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Research Letter

Multiparametric MRI as a Predictor of PSA Response in Patients Undergoing Stereotactic Body Radiation Therapy for Prostate Cancer

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Purpose: To maximize the therapeutic ratio, it is important to identify adverse prognostic features in men with prostate cancer, especially among those with intermediate risk disease, which represents a heterogeneous group. These men may benefit from treatment intensification. Prior studies have shown pretreatment mpMRI may predict biochemical failure in patients with intermediate and/or high-risk prostate cancer undergoing conventionally fractionated external beam radiation therapy and/or brachytherapy. This study aims to evaluate pretreatment mpMRI findings as a marker for outcome in patients undergoing stereotactic body radiation therapy (SBRT).

Methods and Materials: We identified all patients treated at our institution with linear accelerator based SBRT to 3625 cGy in 5 fractions, with or without androgen deprivation therapy (ADT) from November 2015 to March 2021. All patients underwent pretreatment Magnetic Resonance Imaging (MRI). Posttreatment Prostate Specific Imaging (PSA) measurements were typically obtained 4 months after SBRT, followed by every 3 to 6 months thereafter. A 2 sample *t* test was used to compare preoperative mpMRI features with clinical outcomes.

Results: One hundred twenty-three men were included in the study. Pretreatment MRI variables including median diameter of the largest intraprostatic lesion, median number of prostate lesions, and median maximal PI-RADS score, were each predictive of PSA nadir and time to PSA nadir ($P < .0001$). When separated by ADT treatment, this association remained for patients who were not treated with ADT ($P < .001$). In patients who received ADT, the pretreatment MRI variables were each significantly associated with time to PSA nadir ($P < .01$) but not with PSA nadir ($P > 0.30$). With a median follow-up time of 15.9 months (IQR: 8.5-23.3), only 3 patients (2.4%) experienced biochemical recurrence as defined by the Phoenix criteria.

Conclusions: Our experience shows the significant ability of mpMRI for predicting PSA outcome in prostate cancer patients treated with SBRT with or without ADT. Since PSA nadir has been shown to correlate with biochemical failure, this information may help radiation oncologists better counsel their patients regarding outcome after SBRT and can help inform future studies regarding who may benefit from treatment intensification with, for example, ADT and/or boosts to dominant intraprostatic lesions.

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Introduction

Previous research has found that pretreatment mpMRI can predict biochemical failure in patients with intermediate or high-risk prostate cancer receiving conventional external beam or brachytherapy.[1,2] PSA nadir has been shown to be a useful surrogate for longer term biochemical control.[3,4] This study is the first to assess pretreatment mpMRI as a marker for outcome in patients undergoing SBRT.

Methods and Materials

We identified all patients treated at our institution with linear accelerator-based stereotactic body radiation therapy (SBRT) to 3625 cGy in 5 fractions, with or without androgen deprivation therapy (ADT) from November 2015 to March 2021. Risk groups were defined using NCCN criteria.[5]

Patients diagnosed with unfavorable intermediate risk prostate cancer were treated with ADT. Treatment began with a daily dose of bicalutamide 50 mg for 28 days, followed by a leuprolide injection 2 weeks later. ADT continued for 2 months before starting radiation therapy and lasted a total of 6 months. All patients began treatment (either radiation therapy or ADT) within 6 months of being diagnosed with prostate cancer via biopsy.

Patients underwent simultaneous periprostatic SpaceOAR hydrogel and MRI-compatible Cybermark gold fiducial prostate marker (CIVCO Medical Instruments Co, Inc Kalona, IA) placement before starting radiation therapy. CT simulation was performed following rectal Fleet enema.

The planning target volume (PTV) was defined as a 5 mm expansion from the CTV in all dimensions, except posteriorly in which it is a 3 mm expansion as described in Hannan et al.[6] Organ-at-risk (OAR) dosimetry parameters were followed as defined in RTOG 0938.[7] SBRT was delivered using a Varian Truebeam linear accelerator twice-weekly with Eclipse-based planning (Varian Medical Systems, Palo Alto, CA).

