Clinical-Prostate cancer

mpMRI preoperative staging in men treated with antiandrogen and androgen deprivation therapy before robotic prostatectomy

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Abstract

Introduction: Using multiparametric magnetic resonance imaging (mpMRI), we sought to preoperatively characterize prostate cancer (PCa) in the setting of antiandrogen plus androgen deprivation therapy (AA-ADT) prior to robotic-assisted radical prostatectomy (RARP). We present our preliminary findings regarding mpMRI depiction of changes of disease staging features and lesion appearance in treated prostate.

Methods: Prior to RARP, men received 6 months of enzalutamide and goserelin. mpMRI consisting of T2 weighted, $b = 2,000$ diffusion weighted imaging, apparent diffusion coefficient mapping, and dynamic contrast enhancement sequences was acquired before and after neo-adjuvant therapy. Custom MRI-based prostate molds were printed to directly compare mpMRI findings to H&E whole-mount pathology as part of a phase II clinical trial (NCT02430480).

Results: Twenty men underwent imaging and RARP after a regimen of AA-ADT. Positive predictive values for post-AA-ADT mpMRI diagnosis of extraprostatic extension, seminal vesicle invasion, organ-confined disease, and biopsy-confirmed PCa lesions were 71%, 80%, 80%, and 85%, respectively. Post-treatment mpMRI correctly staged disease in 15/20 (75%) cases with 17/20 (85%) correctly identified as organ-confined or not. Of those incorrectly staged, 2 were falsely positive for higher stage features and 1 was falsely negative. Post-AA-ADT T2 weighted sequences best depicted presence of PCa lesions as compared to diffusion weighted imaging and dynamic contrast enhancement sequences.

Conclusion: mpMRI proved reliable in detecting lesion changes after antiandrogen therapy corresponding to PCa pathology. Therefore, mpMRI of treated prostates may be helpful for assessing men for surgical planning and staging. © 2019 Published by Elsevier Inc.

Keywords: Prostate cancer; Androgen deprivation; Enzalutamide; Multiparametric MRI

1. Introduction

For decades, the primary treatments for intermediate- or high-risk prostate cancer have consisted of radical prostatectomy (RP) or radiation therapy. Both have demonstrated long-term efficacy in treating PCa, especially the large proportion comprised of organ-confined, low-grade disease [1]. For aggressive, high-grade PCa that has advanced beyond the prostatic capsule or beyond the prostate altogether with lymph node invasion, RP and radiation therapy demonstrate markedly higher rates of biochemical recurrence, disease progression, and cancer-specific mortality [2−4]. In fact, higher-stage and higher-grade disease account for cancer-specific mortality rates approximately 2 to 3 times those of organ-confined or low-grade disease [2].

To stave off the morbidity and mortality of recurrent and progressed PCa, urologists and medical oncologists have turned to neoadjuvant systemic therapies to bolster primary interventions [5,6]. Although early studies employing traditional androgen deprivation therapy (ADT) failed to show improvements in biochemical recurrence or survival, newer generation antiandrogens, such as enzalutamide, warrant investigation in the neoadjuvant setting [7−9].

Recently completed trials utilizing combinations of these antiandrogens with ADT have demonstrated decreased levels of serum and tissue androgens, tumor androgen receptor activity, tumor cell proliferation, and pathologic tumor burden [10,11]. Moreover, patients experienced pathologic downstaging from clinical stage and early results suggest benefit for recurrence-free survival [10,11]. However, the effects of neoadjuvant therapy do not appear to be uniform among patients and currently there is no established method for preoperatively assessing treatment response and disease extent to guide surgical technique.

Multiparametric magnetic resonance imaging (mpMRI) offers a potential solution to this problem due to its demonstrated ability to preoperatively diagnose, measure, and stage PCa [12−14]. By longitudinally imaging patients during treatment, it may be possible to visualize changes in disease features such as lesion size or evidence of locally-advanced disease. However, there is little research on the effects of antiandrogen therapy on mpMRI depiction of PCa and whether changes seen on mpMRI accurately represent the extent of disease after therapy.

