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How Would MRI-Targeted Prostate Biopsy Alter Radiation Therapy Approaches in Treating Prostate Cancer?

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Abstract

Objectives—To determine if MRI/ultrasound fusion-targeted prostate biopsy (TB) would lead to increased recommendations of aggressive radiotherapy treatments for higher risk prostate cancer compared to systematic biopsy (SB) results.

Methods—Clinicopathologic data of 533 men who underwent both TB and SB from 2014–2017 was analyzed. TB was performed in addition to SB in patients with detection of MRI suspicious lesions. Three patient cohorts were established: (1) biopsy naïve (80/533,15.0%), (2) active surveillance (185/533,34.7%), and (3) prior negative biopsy (268/533,50.3%). Cancer risk categorical criteria were established with recommended radiotherapy treatment for each. Variation of risk classification due to biopsy method for all patients and within each cohort were analyzed using either a chi-squared statistic or Fisher's Exact test. McNemar's pairwise analyses were performed for all risk categories between TB and SB to assess the effects of TB on high-risk cancer identification and subsequent radiotherapy recommendations.

Results—Number of patients within cancer risk categories (1.“No Cancer or Low-Risk”; 2.“More Favorable Intermediate-Risk”; 3.“Less Favorable Intermediate-Risk”; 4.“High-Risk”) varied significantly based on TB and SB pathology among all patients combined($p<0.0001$), in cohort 2($p=0.0005$), and in cohort 3($p<0.0001$). Further, among all patients, TB increased cancer risk classification and correspondingly would result in more aggressive radiotherapy recommendations: “No Cancer or Low-Risk” to “Less Favorable Intermediate-Risk” (29/343, $p<0.0001$) and “No Cancer or Low-Risk” to “High-Risk” (31/353, $p<0.0001$).

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Conclusions—Among men with prostate cancer, TB commonly led to reclassification to a higher risk group, which is accompanied by more aggressive radiotherapy treatment recommendations when compared with SB findings alone.

Keywords

Prostatic adenocarcinoma; Multiparametric MRI; Cancer imaging; Radiation Therapy

INTRODUCTION:

In the United States, Prostate Cancer (PCa) will account for nearly 20% of new cancer diagnoses in men in 2018.¹ The current gold standard for diagnosis is a systematic, but random, extended-sextant needle biopsy using transrectal ultrasound (TRUS)-guidance, called standard biopsy (SB). False negatives and under-grading from SB undersampling of PCa tumor burden is well documented, which may lead to erroneously conservative approaches in treatment recommendations.^{2, 3}

Multiparametric magnetic resonance imaging (MP-MRI) and subsequent MRI/ultrasound (US) fusion-targeted biopsy (TB) of suspicious areas found on MRI, has been shown to have improved utility in optimizing PCa detection and risk stratification by improving detection of clinically-significant PCa foci and reducing over diagnosis of low-grade tumors, compared with SB alone.⁴⁻⁷ As TB is increasingly incorporated into the clinical decision-making process, it will begin to drive an individualized approach in the management of PCa.⁸⁻¹⁰ There have been no large studies evaluating the effects of TB on radiation therapy (RT) recommendations for patients within each of the three primary PCa groups: biopsy naïve, active surveillance (AS), and prior negative biopsy. The purpose of this study is to determine if TB leads to increased recommendations of more aggressive radiotherapy treatments compared to SB pathology results.

METHODS:

This is an IRB approved retrospective analysis of prospectively gathered data of 643 men who underwent prostate biopsy with MRI-targeting at one institution from 2014-2017. Of these, 38 patients were excluded due to prior definitive treatment for PCa, and 72 were excluded due to missing data or having their most recent SB more than 24 months prior to undergoing TB at our institution. Clinicopathologic data was collected from the remaining 533 patients who underwent both SB and TB. Statistical analysis of the entire data set, as well as three individual study cohorts are included. Cohorts were defined based upon PCa status and prior prostate biopsy history: (1) Bx naïve, (2) AS, and (3) prior negative SB. Figure 1 demonstrates the manner by which inclusion criteria were applied to the selected patient records to identify the patient cohorts being investigated in this study.

The imaging protocol for MP-MRI prostate was as previously described.¹¹ All MP-MRIs were interpreted by a multidisciplinary consensus conference consisting of fellowship-trained radiologists and urologic oncologists specializing in prostate MRI to identify and score suspicion levels for lesions found and three-dimensionally segmented for TB.