PSA was obtained before treatment, 4 months after treatment, and every 3 to 6 months thereafter. In men treated with ADT for unfavorable intermediate risk prostate cancer (starting 2 months before radiation therapy for a total of 6 months), PSA was measured monthly until a nadir was achieved. Biochemical PSA failure was defined by the Phoenix definition.[8] A 2 sample *t* test was used to compare preoperative mpMRI features, median tumor diameter (MTD), median number of lesions and Prostate Imaging Reporting & Data System (PI-RADS) version 2 score, with clinical outcomes. Follow-up time was measured from the time radiation therapy was started.

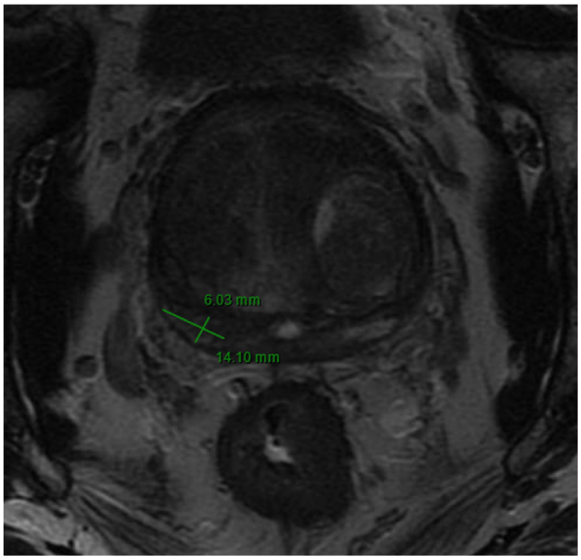

Figure 1 A 71-year-old man with history of favorable intermediate-risk prostate cancer (cT1c, GS 3+4, 5/18 positive cores, PSA 8) post definitive prostate SBRT ending in August 2019 and biopsy on that year confirming max GS 3+4, multifocal disease. Pretreatment multiparametric 3.0 Tesla imaging, including multiplanar T2-weighted images, diffusion-weighted images (including ultra high b-1500 images and ADC map), and dynamic contrast-enhanced images of the prostate. Pre- and post-contrast T1-weighted images of the pelvis were also obtained. One lesion was revealed: 1 right postero-medial, midgland, peripheral zone PI-RADS 4 lesion with size of 14 × 6 mm as measured on ultra high b-1500 image. A 14 × 6 mm lesion is present on the T2-weighted image. *Abbreviations*: ADC = androgen deprivation therapy; GS = Gleason score; PI-RADS = Prostate Imaging Reporting & Data System; PSA = Prostate Specific Antigen; SBRT = stereotactic body radiation therapy.

Results

One hundred twenty-three men were included in the study, with a median age of 72 (interquartile range (IQR): 66-75) and median initial PSA of 7.2 (IQR: 5.3-10.5). Forty-nine percent of patients were Gleason score (GS) 7a and 37% were GS 7b. Eighty-five percent of patients were clinical stage T1c. Eighty-seven percent of patients had intermediate risk disease (Fig. 1). Fifty-six percent of patients were unfavorable intermediate risk. Forty-six percent of patients received ADT (Table 1). Eighty-eight (72%) patients received a PI-RADS score at the time of

Table 1 Patient characteristics

Clinical characteristics	
	Total (n = 123)
Median age in years (IQR)	72 (66-75)
Median initial PSA in ng/mL (IQR)	7.2 (5.3-10.5)
Biopsy Gleason Score, n (%)	
6	15 (12)
7a	60 (49)
7b	45 (37)
9	3 (2)
Clinical T stage, n (%)	
1c	105 (85)
2a	12 (10)
2b	5 (4)
2c	1 (1)
NCCN Risk Stage, n (%)	
Low	13 (11)
Intermediate, favorable	38 (31)
Intermediate, unfavorable	69 (56)
High	3 (2)
ADT	
Yes (%)	56 (46)
No (%)	67 (54)
PI-RADS score	
1 (%)	7 (6)
2 (%)	3 (2)
3 (%)	11 (9)
4 (%)	43 (35)
5 (%)	24 (20)
Not assigned at time of MRI	35 (28)
Median PSA Nadir, ng/mL (IQR)	0.3 (0.1-0.7)
Median time to PSA nadir, months (IQR)	10.5 (4-20)
Median follow-up time, months (IQR)	15.9 (8.5-23.3)
MRI characteristics	
Median diameter, cm (IQR)	1.3 (1-1.7)
Median PI-RADS (IQR)	4 (3-5)
Median number of lesions (IQR)	1 (1-2)

