# The value of magnetic resonance imaging-ultrasound fusion targeted biopsies for clinical decision-making among patients with previously negative transrectal ultrasound biopsy and persistent prostate-specific antigen elevation

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## Abstract

**Introduction:** Targeted biopsy approaches have been shown to increase the detection of clinically significant prostate cancer (csPCa) within index prostate lesions. We report our initial experience with magnetic resonance imaging-ultrasound fusion biopsies (MRI-TB) in a population of men who had a previously negative transrectal ultrasound (TRUS) biopsy, persistent prostate-specific antigen (PSA) elevation, and ongoing suspicion of PCa. Patients were followed prospectively to assess for changes in clinical management following targeted biopsy.

**Methods:** We prospectively followed the first 122 patients undergoing MRI-TB at our institution. All men had clinical suspicion of PCa, prior negative TRUS biopsies, and persistent PSA elevation. A total of 177 index lesions were identified on multiparametric MRI and reviewed using the Prostate Imaging Reporting and Data System (PI-RADS) v2 scoring system. Lesions classified as PI-RADS ≥3 received targeted biopsy. Biopsy-naive patients and those on active surveillance were excluded. The primary outcome was detection rate of csPCa, defined as International Society of Urological Pathology (ISUP) Grade Group (GG) ≥2. Multivariate analysis was used to determine predictors of csPCa on fusion biopsy.

**Results:** Prior to fusion biopsy, patients had a mean of 17.9±8.6 negative core biopsies per patient and a median PSA of 9.5 (standard deviation [SD] 6.2) ng/nl. MRI-TB resulted in diagnosis of csPCa in 42/122 (34.4%) patients. Clinically significant PCa was found in eight (13.1%), 14 (21.9%), and 25 (48.1%) of PI-RADS 3, 4, and 5 lesions, respectively. The location of csPCa was within the peripheral zone (55.3%), transitional zone (40.4%), and central zone (8.5%). Clinical outcomes of patients with newly diagnosed csPCa show 4.8%, 57.1%, and 38.1% receiving active surveillance, radiation treatment, and radical prostatectomy, respectively. Predictors for csPCa were presence of PI-RADS 5 lesions, age, length of time from MRI to biopsy, and smaller prostate volumes.

**Conclusions:** MRI-TB yields high detection rates for csPCa in men with elusive PSA elevation and frequently guides a change in clinical management. Clinical decision-making based on MRI findings and PI-RADS lesion scores are best informed by an understanding of institutional reporting patterns.

## Introduction

Traditional systematic transrectal ultrasound (TRUS)-guided prostate biopsy has the unfortunate limitation of missing lesions that are present outside the range of normal sampling.[1] False-negative rates are as high as 30–45%, resulting in diagnostic uncertainty and undertreatment.[2,3] There is now increasing recommendation to incorporate magnetic resonance imaging (MRI) in the typical workup of suspected localized prostate cancer.[4-6] Compared with targeted biopsy strategies incorporating MRI, standard TRUS biopsies have been shown to miss clinically significant prostate cancers (csPCa), particularly when a patient is harboring disease in the anterior or periurethral portions of the gland.[7-11] In the setting where patients have received a previously negative standard TRUS biopsy, there is robust evidence that an MRI-targeted biopsy (MRI-TB) strategy improves the detection of csPCa and decreases the incidence of clinically insignificant prostate cancer.[12,13] For biopsy-negative patients, a subsequent MRI-TB can result in detection of csPCa in 34% of patients compared to 16% when using TRUS biopsy alone.[14] This often results in a change in clinical management, as a number of patients will require subsequent intervention in the form of surgery, radiation, or active surveillance.

An ideal diagnostic test is one that can reliably and thoroughly detect true incidence of disease, while minimizing detection of insignificant findings, and does so in a timely fashion with minimal interventional risk. Multiparametric MRI is a useful tool in the detection of prostate cancer, with an overall sensitivity of 91% and specificity of 37% in a mixed population of biopsy-naive and previous biopsy patients.[4] Sensitivity rates increase for the detection of higher-grade prostate cancer, and MRI findings have been shown to correlate with prostate risk stratification.[15] MRI-TB offers the advantage and precision to specifically target a lesion, potentially catching prostate cancer in atypical areas that may be missed by routine TRUS biopsy. Repeat TRUS biopsy has limited value in this setting, with one series reporting the detection of csPCa to be as low as 7.7%.[16] There is also diminished cancer detection with subsequent biopsies, and much of the cancer detected is low-risk, at the cost of increased complications and potential overtreatment.[17]

The incorporation of MRI and fusion technology has allowed for more precise sampling of suspicious index lesions, reducing overdetection of disease by traditional methods and increasing the detection of prostate cancer that requires intervention.[8,18] However, there are concerning rates of inter-observer reliability using MRI when scans are re-read by high-volume tertiary center radiologists; in addition, much of the evidence supporting MRI use has been drawn from large tertiary centers.[19] Evidence is limited in smaller, low-volume centers. This study examined the clinical outcome of biopsy-negative men undergoing MRI-TB for suspicion of prostate cancer in a small academic setting.

