Using Prostate Imaging-Reporting and Data System (PI-RADS) Scores to Select an Optimal Prostate Biopsy Method: A Secondary Analysis of the Trio Study

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Abstract

**Background:** While magnetic resonance imaging (MRI)-targeted biopsy (TBx) results in better prostate cancer (PCa) detection relative to systematic biopsy (SBx), the combination of both methods increases clinically significant PCa detection relative to either Bx method alone. However, combined Bx subjects patients to higher number of Bx cores and greater detection of clinically insignificant PCa.

**Objective:** To determine if prebiopsy prostate MRI can identify men who could forgo combined Bx without a substantial risk of missing clinically significant PCa (csPC).

**Design, setting, and participants:** Men with MRI-visible prostate lesions underwent combined TBx plus SBx.

**Outcome measurements and statistical analysis:** The primary outcomes were detection rates for grade group (GG) \(\geq 2\) and GG \(\geq 3\) PCa by TBx and SBx, stratified by Prostate Imaging-Reporting and Data System (PI-RADS) score.

**Results and limitations:** Among PI-RADS 5 cases, nearly all csPCs were detected by TBx, as adding SBx resulted in detection of only 2.5% more GG \(\geq 2\) cancers. Among PI-RADS 3–4 cases, however, SBx addition resulted in detection of substantially more csPCs than TBx alone (7.5% vs 8%). Conversely, TBx added little to detection of csPC among men with PI-RADS 2 lesions (2%) relative to SBx (7.8%).

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Conclusions: While combined Bx increases the detection of csPC among men with MRI-visible prostate lesions, this benefit was largely restricted to PI-RADS 3–4 lesions. Using a strategy of TBx only for PI-RADS 5 and combined Bx only for PI-RADS 3–4 would avoid excess biopsies for men with PI-RADS 5 lesions while resulting in a low risk of missing csPC (1%).

Patient summary: Our study investigated an optimized strategy to diagnose aggressive prostate cancer in men with an abnormal prostate MRI (magnetic resonance imaging) scan while minimizing the risk of excess biopsies. We used a scoring system for MRI scan images called PI-RADS. The results show that MRI-targeted biopsies alone could be used for men with a PI-RADS score of 5, while men with a PI-RADS score of 3 or 4 would benefit from a combination of MRI-targeted biopsy and systematic biopsy.

This trial is registered at ClinicalTrials.gov as NCT00102544.

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1. Introduction

Inaccurate diagnosis of prostate cancer is a longstanding problem in prostate cancer care. Until recently, the biopsy method most commonly used was transrectal ultrasonound-guided 12-core systematic prostate biopsy, which uses a template to ensure evenly spaced biopsies within the prostate, without knowledge of the tumor location within the gland [1]. It has been shown that this technique leads to frequent missed diagnoses, grade misclassification, and a considerable complication rate [2–6].

In the last decade, multiple high-quality studies have demonstrated that prostate magnetic resonance imaging (MRI) followed by MRI-targeted biopsy results in better detection of clinically significant cancer compared to systematic biopsy [7–12]. However, the role for systematic biopsy is now unclear, as recent high-quality studies have demonstrated that systematic biopsies used in combination with MRI-targeted biopsies result in higher detection rates for clinically significant cancer in comparison to MRI-targeted biopsies alone [8,10,11]. Furthermore, it has been shown that use of the two biopsy methods in conjunction (combined biopsy) can greatly reduce the risk of upgrading at the time of prostatectomy [11].

Unfortunately, use of combined biopsy subjects men to sampling of a substantially greater number of biopsy cores (average of 15–18 vs 3–5) [10,11], higher complications rates [6,13,14], and a risk of diagnosis of clinically insignificant prostate cancer [7–12]. As a result, many care providers have expressed an intention to forgo systematic biopsy despite evidence supporting its use in conjunction with MRI-targeted biopsy. The use of MRI-targeted biopsy alone has some merit, as it would lead to a 5% reduction in detection of indolent cancer, an average reduction of 12 biopsy cores per biopsy session, a decrease in interventions, and, potentially, lower rates of biopsy-associated complications. However, use of MRI-targeted biopsy alone risks missing clinically significant prostate cancers [10,11].

In this subset analysis of the Trio study [11] we sought to ascertain whether prebiopsy Prostate Imaging-Reporting and Data System (PI-RADS) scores can be used to determine if any patient groups can reasonably forgo combined biopsy in favor of MRI-targeted biopsy alone, without sacrificing detection of substantial clinically significant cancer [11].