Therefore, we report on preliminary imaging and pathology findings in men with intermediate- and high-risk PCa who underwent antiandrogen plus androgen deprivation therapy (AA-ADT) before robotic-assisted RP (RARP). To determine the feasibility of preoperative mpMRI assessment of PCa and subsequent changes after AA-ADT, this analysis aims to characterize the effects of this neoadjuvant regimen with regard to PCa staging and lesion appearance on mpMRI.

2. Methods

2.1. Study design

This is preliminary report from an open-label, single-arm phase II clinical trial (NCT02430480). Enrolled men underwent mpMRI (imaging protocol described below) at baseline and after 6 months of enzalutamide (160 mg daily) and goserelin (10.8 mg injection given every 12 weeks for 24 weeks) prior to RARP.

2.2. Patient selection

Men eligible for study inclusion had pathology-confirmed intermediate- or high-risk PCa who were medically-fit for RARP. Intermediate-risk PCa was defined as prostate-specific antigen (PSA) 10 to 20 ng/ml, or Gleason score of 7, or clinical stage cT2b or cT2c. High-risk PCa was defined as PSA >20 ng/ml, or Gleason score ≥8, or clinical stage cT3a or cT3b. Suspicion of regional nodal involvement was permitted. Men were excluded with evidence of distant metastasis, hypogonadism (testosterone <100 ng/dl), or prior treatment for PCa (e.g., radiotherapy, brachytherapy, ADT, etc.).

2.3. Imaging and biopsy protocol

Men underwent mpMRI of the prostate at 3 Tesla (Achieva; Phillips Healthcare, Best, The Netherlands) with endorectal coil (BPX-30; Medrad, Pittsburgh, PA) and 16-channel cardiac surface coil (SENSE; Phillips Healthcare. mpMRI sequences consisted of triplanar T2-weighted (T2W), high *b* value (*b* = 2,000) diffusion weighted imaging (DWI), apparent diffusion coefficient mapping, and dynamic contrast enhancement (DCE). For pre-AA-ADT imaging, prostatic lesions were identified and assigned suspicion scores based on the Prostate Imaging Reporting and Data System version 2 scoring system and a previously validated in-house scoring system [15]. Imaging evidence of extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node invasion, and metastases were reported for PCa staging. After neoadjuvant therapy, a second mpMRI was acquired using the same imaging protocol. Prostate Imaging Reporting and Data System version 2 scores were not assigned due to treatment effect [16]. All images were read prospectively by a single radiologist. Prostate and lesion volumes were calculated using software embedded in the picture archiving and communication system after manual contouring.

Initial pathology was determined by 12-core systematic transrectal ultrasound-guided biopsy and/or MRI-transrectal ultrasound targeted biopsy (Tbx) with confirmation by pathologists at our institution. Patients underwent Tbx when indicated by mpMRI as described previously [17].

Table 1
Demographic and baseline characteristics of study cohort.

	Pretreatment
N	20
Age (years), median (IQR)	66 (56−76)
Race, *n* (%)	
White	14 (70%)
Black	3 (15%)
Other	3 (15%)
PSA (ng/ml), median (IQR)	9.45 (5.6−37.5)
Testosterone (ng/dl), median (IQR)	259 (198−391)
Pretreatment mpMRI stage, *n* (%)	
T2	1 (5%)
T3a	12 (60%)
T3b	5 (25%)
T4	2 (10%)
N1	7 (35%)
Gleason group (biopsy), *n* (%)	
2	3 (15%)
3	3 (15%)
4	4 (20%)
5	10 (50%)

2.4. Surgery and pathology protocol

All but 1 RARP surgeries were performed by a single surgeon. Extended lymph node dissection was performed for all patients. Following RARP, whole-mount prostate H&E slides were prepared using MRI-based 3D-printed custom prostate molds [18]. All pathologic specimens were reviewed by a single genitourinary pathologist. Postoperative pathologic staging was assigned, but tumor grade could not be assessed due to treatment effects. Presence or absence of residual tumor was noted from H&E whole-mount pathology.

