TITLE: Evaluating Role of Multi-Parametric MRI and PI-RADS v2 in Increasing the Odds of Identifying Aggressive Prostate Cancer in Men with TRUS Biopsy Gleason Pattern ≤ 3

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INTRODUCTION: Most men undergoing screening with prostate specific antigen (PSA) have indolent, low-grade (Gleason Pattern, or GP ≤ 3) prostate cancer (PC) on trans-rectal ultrasound (TRUS) biopsies. However, TRUS biopsies under-sample prostate tissue and thus, under-estimate clinically significant PC, as defined by more aggressive, higher grade (GP ≥ 4) disease, which is more likely to progress, cause metastases and death. As many as 36 to 47% of men with TRUS biopsy GP ≤ 3 PC are upgraded to GP ≥ 4 on post-operative pathology (POP). Based on the recent extensive evidence, NIH consensus conference highlighted the need to advance diagnostic tools for improving target definition, tissue sampling and prediction of clinically significant PC as a "health research priority."1

SPECIFIC AIM: The aim of this study was to determine whether multi-parametric (mp) MRI and related Prostate Imaging–Reporting and Data System Version 2 (PI-RADS™ v2) can improve prediction of POP GP ≥ 4 in men with a pre-operative TRUS biopsy GP ≤ 3.

BACKGROUND AND RATIONALE: A recent long-term, large-scale multi-center clinical trial showed that increasing PSA and TRUS biopsy GP ≥ 4 (both Primary and Secondary) are the critical factors in long-term PC mortality after radical prostatectomy (RP). Valid concerns about under-grading with TRUS biopsy have led to extensive over-treatment, which has emerged as a national public health priority. To address this challenge, there has been a concerted effort to expedite advancement of mpMRI, which has been shown to improve detection (and exclusion) of clinically significant disease in preliminary studies. Recently, PI-RADS™ v2 standardization was developed, with the primary goal to improve risk stratification even further. This study was conducted to evaluate the role of mpMRI and PI-RADS™ v2 in correctly upgrading TRUS biopsy GP ≤ 3 to POP GP ≥ 4.

METHODS AND MATERIALS: This institutional review board-approved, retrospective study accrued 366 men aged 40 to 80 years old who had abnormal PSA (>4 ng/mL) and/or abnormal digital rectal exam and underwent TRUS biopsy and RP at the Brigham and Women’s Hospital between 2008 and 2014. The two study cohorts included: 1) Patients who had mpMRI, which was performed at least 6 weeks after TRUS biopsy and within 6 months prior to RP (N=190); and 2) Patients who did not have mpMRI prior to RP (N=176). TRUS Biopsy GP ≤ 3 was found in 62 men in the first cohort and in 99 men in the second cohort. MpMRI was defined as “negative” for GP ≥ 4 if PI-RADS v2 scores were 1-3, and “positive” if PI-RADS v2 scores were 4-5. POP served as a reference standard.

Availability of complete standard diagnostic clinical information (including PSA level, POP reports and TRUS biopsy results) was required for both cohorts. All mpMRI exams included in the study were acquired at 3 Tesla (3T) and met technical standards for image acquisition and clinical criteria for acceptable image quality.

Two readers independently reviewed all mpMRI de-identified studies and assigned PI-RADS v2 score at a patient level, based on the dominant lesion. In cases of disagreement between readers, a third radiologist served as an adjudicator and determined a final overall assessment. All reviewers were blinded to clinical information.

In patients who had TRUS Biopsy GP ≤ 3, we compared the odds of upgrading to POP GP ≥ 4 with and without mpMRI, including men with positive (N=38) and negative PI-RADS v2 scores (N=24). Odds of “upgrading” to GP ≥ 4 were analyzed using multivariable logistic regression with SAS software (version 9.3, AS Institute, Cary, NC).

RESULTS: A. Patient Population. More patients in the MRI group were African American, and more men in the control group declined to identify their race and/or ethnicity (see Table 1):
odds ratio: 0.4, 95% CI: 0.1

sta likelihood ratio test = 0.89, P = 0.345). Multivariable regression analysis after adjusting for age, race, TNM stage and PSA, the odds of "upgrading" to POP GP > 4 are over 2 times greater with mpMRI (adjusted odds ratio: 2.1, 95% CI: 1.2-4.1, likelihood ratio test = 4.5, P = 0.034).

C. The Odds of Upgrading TRUS GP ≤ 3 to POP ≥ GP 4 With and Without Positive mpMRI (PI-RADS v2 scores 4-5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive mpMRI (PI-RADS 4-5) (N = 38)</th>
<th>No MRI - Controls (N = 99)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op GP ≥ 4 (Upgrading)</td>
<td>25 (66%)</td>
<td>30 (30%)</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Post-op GP &lt; 3</td>
<td>13 (34%)</td>
<td>69 (70%)</td>
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</tbody>
</table>

*Statistically significant.