2. Patients and methods

2.1. Study design

Beginning in July 2007, patients were enrolled in a prospectively designed, nationally registered, institutional review board–approved clinical trial at the National Cancer Institute (Bethesda, MD, USA) to evaluate the use of MRI-targeted-ultrasound fusion prostate biopsy for detection of prostate cancers (ClinicalTrials.gov, NCT00102544). Patients older than 18 yr with an abnormal digital rectal examination or abnormal prostate-specific antigen (PSA) were eligible for study enrollment. After enrollment, patients underwent multiparametric prostate MRI. Patients found to have a lesion on prostate MRI underwent both MRI-targeted and systematic prostate biopsy in the same setting, regardless of prior biopsy status. Exclusion criteria included prior prostate cancer treatment, absence of MRI-visible prostate lesions, or inability to undergo MRI (body habitus incompatible with MRI equipment, presence of ferrous metallic implants, or claustrophobia). For the purpose of this analysis, only patients who underwent prostate MRI after adoption of the PI-RADS v2.0 scoring system (April 2015) were included. A detailed description of the Trio study methods was previously reported [11].

2.2. MRI protocol

MRI scans were performed using a 3.0-T magnet (Achieva; Philips Healthcare, Cambridge, MA, USA) with an endorectal coil (Medrad BPX-30; Bayer, Whippany, NJ, USA) for all initial scans. In the rare event of contraindications to the use of an endorectal coil (latex allergy, anal fistula, active hemorrhoids, or absence of a rectum) scans were performed without a coil. T2-weighted, diffusion-weighted, and dynamic contrast-enhanced series were obtained, in accordance with PI-RADS v2.0 guidelines [15]. All MRI scans were interpreted by an expert genitourinary radiologist and lesions were assigned a PI-RADS v2.0 score to stratify their risk of prostate cancer according to the imaging findings (Supplementary Table 1) [16]. PI-RADS scores ranged from 1, or normal, to 5, or highly suggestive of cancer. In the event of multiple MRI-visible lesions, the highest PI-RADS score detected was coded as the patient’s reported PI-RADS score. Lesions detected on MRI were labeled for biopsy by the same radiologist who interpreted the study using DynaCAD software (Philips Healthcare) before the prostate biopsy. No more than five biopsy targets were labeled for any individual patient. For large
lesion that extended into a second prostate segment (defined according to systematic biopsy prostate segmentation) or crossed the midline, a second target was placed on that lesion, as previously described [17].

2.3. **Prostate biopsy protocol**

All patients with MRI-visible lesions (PI-RADS score ≥ 2) underwent both transrectal MRI-targeted and systematic biopsies at a single institution in the same setting. MRI-targeted biopsies were performed using UroNav MRI/ultrasound fusion software (Philips Healthcare), followed by a transrectal ultrasound-guided systematic 12-core extended sextant biopsy performed by a second physician, as previously described [11]. Systematic biopsies were performed using standard prostate biopsy segmentation with ultrasound guidance alone [18]. Biopsies were performed by urologists, radiologists, or both. The radiologist who interpreted the MRI and assigned lesions for targeting was never the same person who performed the prostate biopsies.

Among patients who underwent multiple biopsies over time, only results for the first biopsy performed at our institution were included in the study analysis. All biopsies were classified by grade group (GG) [19] and reported in accordance with the START Consortium [20]. All biopsy histopathology was interpreted by a single experienced genitourinary pathologist. The total cancer detection rate was defined as the cancer detection rate with combined biopsy.

2.4. **Data management**

Data were collected prospectively by a dedicated data manager as part of a database designed before the trial started. Data collection began in August 2007 and was culled in January 2019 for data analysis. The highest Gleason score detected by each biopsy method was recorded and coded as GG 1–5.

2.5. **Definition of terms**

Throughout this manuscript, the term combined biopsy refers to the use of systematic and MRI-targeted biopsy in the same setting. The added value for GG ≥2 (or GG ≥3) cancer detection refers to GG ≥2 (or GG ≥3) cancers detected by one biopsy method alone (either MRI-targeted or systematic biopsy) but diagnosed as GG <2 (or GG <3) by the other method. Clinically significant cancer refers to GG ≥2 cancers. However, given that some physicians consider the threshold of GG ≥3 as more clinically relevant, cancer detection rates for GG ≥2 and GG ≥3 are provided in all tables and figures. Clinically insignificant prostate cancer refers to GG 1 cancers.