3. Results

3.1. Patient baseline characteristics

Twenty men completed AA-ADT, imaging, and RARP as part of the study protocol. Demographic and baseline characteristics are summarized in Table 1. Median age was 66 years (interquartile range (IQR) 56−76 years), median
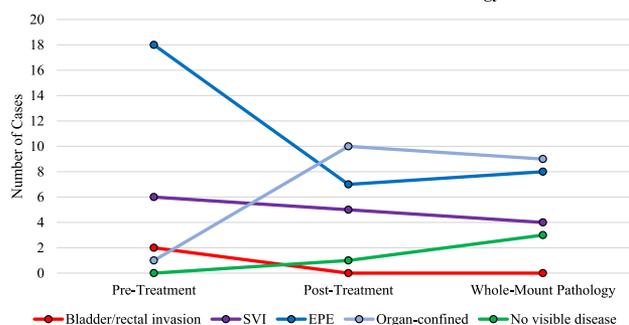

Fig. 1. Changes in PCa staging features detected by mpMRI before and after AA-ADT, then confirmed on post-RARP H&E pathologic analysis.

pre-AA-ADT PSA was 9.45 ng/ml (IQR 5.60−37.48 ng/ml), and median post-AA-ADT PSA was 0.02 ng/ml (IQR undetectable−0.04 ng/ml).

3.2. Imaging features

Before starting AA-ADT, mpMRI indicated bladder or rectal invasion in 2 men (10%), EPE in 18 (90%), SVI in 6 (30%), and organ-confined disease in 1 man (5%). Seven cases (35%) had suspicion of regional nodal metastasis. After AA-ADT, no men were suspected of having bladder or rectal invasion on mpMRI, while 7 (35%), 5 (25%), and 10 (50%) men were suspected of having EPE, SVI, and organ-confined disease, respectively. One man (5%) had no suspicious lesions seen on post-AA-ADT mpMRI (Table 2; Fig. 1).

3.3. Pathology analysis

On whole-mount H&E pathology, there were no (0%) cases of bladder or rectal invasion, 8 (40%) cases of EPE, 4 (20%) cases of SVI, 9 (45%) cases of organ-confined disease, and 3 (15%) cases in which no evidence of PCa was seen (Table 2; Fig. 1). Lymph node invasion was confirmed in 3 (15%) cases. Therefore, for post-AA-ADT mpMRI, the positive predictive value (PPV) and negative predictive value (NPV) for EPE were 71% and 77%, respectively. The PPV and NPV for SVI were 80% and 100%, respectively.

Table 2
mpMRI detection of pathologic features in study cohort before and after AA-ADT.

	Pretreatment (%)	Post-treatment (%)	Pathology (%)
Bladder/rectal invasion	2 (10%)	0 (0%)	0 (0%)
EPE	18 (90%)	7 (35%)	8 (40%)
SVI	7 (35%)	5 (25%)	4 (20%)
Organ-confined disease	1 (5%)	10 (50%)	9 (45%)
No visible disease	0 (0%)	1 (5%)	3 (15%)
Regional LNI (N1)	7 (35%)	7 (35%)	3 (15%)