Patients included in this study all had lesions suspicious for PCa on MP-MRI and underwent prostate biopsy as previously described.¹² SB at our institution consisted of TRUS-guided systematic extended-sextant 12-core biopsy performed in a concurrent session, but following TB sampling. All patients underwent TB using an office-based MRI/US fusion software platform that superimposed real-time TRUS with MP-MRI findings, identifying target lesions for biopsy. At least 2 targeted biopsy cores were obtained for each targeted area of interest segmented on MP-MRI as previously recommended.¹³ All MP-MRI biopsy pathology was reviewed by a single fellowship-trained surgical pathologist specializing in genitourinary disease and reported as previously described for TB.¹⁴

Recommended radiotherapy guidelines for each of the four cancer risk categories, which were derived based on biopsy Gleason score, Prostate Specific Antigen (PSA), and Digital Rectal Exam (DRE)-based clinical staging (Table 1).¹⁵ Cancer risk categories and corresponding radiotherapy recommendations were determined for each patient based on both TB and SB results, also considering PSA and DRE criteria. The Low Risk/No cancer group includes Gleason 6 cancers as well as patients where biopsy detected no cancer, such as patients with a past negative biopsy (Cohort 3). Comparisons of TB and SB were made by analyzing agreement risk categories due to biopsy method using a Bowker's test. Comparative analyses were performed for the entire data set as well as within each cohort. Additionally, a McNemar's test was used to analyze upgrading/downgrading between risk categories due to TB and SB in a pairwise fashion. A 2-sample test for equality of proportions was used to analyze outcomes of the effect of TB on RT recommendations according to the algorithm established in Table 1. A retrospective review of patient records was performed for patients with concurrent TB and SB documenting patient demographics and clinical data.

The reported statistical significance levels were all 2-sided, with a preset threshold of statistical significance: p -value < 0.05.

RESULTS:

A total of 533 patients were identified who met inclusion criteria and underwent both SB and TB. The mean age of patients was 66.0 years ($\pm$ 8.21) and PSA at the time of biopsy of 8.81 ng/mL ($\pm$ 7.65). Supplemental Table 1 demonstrates the demographic and clinical data for all combined patients and within each of our three cohorts, described in Figure 1.

We found significant variability in the number of patients within each cancer risk category due to TB when compared to SB when analyzing all combined patients ($p < 0.0001$). Specifically, TB increased cancer risk classification from a "No Cancer or Low-Risk" or "More Favorable Intermediate-Risk" classification to "High-Risk" in 74/533 patients (13.9%), with a significant number of patients being upgraded in the following categories: "Low-Risk" to "Less Favorable Intermediate-Risk" (29/343 (8.5%), $p < 0.0001$) and "No Cancer or Low-Risk" to "High-Risk" (31/353 (8.8%), $p < 0.0001$). Table 2 illustrates the reclassification of cancer risk categories due to TB, and the number of upgraded patients due to TB can be extrapolated from the presented data. These findings correspond with

aggressive radiotherapy recommendations for an additional 69/533 (13%) patients ($p < 0.0001$) due to TB when compared to SB, as shown in Figure 2.

Our analysis of biopsy naïve patients (Cohort 1) did not find any significant variance in radiation therapy recommendations due to TB ($p = 0.09$). However, TB still resulted in a significant number of patients being upgraded from “No Cancer or Low-Risk” to “Less Favorable Intermediate-Risk” (4/52 (7.7%), $p = 0.046$) within the biopsy naïve cohort, shown in Table 2b.

Among patients on AS (Cohort 2), we found that the use of TB resulted in significant variation in the number of patients within each cancer risk category ($p = 0.0005$) when compared to SB. A significant number of AS patients were upgraded from “No Cancer or Low-Risk” to “Less Favorable Intermediate-Risk” (10/135 (7.4%), $p = 0.04$) due to TB. Table 2c illustrates the reclassification of cancer risk categories due to TB. Within the cohort, TB resulted in more aggressive RT recommendations of all types for 15/185 (8.1%) patients.

We found significant variation in the number of patients within cancer risk categories ($p < 0.0001$) in patients with history of prior negative biopsy (Cohort 3) due to TB when compared to SB. In this cohort, TB upgraded significant numbers of patients from “No Cancer or Low-Risk” to “Less Favorable Intermediate-Risk” (16/156 (10.3%), $p = 0.0004$) and “No Cancer or Low-Risk” to “High-Risk” (28/171 (16.4%), $p < 0.0001$). Table 2d illustrates the reclassification of cancer risk categories due to TB. Within the cohort, TB resulted in increased instances of aggressive RT recommendations of all types for 51/268 (19.0%) patients. A similar distribution of biopsy pathology findings were seen when the cohort analyses were evaluated for patients who underwent concurrent repeat SB at the time of their fusion TB (Supplemental Table 2).