As MRI-targeted biopsy and systematic biopsy could result in diagnosis of different cancer GGs, discrepancies in cancer diagnoses between the biopsy methods were described as misclassifications, which were further subdivided into understaging or missed cancer. Misclassified cancer diagnosis describes any situation in which cancer above a clinical threshold (GG ≥2 or GG ≥3) was detected by one biopsy modality and the other biopsy method assigned a grade group below that threshold. If the second method diagnosed cancer, but below the clinically relevant threshold (GG <2 or GG <3), this was classified as understaging. However, if the second method missed the cancer altogether, this was classified as missed cancer.

2.6. **Outcomes**

Results for the primary outcome of the cancer detection rate for each biopsy method by grade group (GG 1–5) were previously reported [11]. In this subanalysis, the primary hypothesis was that PI-RADS scores could be used to define subsets of patient for whom use of MRI-targeted biopsy alone would result in a low risk of missed clinically significant cancer.

2.7. **Statistical analysis**

For the primary analysis, McNemar’s test was used to compare cancer detection rates between MRI-targeted biopsy and systematic biopsy among the various PI-RADS groups. An adjusted Wald interval was used to calculate the confidence intervals for cancer detection rates and the differences in cancer detection rates between the two biopsy methods for each PI-RADS cohort [21,22]. Bonferroni correction was used to adjust for the eight statistical comparisons of the primary outcome (four PI-RADS groups assessed for GG ≥2 and GG ≥3, resulting in eight outcomes), with statistical significance indicated by p < 0.006. Statistical tests to compare cancer detection rates for combined biopsy with each of its constituent biopsy techniques was not performed as the cancer detection rate for combined biopsy was defined as the highest grade group detected by the two biopsy techniques. In addition, univariate analyses were performed to evaluate for co-relations between the added value of systematic biopsy and various preoperative variables, including patient age, PSA, PSA density, and prostate volume (Supplementary Figs. 2 and 3).

3. **Results**

A total of 723 men met the inclusion criteria, underwent prostate MRI, were assigned a prospective PI-RADS score of 2–5, and subsequently underwent MRI-targeted and systematic prostate biopsy (Fig. 1). PI-RADS 4 and 5 were the most common scores assigned (47.9% and 33.1%, respectively) and a total of 504 men (69.7%) were diagnosed with prostate cancer. Higher PI-RADS scores were associated with a higher rate of detection of any cancer (PI-RADS 5, 94.6%; PI-RADS 4, 62.4%; PI-RADS 3, 49.4%; PI-RADS 2, 37.3%; Table 1). A total of 74.4% percent of men had undergone a previous systematic biopsy and were found to have no cancer or indolent cancer by systematic biopsy before study enrollment. The mean number of cores was 4.7 for MRI-targeted biopsy and 12.1 for systematic biopsy (Table 1).

3.1. **PI-RADS 5 lesions**

Among the 239 men with PI-RADS 5 prostate lesions, 198 clinically significant cancers were detected (82.8%). Nearly all of these 198 clinically significant cancers (97.0%) were detected by MRI-targeted biopsy (n = 192). Among the 239 men with PI-RADS 5 lesions, systematic biopsy only resulted in six more (2.5%) GG ≥2 and two more (0.8%) GG ≥3 cancer diagnoses. Two men classified as GG ≥3 by systematic biopsy were classified as GG 2 by MRI-targeted biopsy (Supplementary Fig. 3). Of six men (2.5%) classified as having GG 2 disease by systematic biopsy, three (1.3%) were understaged as having GG 1 cancer and three (1.3%) were classified as having no cancer by MRI-targeted biopsy (Supplementary Fig. 3). Use of systematic biopsy resulted in no additional detection of GG 4 or GG 5 cancer relative to MRI-targeted biopsy alone. The differences in detection of GG ≥2 (16.7%; p < 0.001) and GG ≥3 (15.5%; p < 0.001)
cancers between MRI-targeted and systematic biopsy were statistically significant (Supplementary Fig. 2).