D. The Odds of Upgrading TRUS GP ≤ 3 to POP ≥ GP 4 With and Without Negative mpMRI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Negative MRI (PI-RADS 1-3) (N = 24)</th>
<th>No MRI - Controls BWH 2008-2014 (N = 99)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op GP ≥ 4 (Upgrading)</td>
<td>5 (21%)</td>
<td>30 (30%)</td>
<td>0.454</td>
</tr>
<tr>
<td>Post-op GP &lt; 3</td>
<td>19 (79%)</td>
<td>69 (70%)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant.

TABLE 4: Yield of POP GP ≥ 4 among patients with TRUS biopsy Gleason ≤ 3 was not significantly changed using negative mpMRI (PI-RADS v2 1-3) compared to no MRI (21% vs. 30%, P = 0.454). This actually demonstrated a lower rate of "upgrading" by 9% using MRI. Logistic regression indicated an unadjusted odds 0.6 times higher with negative PI-RADS vs. no MRI controls (odds ratio: 0.6, 95% CI: 0.2-1.8, likelihood ratio test = 0.89, P = 0.345). Multivariable regression analysis after adjusting for age, race, TNM stage and PSA, indicated a non-significant odds of "upgrading" using MRI with negative PI-RADS (adjusted odds ratio: 0.4, 95% CI: 0.1-1.3, likelihood ratio test = 2.6, P = 0.105).

* Statistically significant. SD = standard deviation, IQR = interquartile range.

TABLE 1: Patient populations in the two study cohorts.

TABLE 2: Detection of POP GP ≥ 4 among patients with TRUS biopsy GP ≤ 3 is significantly higher with mpMRI (irrespecitely of PI-RADS v2 score) compared to no MRI (48% vs. 30%, P = 0.021). This demonstrates an absolute improvement of 18% using mpMRI (95% CI: 3% to 33%). Logistic regression indicates an unadjusted odds over 2 times higher with mpMRI vs. controls (odds ratio: 2.2, 95% CI: 1.2-4.2, likelihood ratio test = 5.3, P = 0.021). Multivariable regression analysis confirmed that adjusting for age, race, TNM stage and PSA, the odds of "upgrading" to POP GP ≥ 4 are nearly 5 times greater with mpMRI (adjusted odds ratio: 4.4, 95% CI: 2.0-9.8, likelihood ratio test = 11.7, P = 0.001).
E. Summary: We have compared the yield of aggressive POP GP ≥ 4 with and without mpMRI in patients with pre-operative TRUS biopsy GP ≤ 3. The rate of POP GP ≥ 4 was 30% in the control group (no MRI) and 48% with MRI (Table 5). In men who had mpMRI (irrespective of PI-RADS v2 score), the odds of correctly upgrading TRUS GP ≤ 3 to POP ≥ GP 4 are predicted at over 2 times greater compared to the control group. In men who had positive mpMRI (PI-RADS v2 score 4-5), the rate of POP ≥ GP 4 is increased even further to 66%, with the odds of correctly upgrading TRUS GP ≤ 3 to POP ≥ GP 4 predicted to be nearly 5-fold greater compared to the control group.

In this study population, negative mpMRI (PI-RADS v2 score 1-3) is associated with a statistically insignificant change in the yield of POP GP ≥ 4 compared to the control cohort (21% vs. 30%, respectively).

<table>
<thead>
<tr>
<th>Yield of Aggressive PC (POP GP ≥ 4)</th>
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<tbody>
<tr>
<td>MRI (Any PI-RADS v2)</td>
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<tr>
<td>Positive MRI (PI-RADS v2 score 4-5)</td>
</tr>
<tr>
<td>Negative MRI (PI-RADS v2 score 1-3)</td>
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<tr>
<td>Controls (no MRI)</td>
</tr>
</tbody>
</table>

*Statistically significant.

### TABLE 5: Summary.

DISCUSSION: Most men undergoing PSA screening have indolent PC (GP ≤ 3) on TRUS biopsies, though a significant fraction of these cases gets upgraded on POP. We have shown that in men diagnosed with indolent disease on pre-operative TRUS biopsy, positive PI-RADS v2 score may increase the probability of correctly upgrading TRUS GP ≤ 3 to POP ≥ GP 4 nearly 5 times. The effect of mpMRI (irrespective of PI-RADS v2 score) on increased odds of upgrading indolent PC on TRUS biopsy to aggressive disease on POP most likely reflects a strong effect of positive PI-RADS v2 scores.

These results are in alignment with recent data indicating a promising role of mpMRI and/or PI-RADS v2 in improving prediction of high-grade PC on POP and its discrimination from low-grade disease compared to TRUS biopsy in a surgical population.7,8

CONCLUSION: Our study shows that mpMRI and positive PI-RADS v2 scores can improve risk stratification and selection of patients for surgical treatment compared to TRUS biopsies. While these data indicate that mpMRI and PI-RADS v2 may significantly alter patient management strategy and address an important public health challenge in PC evaluation and care, further prospective, multi-center clinical trials are required. In the interim, TRUS biopsy will continue to be needed as a part of a standard diagnostic evaluation for treatment decisions.

### REFERENCES