Abbreviations: ADT = androgen deprivation therapy; IQR = interquartile range; MRI = Magnetic Resonance Imaging; PI-RADS = Prostate Imaging Reporting & Data System; PSA = Prostate Specific Antigen.

MRI (Table 1). The remaining 28% of patients were not assigned a PI-RADS score.

With a median follow-up time of 15.9 months (IQR: 8.5-23.3), the median time to PSA nadir and median PSA nadir were 10.5 months and 0.3 ng/mL, respectively (Table 1). Only 3 patients (2.4%) experienced biochemical recurrence as defined by the Phoenix criteria.[8]

On pretreatment MRI, median number of lesions, MTD, and median maximal PI-RADS scores were 1 (IQR: 1-2), 1.3 cm (IQR: 1-1.7), and 4 (IQR: 3-5), respectively (Table 1). Pretreatment MRI variables including MTD, median number of prostate lesions, and median maximal PI-RADS score were each predictive of PSA nadir and time to PSA nadir ($P < .0001$).

In patients treated with ADT, initial median PSA was 8.6 (IQR: 5.6-11.0). Median time to PSA nadir was 4 months (IQR: 4-8.8) and median PSA nadir was 0.11 ng/mL (IQR: 0.01-0.21). Median number of lesions was 1 (IQR: 1-1.5), median MTD was 1.15 cm (IQR: 1-1.4), and median PI-RADS was 4 (3.5-5) (Table 2). In patients not treated with ADT, initial median PSA was 7.1 ng/mL (IQR: 5.0-9.2), median time to PSA nadir was 16.5 months (IQR: 9.75-23), $P < .0001$ and median PSA nadir was 0.53 ng/mL (IQR: 0.26-1.0), $P < .0001$. Median number of lesions was 2 (IQR: 1-2), median MTD was 1.3 (IQR: 0.9-1.7), median PI-RADS was 4 (4-4) (Table 2). When separated by ADT treatment, pretreatment MRI variables including median MTD, median number of prostate lesions, and median maximal PI-RADS score were each predictive of PSA nadir and time to PSA nadir in patients who were not treated with ADT ($P < .001$). In patients who received ADT, the pretreatment MRI variables were each significantly associated with time to PSA nadir ($P < .01$) but not with PSA nadir ($P > 0.30$).

Discussion

We show significant ability of mpMRI for predicting PSA outcome in patients treated with SBRT with or without ADT. The NCCN's current method for assessing the risk of prostate cancer involves taking into account factors such as the clinical T-stage, the patient's pretreatment PSA level, Gleason score, lymph node involvement, and distant metastases.[9] Pretreatment MRI information, including MTD, and PI-RADS score, is not considered in this risk stratification.

There have been numerous studies examining the predictive ability of MRI for pathologic features after radical prostatectomy,[10] but few studies on MRI predictive ability in patients undergoing definitive radiation therapy.[10,11] A prior study looked into prostate outcomes in relation to MRI features in patients treated with SBRT (median, 40 Gy in 5 fx); however, this study examined findings on posttreatment biopsy and did not specifically examine PSA trends posttreatment.[12] Recently published data in the setting of brachytherapy boost has shown that patients with intermediate and high-risk prostate cancer who have maximum tumor diameter greater than 24 mm have a 31% chance of biochemical failure at 5 years, compared

Table 2 Medians and Interquartile Ranges of patient pretreatment MRI characteristics and key PSA statistics, separated by patients who received ADT treatment and patients who did not receive ADT