## Methods

### Patient selection

This study received ethics approval by the Newfoundland and Labrador Health Research Ethics Board (HREB 20192982). This prospective study was performed between September 2018 and July 2020 following the inception of MRI-TB technique at a single tertiary care center in Atlantic Canada. Our cohort of men all had at least one previous systematic TRUS biopsy with ongoing clinical suspicion of prostate cancer via persistent prostate-specific antigen (PSA) elevation. Patients then received a prostatic MRI followed by MRI-TB if an index lesion was found to be Prostate Imaging Reporting and Data System (PI-RADS) 3 or greater. Patients were followed prospectively to identify any change in clinical management as result of their targeted biopsy findings. Exclusion criteria included patients with normal prostatic MRI, PI-RADS <3 lesions, and men receiving MRI-TB as part of active surveillance.

### Imaging acquisition and biopsy protocol

Multiparametric prostatic MRI was performed using either a 1.5 T or 3T MRI scanner (Siemens) and reported by one of six MRI subspecialty radiologists. Index lesions on MRI were reviewed using the PI-RADS v2 scoring system, with scores ranging from 1–5 to indicate the likelihood of csPCa. MRI-TB was performed in patients with PI-RADS 3 or greater index lesions. BkFusion ultrasound (US) technology and MIM software was used to fuse the US and MRI imagery in conventional manner. Three-dimensional contouring of index lesions was performed by the interpreting radiologist. Biopsies were performed by one of eight urologists at the Health Sciences Centre in St. John's, Newfoundland and Labrador. Transrectal biopsies were performed under local periprostatic anesthetic with the patient in left lateral position. The exact number of biopsy cores per index lesion was at the discretion of the surgeon based upon US findings and clinical judgement. Core biopsy tissue was centrally reviewed by two genitourinary subspecialty-trained pathologists prior to a consensus diagnosis. Clinically significant prostate cancer was defined as International Society of Urological Pathology (ISUP) Grade Group (GG) score ≥2.

### Statistical analysis

Descriptive statistics and frequencies were reported for all patients. Logistic regression was performed to predict risk of csPCa using the following variables: MRI to fusion days, biopsy to fusion days, prostate volume, PI-RADS lesion, tumor location, tumor zone, PSA, PSA density, and age. Only those variables with a p value ≤0.05 on univariate analysis were entered into the multivariate model. PI-RADS lesions and tumor location were included as bivariate variables in the multivariate analysis. All statistical analyses were performed by a biostatistician using IBM SPSS Statistics 25.

## Results

### Demographics

The study included 122 patients with a median age of 65 years (range 44–80) (Table 1). Participants had a median PSA of 9.5 ng/ml (standard deviation [SD] 6.2 ng/ml), a median PSA density of 0.188 ng/ml/cc (SD 0.164 ng/ml/cc), and a median prostate volume on MRI of 59.9 $cm^3$ (SD 43.8 $cm^3$). The median interval from mpMRI to fusion biopsy was 75 days (SD 131.9 days). Prior to fusion biopsy, patients had a mean of 17.9±8.6 negative core biopsies per patient. During fusion biopsy, patients had a mean of 2.8±1.1 core biopsies per index lesion.

**Table 1. Demographics in patients with persistent PSA elevation and previously negative TRUS prostate biopsy now undergoing MRI-US fusion prostate biopsy (n=122)**

| | Mean/median (SD) |
|---|---|
| Age (years) | 64.4/65.0 (7.1) |
| Most recent PSA (ng/ml) | 11.5/9.5 (6.2) |
| PSA density (ng/ml/cc) | 0.217/0.188 (0.164) |
| Prostate volume ($cm^3$) | 77.3/59.9 (43.8) |
| Interval between MRI and fusion biopsy (days) | 128.33/75.0 (131.9) |
| Number of cores per lesion | 2.8/3.0 (1.1) |
| Number of cores per patient prior to fusion Bx | 17.9/12 (8.6) |

Bx: biopsy; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; SD: standard deviation; TRUS: transrectal ultrasound; US: ultrasound.