Values sum beyond 20 due to presence of multiple features in the same prostate.
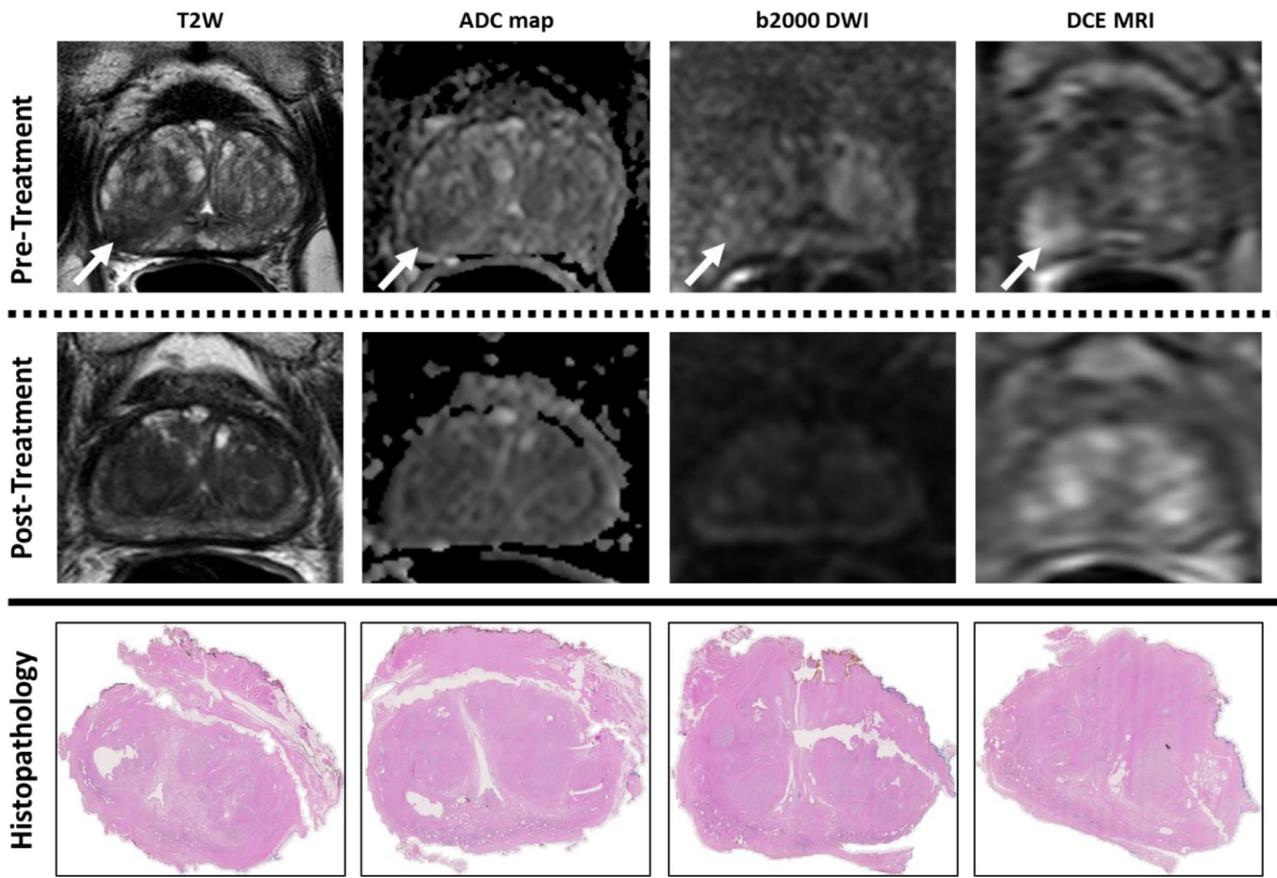
Fig. 2. A 61 year-old African American male presented with serum PSA = 17.29 ng/ml. Pretreatment mpMRI (top row) demonstrated a PI-RADSv2 5 lesion in the right apex-mid peripheral zone (arrow) measuring 2.8 cm in greatest axial dimension in the axial T2W MRI, which shows restricted diffusion on ADC map and b2000 DWI with increased vascularity on DCE MRI. The lesion was suspicious for extraprostatic extension. A 12-core TRUS Sbx yielded 2 cores positive for Gleason 8 (4 + 4) cancer and 2 cores positive for Gleason 7 (4 + 3) cancer; MRI-TRUS Tbx detected Gleason 8 (4 + 4) cancer at that lesion. After 6 months of neoadjuvant enzalutamide + ADT, post-treatment mpMRI (middle row) detected no suspicious lesion in any pulse sequence. No evidence of malignancy was seen on postsurgical H&E whole-mount pathology (bottom row).

The PPV and NPV for organ-confined disease were 80% and 90%, respectively (Table 3).

Post-AA-ADT mpMRIs accurately staged 15 of 20 (75%) cases. Four of 5 cases with SVI, 2 of 4 cases with EPE (but without SVI), 8 of 10 cases with organ-confined disease, and 1 case without visible disease were each confirmed on H&E pathology (Fig. 2). Of the 5 cases incorrectly staged, 4 were falsely positive for higher stage features (1 case of SVI, 2 of EPE, and 1 of organ-confined disease) and 1 was falsely negative (EPE not detected on mpMRI).