DISCUSSION:

MP-MRI continues to gain traction as an advantageous tool in the diagnosis and management of PCa. It has been shown to be a multidimensional diagnostic tool with implications for initial assessment of suspected PCa in men being considered for prostate biopsy, diagnosis and staging of PCa, and in selection of appropriate treatment modalities. The specificity of pre-biopsy MP-MRI is highlighted by studies showing that MP-MRI detecting highly suspicious lesions have a strong correlation with the presence of clinically-significant PCa (Gleason ≥ 7).^{4, 16} Additionally, TB has been shown to improve detection of clinically-significant PCa (Gleason ≥ 7) when compared to SB, while limiting the detection of indolent PCa (Gleason 6).⁴⁻⁷ It is also well established that, when compared to SB, TB results in significant upgrading of low grade cancers.^{3, 5, 6} Our study supports current body of literature in finding that, among our patients, TB resulted in cancer upgrading from low-risk to clinically-significant cancers ($p < 0.0001$ for Gleason 6/Grade Group (GG) 1 to both Gleason 4+3/GG 3 and Gleason ≥ 8 /GG ≥ 4). We also determined that TB found less of the clinically-insignificant, Gleason 6 cancers than SB. Furthermore, among all combined patients, we found that cancers which would result in more aggressive radiotherapy and androgen suppression recommendations (Gleason 4+3/GG 3 and Gleason ≥ 8 /GG ≥ 4) were

identified with increased frequency by TB when compared to SB ($p < 0.0001$), seen in Figure 2.

The vast body of evidence of MP-MRI and TB superiority over SB alone in grading of prostate malignancies also inspired interest in the expanded potential of this technology. TB has been shown to be superior to SB in detecting core length and cancer core invasion, and MP-MRI has been shown to provide improved detection of extra-prostatic extension, including seminal vesicle invasion (SVI), indicating T3b and “very high-risk” disease.^{6, 17-19} Improved accuracy of preoperative prognosis provided by MP-MRI may allow for proper counseling of PCa patients prior to radical prostatectomy, or may open discussion with patients on alternative treatment pathways for high-risk disease known to carry a worse prognosis that may benefit from multimodal therapies.²⁰

Perhaps the most important role of MP-MRI and TB is in improving risk stratification of patients suspected of having PCa. When compared with SB, TB has been found to better predict Gleason grading found on histopathology and reduce upgrading following radical prostatectomy^{21, 22}. With improved sensitivity and specificity for high-risk cancers (Gleason 7) and more accurate detection of extraprostatic tumor extension, TB can lead to less under diagnosis and provide clinicians with greater ability to appropriately counsel and manage PCa patients. Additionally, with added confidence that TB reduces upgrading after surgical resection, clinicians may be better equipped to identify candidates for radical prostatectomy and guide extent of lymphadenectomy performed.

Of course, the impetus for all the aforementioned investigations is the underlying conjecture that, as imaging plays a large role in management of all other types of solid tumors, MP-MRI has the potential to alter clinical decision making for PCa patients as well. MP-MRI may safely aid in selecting AS patients due to its superior negative predictive value when compared to SB by ruling out otherwise occult, clinically-significant PCa.^{23, 24} When clinically feasible, we commonly perform the MRI and TB within the first year after initial diagnosis of low-grade PCa considering AS to assess for otherwise occult clinically-significant PCa. It may also aid in predicting the probability of PCa upgrading on subsequent TB, allowing for deferred biopsy in certain AS patients.¹¹ In addition, TB has been shown to downgrade PCa in some AS patients with initial SB, indicating that early incorporation of TB into the initial AS eligibility criteria may limit reclassification of patients as ineligible for AS at follow-up biopsy.²⁵ Our study found that TB identified cancer grade progression which resulted in upgrading 57/185 (30.1%) patients presenting with Gleason 6/GG 1 PCa in our AS cohort to a higher risk category. Of these, 30/185 (16.2%) upgraded patients correlated with more aggressive RT recommendations. These findings suggest that TB may help in identifying under-diagnosed patients currently on AS, further substantiating the claim that MP-MRI may provide benefit in the management of AS patients by culling out those with otherwise occult foci of higher grade PCa.

