$\rho = 0.40$	NS
Mean K ^{trans}	$\rho = 0.76$	0.04	$\rho = 0.48$	NS
Mean ADC 1400	$\rho = -0.74$	0.045	$\rho = -0.35$	NS
Minimal ADC 1400	$\rho = -0.79$	0.028	$\rho = -0.43$	NS

ADC, apparent diffusion coefficient; AUC₉₀, area under the plasma concentration time curve for the first 90 seconds after injection of the contrast agent; K^{trans}, forward volume transfer constant; RCB, residual cancer burden.