### 3.2. **PI-RADS 4 lesions**

Among men with PI-RADS 4 lesions (n = 346), MRI-targeted biopsy detected more clinically significant cancer than systematic biopsy (GG ≥2: 35.8% vs 28.0%; p = 0.003; GG ≥3: 13.9% vs 9.8%; p = 0.035; Fig. 2 and Supplementary Fig. 2). However, systematic biopsy detected an additional 7.5% more GG ≥2 and 3.5% more GG ≥3 cancers that were not detected by MRI-targeted biopsy alone (Fig. 2 and Supplementary Fig. 2). As well as detecting more clinically significant cancers, addition of systematic biopsy resulted in 28 (8.1%) more diagnoses of clinically insignificant cancer.

### 3.3. **PI-RADS 3 lesions**

Unlike the group with PI-RADS 4–5 lesions, the cohort with PI-RADS 3 lesions (n = 87) had more clinically significant cancers detected by systematic biopsy relative to MRI-targeted biopsy, although this difference was not statistically significant (17.2% vs 13.8%; p = 0.54; Fig. 2 and Supplementary Fig. 2). Similar to the PI-RADS 4 group, systematic biopsy contributed to significant additional detection of GG ≥2 and GG ≥3 cancers relative to MRI-targeted biopsy alone (8.0% and 3.4%, respectively; Fig. 3 and Supplementary Fig. 4). Furthermore, addition of systematic biopsy in this group also resulted in diagnosis of 14 more (16.1%) indolent cancers.

### 3.4. **PI-RADS 2 lesions**

For men with PI-RADS 2 lesions (n = 51), systematic biopsy detected more clinically significant cancers than MRI-targeted biopsy (15.7% vs 9.8%; p = 0.37; Fig. 2 and Supplementary Fig. 2). Unlike men with higher PI-RADS scores, for men with PI-RADS 2 lesions MRI-targeted biopsy resulted in minimal additional diagnoses of GG ≥2 and GG ≥3 cancers (2% and 2%, respectively; Fig. 3 and Supplementary Fig. 4). Interestingly, clinically significant cancer was detected by combined biopsy in 17.6% (n = 9) of men with PI-RADS 2 lesions (Fig. 2). Systematic biopsy alone detected eight of the nine GG ≥2 cancers detected by MRI-targeted biopsy, while MRI-targeted biopsy only resulted in one clinically relevant upgrading event (Supplementary Fig. 3).

### 3.5. **Opportunities for MRI-targeted biopsy alone**

Collectively, the added value of GG ≥2 and GG ≥3 cancer detection by systematic biopsy was low among patients with PI-RADS 5 lesions (2.5% and 0.8%, respectively). Moreover, MRI-targeted biopsy resulted in minimal additional detection of clinically significant cancer (2%) in the PI-RADS 2 cohort. However, men with PI-RADS 3–4 lesions had substantially more diagnoses of clinically significant cancers by combined biopsy. Therefore, if a decision was made to forgo systematic biopsy for the PI-RADS 5 group and forgo MRI-targeted biopsy for the PI-RADS 2 cohort, then 290 men (40.1%) would be spared a combined biopsy.
These men would be subjected to sampling of an average of 12.1 fewer biopsy cores compared to combined biopsy. Such a strategy would result in a low risk of misclassifying GG ≥2 cancer diagnoses of only 1.0% (n = 7) of all men who underwent biopsy (Table 2). Among the seven men (1%) in the entire study population who would have been missed by this strategy, four (0.6%) would have been understaged as GG 1 and three (0.4%) would have been misdiagnosed as having no cancer.

Attempts to further subdivide the PI-RADS 2–5 and PI-RADS 3–4 groups by age, PSA, PSA density, or prostate volume to define a further population who could reasonably forgo systematic biopsies did not reach the threshold for statistical significance. These results are discussed extensively in the Supplementary material (Supplementary Figs. 1 and 2).