Despite the body of knowledge surrounding the benefits of performing MP-MRI and TB to SB, understanding is still lacking on the effects of their integration into patient care on the multidisciplinary treatment of PCa as it has not been widely adopted worldwide in the majority of centers offering prostate biopsy.²⁶ TB has largely been discussed as a beneficial

tool for urologists; however, it may also have significant clinical applications for radiation oncologists. In patients seeking radiotherapy as definitive PCa treatment, the detailed anatomical picture provided by MP-MRI has been found to alter radiation treatment planning for advanced disease, such as lesions with extra-prostatic extension.^{20, 27} Reed et al. has published the only study that we have identified which investigates the effects of TB on RT decision-making for PCa. Their study of 73 PCa patients found that incorporating TB into treatment planning resulted in intensified ADT treatments in 16% of patients.⁹ Our study resulted in similar findings, with ADT being appropriate in an additional 69/533 (13%) of patients due to TB when compared to SB alone ($p < 0.0001$). Our study went further and determined that TB would result 138/533 (26%) more occurrences of recommendations for all types of aggressive radiotherapy treatments as defined in Table 1 for PCa GG 3 compared to SB ($p < 0.0001$). This illustrates the superiority of TB in finding otherwise occult, clinically-significant cancers.

As further investigation continues to explore the entire scope of application for TB, it will greatly contribute the evolution of PCa management toward more individualized patient care. Further, a multidisciplinary approach in interpreting findings may augment team-based care plans and improve patient outcomes by allowing greater access to alternative treatments such as radiotherapy that may not be readily available to all PCa patients based on established referral patterns.

Strengths of this study include a well-corroborated and standardized procedure for imaging, TB, and biopsy sextant mapping for the localization of PCa foci. Patients in this study analysis underwent both SB as well as TB, each acting as his own internal control. Thus far, we have not assessed the diagnostic yield of TB in isolation, without SB though this is an area of investigation at our institution and other centers with extensive TB experience. This study also includes one of the largest sample sizes from a single institution for the analysis of the effects of TB on RT management. Additionally, our sample contained data from a diverse group of patients, with representation from biopsy naive, AS, and prior negative biopsy patients. The division of our data set into corresponding cohorts allows for more detailed analysis of the advantages of TB for the various clinical backgrounds of PCa patients.

We acknowledge that this study has limitations. Data was collected from a single institution with recognized experience in MP-MRI and TB which may not be extrapolated to all centers earlier in their learning curve of these techniques. Biopsy grading is known to vary somewhat compared to radical prostatectomy specimen pathology, however only a minority of patients had RP pathology available for review from this large patient cohort with many on AS and several electing to pursue RT. AS patients referred for confirmation of AS from an outside institution who underwent only TB at our institution were assumed to be low-risk as clinical parameters including PSA and PSA density was not always definitively known from the time of initial biopsy prior to referral. Additionally, family history of PCa was not consistently acquired across all patients included in this retrospective data collection and hence not used as a variable for analysis. Similarly, past negative biopsy patients referred from an outside institution who only underwent TB at our institution were assumed to be cancer free based on outside pathology referral. These patients represent only subsets of

Cohorts 2 and 3; however, this could skew the grade grouping in these cohorts. Our hypothesis was tested with a theoretical model, which assumes the recommendation of predetermined RT regimens based on limited clinical data and did not result in actual changes in management. In practice, clinicians may not adhere to such stringent guidelines when recommending RT treatments as treatment will always hinge on patient-specific factors. Furthermore, there is no existing consensus agreement of guidelines for RT treatments.

CONCLUSIONS:

Among men with PCa, TB commonly led to reclassification to a higher risk group, which is likely to be accompanied by more aggressive RT recommendations when compared with SB findings alone. Future prospective studies are needed to validate the degree of altered clinical recommendations regarding radiotherapy approaches due to TB in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

AS	active surveillance
Bx	biopsy
DRE	digital rectal exam
GG	Grade Grouping
PCa	Prostate Cancer
US	Ultrasound
TRUS	Transrectal ultrasound
MP-MRI	multiparametric magnetic resonance imaging
ADT	Androgen deprivation therapy
EBRT	External beam radiation therapy
RT	Radiation therapy
SBRT	Stereotactic body radiation therapy

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Figure 1:

Flowchart for study inclusion among men undergoing MRI targeted prostate biopsy.

PCa = prostate cancer; SB= standard biopsy; TB = targeted biopsy; MRI = magnetic resonance imaging

Figure 2:

Number of radiotherapy recommendations given to all patients based on cancer risk category assignment due to prostate biopsy Gleason score, PSA, and DRE staging.

ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; LNs = lymph nodes

Table 1 –

Prostate Cancer risk category classification criteria and associated radiotherapy recommendations.