Pretreatment MRI Characteristics	ADT	(IQR)	No ADT	(IQR)
Median number of lesions	1	(1-1.5)	2	(1-2)
Median MTD (cm)	1.15	(1-1.4)	1.3	(0.9-1.7)
Median PI-RADS score	4	(3.5-5)	4	(4-4)
PSA Response	**ADT**	**(IQR)**	**No ADT**	**(IQR)**
Median initial PSA (ng/mL)	8.6	(5.6-11.0)	7.1	(5.0-9.2)
Median time to PSA nadir (months)	4	(4-8.8)	16.5	(9.75-23)
Median PSA nadir (ng/mL)	0.11	(0.01-0.21)	0.53	(0.26-1.0)

Abbreviations: ADT = androgen deprivation therapy; IQR = interquartile range; MRI = Magnetic Resonance Imaging; MTD = median tumor diameter; PI-RADS = Prostate Imaging Reporting & Data System; PSA = Prostate Specific Antigen.

with only a 4% chance in patients with maximum tumor diameter less than or equal to 24 mm.[13] This suggests that MTD may be a relevant factor in determining outcomes for patients undergoing definitive radiation therapy. Our study shows that in a cohort of predominantly intermediate risk disease patients undergoing SBRT, MTD remains an important predictor of oncologic outcome.

Eighty-seven percent of patients included in this study had intermediate risk disease, a notoriously heterogenous risk group.[9] The categorization of intermediate-risk patients into favorable and unfavorable groups helps further stratify patients, but is insufficient as there is still significant variability within each subgroup.[9] Proper stratification is essential to make the best decision regarding treatment approach for intermediate-risk prostate cancer patients. Radical prostatectomy, radiation, partial gland ablation, and active surveillance are all viable options for certain subgroups of intermediate-risk patients.[14] Definitive radiation therapy also varies by risk group, with prophylactic lymph node radiation not performed routinely and ADT not administered for patients with favorable intermediate risk prostate cancer.[15] The use of MRI results can increase the accuracy of risk classification, and subsequent treatment recommendations. Inclusion of MRI data in the European Association of Urology (EAU) risk classification resulted in upstaging in the EAU risk group and treatment in up to 31% of cases.[16]

The indications for use of ADT with prostate SBRT are still being defined.[1] In a study of 147 patients who received both SBRT and ADT for prostate cancer, there was no significant difference in 5-year biochemical failure rate between those who received ADT and those who did not (92.6% vs 91.3%, $P = .71$).[17] However, there was no standard criteria for ADT use. Additionally, studies have shown that treating MRI-detected prostate lesions with a focal boost can improve biochemical disease-free survival without affecting toxicity and quality of life.[18,19] Our study suggests that mpMRI results can play an important role in informing future studies toward determining who may benefit from treatment intensification using ADT and/or intraprostatic boost for dominant prostate cancer lesion(s).

The study has several limitations, including the use of single-center retrospective data, and a relatively short follow-up period. However, PSA nadir has been shown to be a useful surrogate for longer term biochemical control.[3,4] The subjective measurement of MTD and differences in MRI technology may result in underestimation of lesion size.[20] Studies have found PI-RADS score to have at least moderate interobserver agreement, but some raise concerns about its reproducibility.[20] Our findings linking PI-RADS score to clinical outcomes rely on review by radiologists at a major academic center, which could limit generalization. To at least partially address these issues, we also examined largest axial tumor dimension as a predictor of outcome as it may be more objective and easier to assess without specialized training. An additional limitation of this study is that statistical analysis examined the relationship between pretreatment MRI characteristics and median time to PSA nadir. Future prospective studies could better standardize follow-up PSA collection, and better characterize this relationship between pretreatment MRI characteristics and time to PSA nadir through time-to-event statistics. A further limitation is that only 3 of the 123 patients had high risk disease, which may affect the generalizability of this study to patients with high-risk prostate cancer.

Conclusion

Our findings demonstrate the capability of mpMRI in predicting PSA outcome in patients undergoing SBRT with or without ADT. As PSA nadir has been linked to biochemical failure, this information can assist radiation oncologists in counseling patients and informing future studies toward determining who may benefit from treatment intensification using ADT or selective intraprostatic boost for visualized prostate cancer lesions.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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