### Table 1 – Patient demographics and clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 723)</th>
<th>Bx-naive (n = 185)</th>
<th>Prior Bx (n = 538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± standard deviation (yr)</td>
<td>64.4 ± 7.5</td>
<td>65 ± 7.6</td>
<td>64.3 ± 7.4</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>554 (76.6)</td>
<td>142 (76.8)</td>
<td>412 (76.6)</td>
</tr>
<tr>
<td>Black</td>
<td>96 (13.3)</td>
<td>21 (11.4)</td>
<td>75 (13.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>30 (4.2)</td>
<td>10 (5.4)</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (0.7)</td>
<td>1 (0.5)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (2.2)</td>
<td>3 (1.6)</td>
<td>13 (2.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (3.0)</td>
<td>8 (4.3)</td>
<td>14 (2.6)</td>
</tr>
<tr>
<td>Median prostate-specific antigen, ng/ml (IQR)</td>
<td>6.0 (4.7–9.8)</td>
<td>5.6 (4.3–8.1)</td>
<td>7.5 (5–10.3)</td>
</tr>
<tr>
<td>Maximum prostate-specific antigen (ng/ml)</td>
<td>113.6</td>
<td></td>
<td>98.6</td>
</tr>
<tr>
<td>Tumor stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>219 (30.3)</td>
<td>63 (34.1)</td>
<td>156 (29.0)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>504 (69.7)</td>
<td>122 (66.0)</td>
<td>382 (71.0)</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>443 (61.3)</td>
<td>99 (53.5)</td>
<td>344 (63.9)</td>
</tr>
<tr>
<td>T2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T2a</td>
<td>45 (6.2)</td>
<td>16 (8.7)</td>
<td>29 (5.4)</td>
</tr>
<tr>
<td>T2b</td>
<td>6 (0.8)</td>
<td>4 (2.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>T2c</td>
<td>10 (1.4)</td>
<td>3 (1.6)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>T3a</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T3b</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median prostate volume, cm³ (IQR)</td>
<td>53 (40–73)</td>
<td>50 (39–66)</td>
<td>54.5 (40–76)</td>
</tr>
<tr>
<td>Maximum prostate volume (cm³)</td>
<td>420</td>
<td>140</td>
<td>420</td>
</tr>
<tr>
<td>Prior biopsy result, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy-naive</td>
<td>185 (25.6)</td>
<td>185 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>538 (74.4)</td>
<td>-</td>
<td>538 (100)</td>
</tr>
<tr>
<td>Negative</td>
<td>257 (35.6)</td>
<td>-</td>
<td>257 (47.77)</td>
</tr>
<tr>
<td>Positive</td>
<td>281 (38.9)</td>
<td>-</td>
<td>281 (52.23)</td>
</tr>
<tr>
<td>PI-RADS category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-RADS 2</td>
<td>51 (71)</td>
<td>10 (5.4)</td>
<td>41 (7.6)</td>
</tr>
<tr>
<td>PI-RADS 3</td>
<td>87 (12)</td>
<td>21 (11.4)</td>
<td>66 (12.3)</td>
</tr>
<tr>
<td>PI-RADS 4</td>
<td>346 (47.9)</td>
<td>88 (47.6)</td>
<td>258 (48)</td>
</tr>
<tr>
<td>PI-RADS 5</td>
<td>239 (33.1)</td>
<td>66 (35.7)</td>
<td>173 (32.2)</td>
</tr>
<tr>
<td>PSA density quartiles, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.1 ng/ml/cm³</td>
<td>281 (38.9)</td>
<td>77 (41.6)</td>
<td>204 (37.9)</td>
</tr>
<tr>
<td>0.1–0.15 ng/ml/cm³</td>
<td>176 (24.3)</td>
<td>54 (29.2)</td>
<td>122 (22.7)</td>
</tr>
<tr>
<td>&gt;0.15–0.2 ng/ml/cm³</td>
<td>114 (15.8)</td>
<td>23 (12.4)</td>
<td>91 (16.9)</td>
</tr>
<tr>
<td>&gt;0.2 ng/ml/cm³</td>
<td>152 (21)</td>
<td>31 (16.8)</td>
<td>121 (22.5)</td>
</tr>
<tr>
<td>Mean number of biopsy cores ± standard deviation (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted biopsy cores</td>
<td>4.7 ± 2.5</td>
<td>5.0 ± 2.9</td>
<td>4.5 ± 2.4</td>
</tr>
<tr>
<td>Positive targeted biopsy cores</td>
<td>2.0 ± 2.5</td>
<td>2.4 ± 3.1</td>
<td>1.9 ± 2.2</td>
</tr>
<tr>
<td>Systematic biopsy cores</td>
<td>12.1 ± 0.5</td>
<td>12.0 ± 0.3</td>
<td>12.1 ± 0.6</td>
</tr>
<tr>
<td>Positive systematic biopsy cores</td>
<td>2.1 ± 2.7</td>
<td>2.6 ± 3.1</td>
<td>1.9 ± 2.4</td>
</tr>
</tbody>
</table>

Bx = biopsy; IQR = interquartile range; PI-RADS = Prostate Imaging-Reporting and Data System.