As part of the preliminary assessment, diagnostic performance of post-AA-ADT mpMRI for previously-confirmed PCa lesions was assessed by each pulse sequence (Table 4; Supplementary Table 1). Post-AA-ADT mpMRI performance for each pulse sequence was characterized as strongly positive, weakly positive, or negative. The T2W sequence displayed the greatest number of pathologically-confirmed PCa lesions with strongly positive signals while $b = 2,000$ DWI and DCE sequences more frequently displayed PCa lesions as weakly positive or negative (Fig. 3). T2W also performed slightly better at representing benign tissue (i.e., without tumor seen on H&E pathology) when no positive signal was displayed as compared to $b = 2,000$ DWI and DCE, NPV = 67%, 60%, and 40%, respectively.

Table 3
Diagnostic performance of post-treatment mpMRI for predicting pathologic findings.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lesion PCa[a]	0.94 (0.84−1.0)	0.67 (0.36−0.97)	0.85 (0.69−1.0)	0.86 (0.60−1.0)
EPE	0.63 (0.29−0.96)	0.83 (0.62−1.0)	0.71 (0.38−1.0)	0.77 (0.54−1.0)
SVI	1.00 (1.0−1.0)	0.94 (0.82−1.0)	0.80 (0.45−1.0)	1.00 (1.0−1.0)
Organ-confined	0.89 (0.68−1.0)	0.82 (0.59−1.0)	0.80 (0.55−1.0)	0.90 (0.71−1.0)

[a] Confirmed as PCa by Tbx.

Table 4
Signal positivity for index lesions on post-treatment mpMRI by pulse sequence and later confirmed as PCa positive or negative on postsurgery H&E whole-mount pathology.

		T2W	DWI	DCE
Path PCa+ ($n = 16$)	Strongly positive (++)	11	2	4
	Weakly positive (+)	4	12	8
	Negative (−)	1	2	3
Path PCa− ($n = 4$)	Strongly positive (++)	1	0	0
	Weakly positive (+)	1	1	2
	Negative (−)	2	3	2

Index lesions defined as lesion with largest axial diameter measured on MRI and/or highest Gleason Score of the lesion from Tbx.
DWI = $b = 2,000$ diffusion weighted imaging. DCE = dynamic contrast enhancement. DCE sequence was not available for 1 patient.
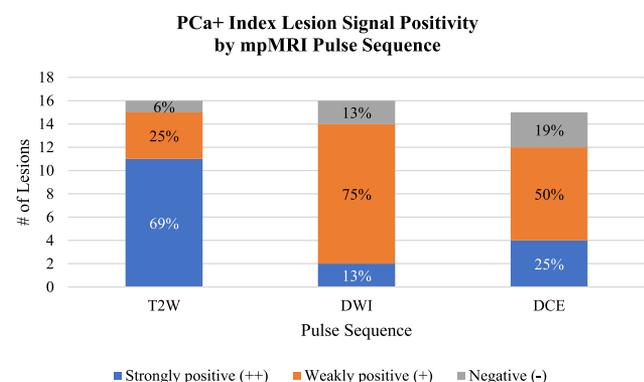

Fig. 3. Signal positivity for index lesions on post-treatment mpMRI by pulse sequence and later confirmed as PCa positive or negative on postsurgery pathology. Index lesions defined as lesion with largest axial diameter measured on MRI and/or highest Gleason score (GS) of the lesion from Tbx. DWI = b2000 diffusion weighted imaging. DCE = dynamic contrast enhancement. DCE sequence was not available for 1 patient.

The combined interpretation of the 3 pulse sequences on mpMRI yielded a PPV and NPV for pre-AA-ADT Tbx-positive PCa lesions of 85% and 86%, respectively (Table 4).