### Diagnostic yield of MRI-TB

MRI-TB resulted in the diagnosis of PCa in 54/122 (44.3%) patients. Clinically significant PCa was found in five (7.8%), 14 (21.2%), and 23 (44.2%) of PI-RADS 3, 4, and 5 lesions, respectively. Clinically significant PCa was found within the peripheral zone (54.8%), transitional zone (40.5%), and central zone (9.5%) (Table 2). The location of csPCa lesions were within the anterior gland (n=23, 48.9%), mid-gland (n=16, 34.0%), and posterior gland (n=8, 17.0%) (Table 2).

### Clinical outcomes and location

Clinical outcomes of patients with newly diagnosed csPCa show 4.8%, 57.1%, and 38.1% undergoing active surveillance, radiation treatment, and radical prostatectomy, respectively (Table 3). Of the 122 patients who participated in the study, 40 patients (32.8%) ultimately chose treatment in the form of surgery or radiation therapy following a diagnosis of csPCa.

### Multivariate analysis

Results of univariate analysis are presented in Table 4 and multivariate logistic regression model in Table 5. Increasing PI-RADS score was associated with csPCa, as patients with PI-RADS 5 lesions were 3.7 times more likely to have csPCa when compared to other lesions (PI-RADS 3 or 4). Increasing age was associated with diagnosis of csPCa, while greater length of time from MRI to fusion and increased prostate volume were associated with a reduction in risk of csPCa. Lesion location and PSA density were not found to be significant.

**Table 2. Prostate cancer detection by PI-RADS score and lesion location in patients undergoing MRI-US fusion prostate biopsy**

| | |
|---|---|
| Cancer detection per patient (n=122) | |
| % positive on MRI-US fusion Bx | 44.3% |
| % negative on MRI-US fusion Bx | 55.7% |
| Patients with PCa (GG ≥1) | 54 (44.3%) |
| Patients with csPCa (GG ≥2) | 42 (34.4%) |
| Cancer detection per lesion (n=177) | |
| % positive on MRI-US fusion bx | 36.2% |
| % negative on MRI-US fusion bx | 63.8% |
| Lesions with PCa (GG ≥1) | 64 (36.2%) |
| Lesions with csPCa (GG ≥2) | 47 (26.6%) |
| Lesions detected by PI-RADS type | |
| PI-RADS 3 | 61 |
| PI-RADS 4 | 64 |
| PI-RADS 5 | 52 |
| PCa (GG1) by lesion score | |
| PI-RADS 3 | 5 (8.2%) |
| PI-RADS 4 | 8 (12.5%) |
| PI-RADS 5 | 4 (7.7%) |
| csPCa by lesion score | |
| PI-RADS 3 | 8 (13.1%) |
| PI-RADS 4 | 14 (21.9%) |
| PI-RADS 5 | 25 (48.1%) |
| csPCa by lesion zone | |
| Peripheral | 26 (55.3%) |
| Transition | 19 (40.4%) |
| Central | 4 (8.5%) |
| csPCa by lesion location | |
| Anterior | 23 (48.9%) |
| Midgland | 16 (34.0%) |
| Posterior | 8 (17.0%) |

Bx: biopsy; csPCa: clinically significant prostate cancer; GG: grade group; MRI: magnetic resonance imaging; PCa: prostate cancer; PI-RADS: prostate imaging reporting and data system. US: ultrasound.

## Discussion

In this population of TRUS biopsy-negative men who underwent MRI-TB for persistently elevated PSA, the detection rate of csPCa was found to be 34.4%. This led to a substantial change in clinical management, as most patients consequently chose to undergo radical prostatectomy or radiation therapy. A large percentage of csPCa was found in anterior lesions (48.9%), suggesting that disease may be persistent in this area after an initial negative TRUS biopsy. These findings are consistent with established literature sug-

**Table 3. Clinical outcomes of patients following detection of csPCa on MRI-TB**

| | |
|---|---|
| Patients with csPCa (GG ≥2) | 42/122 (34.4%) |
| Resulting treatment received by patients with csPCa | |
| Active surveillance | 2 (4.8%) |
| Radiation treatment | 24 (57.1%) |
| Radical prostatectomy | 16 (38.1%) |

csPCa: clinically significant prostate cancer; GG: grade group; MRI-TB: magnetic resonance imaging-targeted biopsy.