### 4. Discussion

The introduction of MRI-targeted biopsies has led to a dramatic improvement in the detection of clinically significant prostate cancers; however, several studies have demonstrated that the use of MRI-targeted biopses alone would lead to missed diagnoses of clinically significant cancer and moderate upgrading rates at prostatectomy [10,11]. As a result, several recent publications have advocated for the use of MRI-targeted and systematic biopsies in combination to improve the diagnostic accuracy of prostate biopsies and reduce the risk of upgrading at the time of prostatectomy [7,10,11]. However, the use of combined MRI-targeted and systematic biopsy subjects patients to sampling of a higher number of biopsy cores, the risk of complications, and the risk of more diagnoses of...
indolent cancer than with use of MRI-targeted biopsy alone [7,10,11,23,24]. An improved biopsy strategy would allow for stratification of men at risk of prostate cancer into groups of those who would benefit from combined biopsy and those who would be adequately staged with MRI-targeted biopsy alone.

Our study demonstrates that prostate MRI can identify men who could reasonably forgo combined prostate biopsy with a minimal risk of missing diagnosis of a clinically significant cancer. Specifically, MRI-targeted biopsy detected nearly all clinically significant cancers among men with PI-RADS 5 lesions (97.0%). Conversely, among men with PI-RADS 2 lesions, addition of MRI-targeted biopsy resulted in minimal additional detection of clinically significant cancer (2.0%) relative to systematic biopsy alone. Finally, among the PI-RADS 3 and 4 groups, the added value of systematic biopsy was substantial (7.5% and 8.0% more detection of clinically significant cancer, respectively), suggesting that the use of combined MRI-targeted and systematic biopsy adds significant value for these groups.

These findings provide granularity to our previously reported results indicating that combined biopsy yields substantially higher detection of clinically significant cancer (5.8% more GG ≥2) compared to MRI-targeted biopsy alone for all men with MRI-visible prostate lesions [11]. With this subset analysis we found that the benefits of combined biopsy were concentrated in the PI-RADS 3 and PI-RADS 4 groups, suggesting that use of combined biopsy should be largely limited to men with PI-RADS 3–4 lesions.

These modifications in biopsy strategies on the basis of PI-RADS risk stratification would lead to 40.1% of patients avoiding a combined biopsy and risk a 1% rate of misdiagnosis among the entire cohort with abnormal prostate MRI. For patients avoiding combined biopsy, this would mean an average of 12.1 fewer biopsy cores, less biopsy-related morbidity, a shorter procedure time, lower procedure complexity, and a lower health care burden compared to combined biopsy, while maintaining the benefits of combined biopsy for 99% of the population [6,14,25–29].

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The general practice by some physicians has been to forgo prostate biopsy for men with PI-RADS 2 prostate lesions [12,30]. This conclusion was reached on the basis of multiple publications demonstrating that MRI-targeted biopsy yields low detection rates for clinically significant cancer among men with PI-RADS 2 lesions (0–9.6%) [19,20,31,32]. However, in those studies, most men did not undergo simultaneous systematic prostate biopsy to ascertain if prostate cancer could be detected outside of the targeted region. In our series, clinically significant cancer was found in slightly more than one in six men (17.6%) with a PI-RADS 2 lesion, and nearly all of these lesions were detected by systematic biopsy. Similar findings were reported by Stabile et al [33] and Rouviere et al [10], with detection rates for clinically significant cancer of 8% and 18%, respectively, with systematic biopsy (vs 0% with targeted biopsy) among men with low-risk MRI findings. Ultimately, these results suggest that MRI-targeted biopsy yields limited detection of clinically significant cancer for men with PI-RADS 2 lesions.

This study has several limitations. The patients enrolled were referrals and the referral patterns for our institution may not reflect those in the broader community, contributing to possible selection bias. Our institution has extensive experience in performing and interpreting prostate MRI and obtaining MRI-targeted biopsies. Similar results may not be
Table 2 – Risks and benefits of a modified biopsy strategy by PI-RADS score