Low-Risk PCa <ul style="list-style-type: none"> - Gleason 6, GG 1 - and PSA <10 ng/mL - and T2b by DRE 	<ul style="list-style-type: none"> - Fractionated EBRT or - SBRT or - Brachytherapy without EBRT
More Favorable Intermediate-Risk PCa <ul style="list-style-type: none"> - Gleason 3+4=7, GG 2 - or PSA 10-20 ng/mL - or T2c by DRE 	<ul style="list-style-type: none"> - Same as Low-Risk PCa
Less Favorable Intermediate-Risk PCa <ul style="list-style-type: none"> - Gleason 4+3=7, GG 3 - or PSA 10-20 ng/mL - or T2c by DRE 	<ul style="list-style-type: none"> - Short Term ADT (4 – 6 mo.) with either - Fractionated EBRT or - Brachytherapy with EBRT
High-Risk PCa <ul style="list-style-type: none"> - Gleason ≥8, GG ≥3 - or PSA ≥20 ng/mL - or T3a by DRE 	<ul style="list-style-type: none"> - Long Term ADT (18 – 28 mo.) with either - Fractionated EBRT including Pelvic LNs or - EBRT with brachytherapy boost

PCa = prostate cancer; GG = Grade Group; PSA = prostate specific antigen; DRE = digital rectal exam; EBRT = external beam radiotherapy; SBRT = stereotactic body radiotherapy; ADT = androgen deprivation therapy; LNs = lymph nodes

Table 2 –

Comparison of pathology from Standard Extended-Sextant Biopsy and Targeted MRI/Ultrasound Fusion Biopsy. (a) Combined Data Set (all Cohorts), (b) Biopsy Naïve Patients (Cohort 1), (c) Active Surveillance Patients (Cohort 2), and (d) Prior Negative Biopsy Patients (Cohort 3)

		Standard Extended-Sextant Biopsy Results				Totals	
		No Cancer or Low-Risk PCa	Intermediate-Risk PCa	High-Risk PCa			
MRI/US Fusion-Targeted Biopsy Results		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	More Favorable Gleason 3+4 or PSA 10-20 ng/mL or T2b	Less Favorable Gleason 4+3 or PSA 10-20 ng/mL or T2b	Gleason 8 or PSA ≥ 20 ng/mL or T3a		
a. Combined Data Set (all Cohorts)							
No Cancer or Low-Risk PCa		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	304	9	1	0	314
Intermediate-Risk PCa	Gleason 7 or PSA 10-20 ng/mL or T2b	More Favorable Gleason 3+4	66	49	0	3	118
		Less Favorable Gleason 4+3	30	6	8	1	45
High-Risk PCa		Gleason 8 or PSA ≥ 20 ng/mL or T3a	31	6	1	18	56
		Totals	431	70	10	22	533
b. Biopsy Naïve Patients (Cohort 1)							
No Cancer or Low-Risk PCa		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	45	2	0	0	47
Intermediate-Risk PCa	Gleason 7 or PSA 10-20 ng/mL or T2b	More Favorable Gleason 3+4	0	10	0	3	13
		Less Favorable Gleason 4+3	4	1	3	1	9
High-Risk PCa		Gleason 8 or PSA ≥ 20 ng/mL or T3a	1	0	1	9	11
		Totals	50	13	4	13	80
c. Active Surveillance Patients (Cohort 2)							
No Cancer or Low-Risk PCa		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	122	5	1	0	128
Intermediate-Risk PCa	Gleason 7 or PSA 10-20 ng/mL or T2b	More Favorable Gleason 3+4	22	14	0	0	36
		Less Favorable Gleason 4+3	10	1	2	0	13
High-Risk PCa		Gleason 8 or PSA ≥ 20 ng/mL or T3a	2	3	0	3	8
		Totals	156	23	3	3	185

		Standard Extended-Sextant Biopsy Results				Totals	
		No Cancer or Low-Risk PCa	Intermediate-Risk PCa	High-Risk PCa			
MRI/US Fusion-Targeted Biopsy Results		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	More Favorable Gleason 3+4 or PSA 10-20 ng/mL or T2b	Less Favorable Gleason 4+3 or PSA 10-20 ng/mL or T2b	Gleason 8 or PSA 20 ng/mL or T3a		
d. Prior Negative Biopsy Patients (Cohort 3)							
No Cancer or Low-Risk PCa		Gleason 6 and PSA < 10 ng/mL and T2a (by DRE)	137	2	0	0	139
Intermediate-Risk PCa	Gleason 7 or PSA 10-20 ng/mL or T2b	More Favorable Gleason 3+4	44	25	0	0	69
		Less Favorable Gleason 4+3	16	4	3	0	23
High-Risk PCa		Gleason 8 or PSA 20 ng/mL or T3a	28	3	0	6	37
		Totals	225	34	3	6	268

PCa = prostate cancer; MRI = magnetic resonance imaging; US = ultrasound; PSA = prostate specific antigen; DRE = digital rectal exam