4. Discussion

This study reports our initial experience using mpMRI to assess the effects of antiandrogen and androgen deprivation therapy on PCa staging before surgery in addition to its correlation with final H&E pathology. In doing so, we provide insight to how urologists, medical oncologists, and radiologists can interpret imaging of AA-ADT-treated prostates to assess whether high-risk patients are candidates for prostatectomy after neoadjuvant therapy. Our study is unique in that we utilized custom 3D-printed prostate molds based on post-AA-ADT mpMRI measurements of the prostate and tumor for whole-mount preparation. From this we were able to better correlate MRI features with histopathology for more precise cancer detection and localization [18].

The majority of men exhibited loss of locally-advanced features initially seen on pre-AA-ADT mpMRI when compared to whole-mount H&E pathology. Although some cases were incorrectly staged on post-AA-ADT mpMRI, all but 1 had less advanced disease than suspected. Our results demonstrate relatively strong predictive power in depicting cancerous prostate lesions and locally-advanced disease. This compares favorably to what is seen in treatment-naïve patients. In a recent meta-analysis of 75 studies (9796 patients) on mpMRI staging of PCa, sensitivity, and specificity for detection of locally-advanced disease were 0.61 (95% confidence interval 0.54−0.67) and 0.88 (95% confidence interval 0.85−0.91), respectively [19]. Therefore, in planning for prostatectomy after androgen ablation, our results suggest that mpMRI can reliably depict disease extent with infrequent upstaging on pathology. This allows the surgeon to more confidently assess the disease stage and determine appropriateness of surgical intervention.

As a secondary goal, we sought to evaluate how well different mpMRI pulse sequences depict tumors after antiandrogen and androgen deprivation therapy. In a case report analyzing specific mpMRI changes after neoadjuvant enzalutamide monotherapy, apparent diffusion coefficient values increased and DCE-imaging tumor perfusion decreased making lesions appear less well-defined [20]. We found that DWI and DCE images depicted PCa lesions less clearly compared to T2W and had higher false negative rates. When correlating longitudinal changes on mpMRI with pathological findings, analysis was limited to cancer-specific changes, i.e., only in lesions with pre-AA-ADT positive Tbx findings. In the setting of neoadjuvant treatment, verifying missed lesions on pre-AA-ADT mpMRI and Tbx is otherwise impossible at final pathology. Given the severe histopathologic changes induced by the neoadjuvant regimen, we considered pathologic positivity based on prostate hemisphere when more than one Tbx-positive lesion was present on the same side of the prostate. This occurred in only 2 cases and in no cases was there evidence of residual tumor in a hemisphere in which no Tbx-positive lesions had been detected. As we are actively investigating other methods for detecting PCa in treated prostate tissue, we report residual tumor in this preliminary analysis based on its presence or absence seen in H&E whole-mount pathology given that this is the current practiced method for PCa pathology evaluation after surgery.

It is difficult to assess the specific impact of enzalutamide on extent of disease and, more importantly, long-term outcomes. In a pooled analysis of 3 separate neoadjuvant therapy trials, McKay et al. [10] found similar rates of locally-advanced disease for patients treated with abiraterone and ADT versus enzalutamide and ADT. It remains to be seen what, if any, effect these newer neoadjuvant regimens will have on long-term prognosis, but our preliminary results suggest that urologists can rely on mpMRI for preoperative staging even in the postneoadjuvant therapy setting.

There are several limitations to this study. First, this is an initial analysis of study findings and although patient accrual is ongoing, our sample size is small [10,11].

Second, this study did not employ a placebo control arm. Given the extremely high-risk nature of our study patients, it is very challenging to assign a matched cohort for comparison since few patients with such advanced disease would go on to surgery without additional therapies. The presented preliminary analysis is based on qualitative evaluation of mpMRI in the setting of neoadjuvant treatment using a single reader. Once the phase II clinical trial is completed, we will evaluate mpMRI response with more readers, which will enable a more objective approach for noninvasive evaluation of treated patients.

5. Conclusion

We demonstrate that mpMRI successfully characterizes PCa after antiandrogen and androgen deprivation therapy, and effectively documents morphologic changes to the prostate and lesions. This has important implications for urologists when preoperatively assessing disease responsiveness as well as determining surgical candidacy and planning.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.01.012.

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