<table>
<thead>
<tr>
<th>Group</th>
<th>Suggested Bx strategy</th>
<th>Risk of Suggested Bx Strategy</th>
<th>Benefit of Suggested Biopsy Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-RADS 5 (n = 239)</td>
<td>TBx only</td>
<td>GG ≥ 2: 1.3% (n = 3) understaged, 1.3% (n = 3) missed</td>
<td>100% of men (n = 239) could avoid SBx</td>
</tr>
<tr>
<td>PI-RADS 4 (n = 346)</td>
<td>Combined TBx and SBx</td>
<td>12 additional Bx cores</td>
<td>GG ≥ 2: 7.5% (n = 26) more diagnoses</td>
</tr>
<tr>
<td>PI-RADS 3 (n = 87)</td>
<td>Combined TBx + SBx</td>
<td>12 additional Bx cores</td>
<td>GG ≥ 2: 3.5% (n = 12) more diagnoses</td>
</tr>
<tr>
<td>PI-RADS 2 (n = 51)</td>
<td>SBx only (if Bx indicated)</td>
<td>GG ≥ 2: 2% (n = 1) understaged, 0% (n = 0) missed</td>
<td>100% of men (n = 51) could avoid TBx</td>
</tr>
<tr>
<td>Overall (n = 723)</td>
<td>PI-RADS 5: TBx</td>
<td>Small increase in the risk of misdiagnosis of csPC</td>
<td>Combined Bx avoided by 290 (40.1%) men</td>
</tr>
<tr>
<td>PI-RADS 3–4: TBx + SBx</td>
<td>GG ≥ 2: 0.6% (n = 4) understaged, 0.4% (n = 3) missed</td>
<td>GG ≥ 2: 4.6% (n = 33) more diagnoses</td>
<td></td>
</tr>
<tr>
<td>PI-RADS 2: SBx only</td>
<td>GG ≥ 3: 0.4% (n = 3) understaged, 0% (n = 0) missed</td>
<td>GG ≥ 3: 2.1% (n = 15) more diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

Bx = biopsy; csPC = clinically significant prostate cancer; GG = grade group; PI = RADS = Prostate Imaging-Reporting and Data System; SBx = systematic Bx; TBx = transrectal ultrasound-visible biopsy.

obtained at other institutions until proficiency with these practices is developed. In addition, our study was conducted at a single institution, which may limit generalizability. Since MRI-targeted biopsies were performed before systematic biopsies, there is a possibility that the physician performing the systematic biopsy may have been influenced by ultrasound-visible changes when performing systematic prostate biopsies, even though attempts were made to reduce this possibility. Furthermore, while the use of two biopsy cores per MRI-visible target resulted in detection of substantially more clinically significant cancer than with systematic biopsy, some recent studies have suggested that a higher number of biopsy cores may result in an increase in the detection of clinically significant cancer [10,34–36]. This study used transrectal biopsy to diagnose prostate cancer and these findings may not apply for transperineal biopsy, as a transperineal approach may provide superior access to the apical and anterior regions of the prostate. In addition, it has been shown that use of a transperineal approach results in a lower infection risk than a transrectal approach for prostate biopsy [37,38]. Similarly, MRI-visible lesions were not stratified on the basis of their zonal location within the prostate, which may have resulted in a better positive predictive value of MRI-targeted biopsy within certain prostate regions. For physicians considering focal therapy, combined biopsy would be valuable for surgical planning by confirming to absence of prostate cancer outside of the MRI targets. Finally, within our discussion we felt that a 1% rate of misdiagnosis would be an acceptable threshold to forgo a secondary biopsy method. However, this threshold is ultimately subjective, and the individual risk tolerance of the patient and physician should be taken into account when making clinical decisions within the context of these data.

5. Conclusions

While combined MRI-targeted and systematic prostate biopsy leads to greater detection of clinically significant cancer among men with MRI-visible prostate lesions relative to either method alone, these benefits appear to occur largely for men with PI-RADS 3–4 lesions. Adding systematic biopsy confers limited additional benefit in detection of clinically significant cancer for men with PI-RADS 5 lesions. Conversely, MRI-targeted biopsy shows limited added value for men with PI-RADS 2 lesions. Using a strategy of combined biopsy only for cases with PI-RADS 3–4 results would lead to 40.1% of men with an MRI-visible lesion avoiding excess biopsies and associated potential risks/complications while maintaining the superior diagnostic accuracy of combined biopsy.

Author contributions: Michael Ahdoot had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtaining funding: Linehan, Merino, Choyke, Wood, Pinto.


Supervision: Linehan, Merino, Choyke, Shih, Wood, Pinto.
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CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euo.2021.03.004.

References


[33] Stabile A, Dell’Oglio P, De Cobelli F, et al. Association between Prostate Imaging Reporting and Data System (PI-RADS) score for the index lesion and multifocal, clinically significant prostate can-