**Table 4. Univariate analysis of factors predicting the detection of csPCa by MRI-US fusion biopsy in patients with prior negative TRUS biopsy and persistent PSA elevation (n=122)**

| Feature | Prostate cancer, n (%) | No prostate cancer, n (%) | Odds ratio (95% CI) | p |
|---|---|---|---|---|
| mpMRI to fusion (days) | | | 0.995 (0.992–0.999) | 0.012* |
| Biopsy to fusion biopsy (days) | | | 1.000 (0.999–1.000) | 0.556 |
| Prostate volume on MRI | | | 0.981 (0.971–0.991) | 0.000* |
| PI-RADs lesions | | | | |
| 3 | 8 (13.1) | 53 (86.9) | 0.298 (0.129–0.688) | 0.005* |
| 4 | 14 (21.9) | 50 (78.1) | 0.679 (0.331–1.392) | 0.290 |
| 5 | 25 (48.1) | 27 (51.9) | 4.335 (2.126–8.841) | 0.000* |
| Index tumor location | | | | |
| Mid-gland | 16 (18.8) | 69 (81.2) | 0.456 (0.228–0.914) | 0.027* |
| Anterior | 23 (46.0) | 27 (54.0) | 3.656 (1.794–7.449) | 0.000* |
| Posterior | 8 (19.0) | 34 (81.0) | 0.579 (0.246–1.362) | 0.211 |
| Index tumor zone | | | | |
| Central | 4 (26.7) | 11 (73.3) | 1.006 (0.3304–3.329) | 0.992 |
| Transitional | 17 (20.7) | 65 (79.3) | 0.567 (0.285–1.127) | 0.105 |
| Peripheral | 26 (32.5) | 54 (67.5) | 1.743 (0.889–3.414) | 0.106 |
| PSA | | | 1.105 (1.003–1.108) | 0.038* |
| PSA density | | | 68.33 (6.990–668.032) | 0.000* |
| Age | | | 1.061 (1.008–1.118) | 0.024* |

*Statistically significant (p<0.05). CI: confidence interval; csPCa: clinically significant prostate cancer; MRI: magnetic resonance imaging; PCa: prostate cancer; PI-RADS: prostate imaging reporting and data system; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; US: ultrasound.

gesting the benefit of MRI-TB in the biopsy-negative setting. In a multi-institutional cohort of 779 patients conducted by Sidana et al,[20] the csPCa detection rate by MRI-TB was found to be 26.3%. In a systematic review and meta-analysis by Schoots et al,[8] MRI-TB in biopsy-negative patients outperformed TRUS, with a relative sensitivity of 1.54 (95% confidence interval 1.05–2.26) for the detection of csPCa. Our data confirms the utility of MRI-TB to detect elusive disease and suggests that a significant number of these patients (32.8%) will eventually require treatment.

**Table 5. Multivariate logistic regression model for the prediction of csPCa on MRI-fusion biopsy in men with prior negative TRUS biopsy and persistent PSA elevation (n=122)**

| Feature | Odds ratio (95% CI) | p |
|---|---|---|
| mpMRI to fusion (days) | 0.996 (0.992–1.000) | 0.038* |
| Prostate volume on MRI | 0.971 (0.952–0.990) | 0.003* |
| PI-RADs lesions[1] | | |
| 3 | 1.007 (0.332–3.055) | 0.990 |
| 5 | 3.698 (1.411–9.691) | 0.008* |
| Index tumor location[2] | | |
| Mid-gland | 0.910 (0.309–2.679) | 0.865 |
| Anterior | 2.665 (0.850–8.354) | 0.093 |
| PSA | 1.021 (0.905–1.152) | 0.734 |
| PSA density | 0.347 (0.002–57.831) | 0.685 |
| Age | 1.078 (1.006–1.156) | 0.034* |

[1]Reference variable: Other PI-RADS lesions. [2]Reference variable: Other lesion location.
*Statistically significant (p<0.05). CI: confidence interval; csPCa: clinically significant prostate cancer; mp: multiparametric; MRI: magnetic resonance imaging; PCa: prostate cancer; PI-RADS: prostate imaging reporting and data system; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; US: ultrasound.

We found csPCa detection rates of 7.8%, 21.2%, and 44.2% for PI-RADS 3, 4, and 5 lesions, respectively, which could be considered low when initially comparing to contemporary series. The European Association of Urology reports a working range of detection by PI-RADS score, with rates of 4–27% (PI=RADS 3), 32–60% (PI-RADS 4), and 67–83% (PI-RADS 5).[21] A large meta-analysis performed by Park et al reported detection rates as 17%, 46%, and 75%, for PI-RADS 3, 4, and 5, respectively.[22] However, such series involve a heterogenous mix of biopsy-naive and previous biopsy patients, and thus differ from our population composed solely of previous biopsy-negative patients. In fact, our results are similar to Sathianathen et al, who reported a lower detection rate of csPCa — 3%, 16%, and 58% for PI-RADS 3, 4, and 5, respectively — in previous biopsy patients when compared to biopsy-naive patients or patients on active surveillance.[23] In reality, the lower detection rates per PI-RADS 4 and 5 lesions identified in our study is likely multifactorial and portrays the trials and tribulations of a new biopsy technique, new contouring software, and associated learning curves.

We confirmed that PI-RADS 5 lesions were associated with higher detection rates of csPCa by targeted biopsy, with an odds ratio of 3.7, in comparison to either PI-RADS 3 or 4 lesions. However, neither PI-RADS 3 nor 4 lesions were significantly associated with higher detection rates in our study — a discovery plausibly reflective of our sample size, learning curve, and/or institutional reporting patterns. Previous publications indicated that when radiologists in tertiary centers re-evaluated prostate MRIs performed at a

regional center, there was disagreement in as many as 54% of reports, with second reads resulting in an improved positive predictive value and negative predictive value.[19] Thus, there is concern for the application of MRI ubiquitously in settings with limited access and detection rates likely more pragmatic, as in our results. Outside of a high-volume center, Kohestani et al showed that there was only moderate agreement (κ=0.41) between readers.[24] These findings and limitations of MRI usage, as well as local reporting rates, should be taken into account when counselling a patient with clinical suspicion of PCa. For patients undergoing repeat biopsy for persistent suspicion of csPCa, MRI-TB consistently outperforms TRUS, yet there remains concern for disease that is potentially also missed on MRI-TB. The quantity of missed disease has been widely reported as 5.6–15%,[23] and thus the decision to perform concurrent systematic biopsy alongside MRI-TB should be made based on individualized PCa risk and risk tolerance. Current recommendations are based on a followup analysis of the FUTURE trial,[14] which looked at patients receiving both MRI-TB and standard biopsies. In a core-by-core analysis, standard TRUS biopsy resulted in an additional csPCa diagnosis of 1.3% that would have been missed if only MRI-TB was performed. This is balanced against the potential for increased adverse effects with MRI-TB plus standard TRUS biopsy, as more biopsy cores infers a longer procedure time, greater patient discomfort, and possibly increased risk of bleeding. Indeed, Arsov et al[25] found that one csPCa diagnosis was the result of 19 MRI-TB cores, compared to 55 when using standard TRUS biopsy.

### Limitations

Our study has several limitations. First, patients undergoing fusion biopsy only had MRI-TB completed at the time of the procedure, limiting our ability to directly compare detection rates to a standard TRUS biopsy method.

Another limitation includes the extended time interval between mpMRI and fusion biopsy. The large deviation in time is representative of the challenges faced by patients in Newfoundland. The large geographic area covered by our tertiary care center, companied with a small number of MRI scanners and unpredictable weather conditions, often result in appointment delays. Initial technical issues were also experienced with contouring software, which led to a transient delay in performance of targeted biopsies until resolved. Greater duration from imaging to MRI-TB can conceptually result in lesion growth during that time, increasing the positive detection rate upon TB, particularly in smaller-volume prostates. Albeit this could also influence contour positioning if prostate gland geometry had altered in the interim.

Thirdly, data collection for this study began with inception of MRI-US fusion biopsies at our center, possibly limiting the applicability of early biopsies completed during the initial learning curve experienced by both radiology and urology staff.

Fourthly, each radiologist individually reported their MRI findings without a central review panel, thus creating inter-reader variability.

Finally, when performing MRI-TB the previously mapped fusion image may undergo compression by the endorectal US probe, affecting the precision of biopsy, particularly when aiming for smaller lesions. The device used in this study does not accommodate for this gland compression, whereas other series may have varied results based on devices that do accommodate.

Despite these limitations, we believe our findings are still valid and reflect the real-world utility of prostate fusion biopsies in a pragmatic setting. We believe this data will be of interest to community urology or small academic centers contemplating or beginning MRI-US fusion biopsy techniques. Few smaller centers have published similar series, despite the importance of quality assurance to confirm that local data is in keeping with large center studies.

## Conclusions

In patients with previous negative TRUS biopsies, csPCa was detected by MRI fusion biopsies in 34.4% of cases, leading to a change in clinical management for many of these patients. It is important to establish institutional detection rates of PI-RADS lesions, as this can significantly affect the clinical management of PCa patients.

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This paper has been peer-reviewed.

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