Value of 3-Tesla multiparametric magnetic resonance imaging and targeted biopsy for improved risk stratification in patients considered for active surveillance

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Objective
To evaluate the role of multiparametric magnetic resonance imaging (mpMRI) of the prostate and transrectal ultrasonography guided biopsy (TRUS-Bx) with visual estimation in early risk stratification of patients with prostate cancer on active surveillance (AS).

Patients and Methods
Patients with low-risk, low-grade, localised prostate cancer were prospectively enrolled and submitted to a 3-T 16-channel cardiac surface coil mpMRI of the prostate and confirmatory biopsy (CBx), which included a standard biopsy (SBx) and visual estimation-guided TRUS-Bx. Cancer-suspicious regions were defined using Prostate Imaging Reporting and Data System (PI-RADS) scores. Reclassification occurred if CBx confirmed the presence of a Gleason score ≥7, greater than three positive fragments, or ≥50% involvement of any core. The performance of mpMRI for the prediction of CBx results was assessed. Univariate and multivariate logistic regressions were performed to study relationships between age, prostate-specific antigen (PSA) level, PSA density (PSAD), number of positive cores in the initial biopsy, and mpMRI grade on CBx reclassification. Our report is consistent with the Standards of Reporting for MRI-targeted Biopsy Studies (START) guidelines.

Results
In all, 105 patients were available for analysis in the study. From this cohort, 42 (40%) had PI-RADS 1, 2, or 3 lesions and 63 (60%) had only grade 4 or 5 lesions. Overall, 87 patients underwent visual estimation TRUS-Bx. Reclassification among patients with PI-RADS 1, 2, 3, 4, and 5 was 0%, 23.1%, 9.1%, 74.5%, and 100%, respectively. Overall, mpMRI sensitivity, specificity, positive predictive value, and negative predictive value for disease reclassification were 92.5%, 76%, 81%, and 90.5%, respectively. In the multivariate analysis, only PSAD and mpMRI remained significant for reclassification (P < 0.05). In the cross-tabulation, SBx would have missed 15 significant cases detected by targeted biopsy, but SBx did detect five cases of significant cancer not detected by targeted biopsy alone.

Conclusion
Multiparametric magnetic resonance imaging is a significant tool for predicting cancer severity reclassification on CBx among AS candidates. The reclassification rate on CBx is particularly high in the group of patients who have PI-RADS grades 4 or 5 lesions. Despite the usefulness of visual-guided biopsy, it still remains highly recommended to retrieve standard fragments during CBx in order to avoid missing significant tumours.

Keywords
prostate multiparametric magnetic resonance, targeted prostate biopsy, transrectal ultrasound targeted biopsy, active surveillance, visual estimation prostatic targeted biopsy

Introduction
Prostate cancer remains the number one cancer diagnosis in North American and European men [1]. The widespread use of PSA tests has led to a high diagnosis rate of low-risk disease, which has raised concerns about overtreatment of prostate cancer [1,2].

Active surveillance (AS) was introduced in an attempt to decrease overtreatment of indolent prostate cancer and defer
curative treatment of those patients with objective evidence of disease progression after a period of observation [2]. However, a potential problem with AS is that conventional prostate biopsy under-samples roughly one-third of cases when compared with the prostatectomy specimen [3]. Furthermore, even the most stringent criteria misclassifies up to 42% of cases that actually harbour unfavourable pathological features at radical prostatectomy [4].

Prostate cancer care has shifted from detection and treatment of all men to identifying and treating only those with clinically significant disease [5]. Therefore, novel tools to improve risk stratification of patients are needed to better select appropriate candidates for AS [6].

Serum, urinary, and histopathology markers as well as imaging studies are under extensive investigations in order to help fill this important gap in urological oncology clinical practice [6]. Multiparametric MRI (mpMRI) is currently the most studied test and has shown to improve the identification of patients that have cancers with a higher Gleason score [4]. Other groups also examined mpMRI in the confirmatory biopsy (CBx) setting and discovered that targeting the most aggressive areas, known as cancer-suspicious regions (CSRs), is feasible and yields better prediction of risk stratification among men considered for AS [4].

The use of mpMRI and fusion-guided TRUS biopsy for AS patients has enabled targeting particular prostate areas suspicious for high-grade disease by using specific software. Most groups have published their experience with this specific population using fusion-guided TRUS-Bx [4]. Only one group has published their experience with a MR in-bore biopsy device that fuses images and performs biopsies without the need for TRUS [7]. Unfortunately, those techniques are expensive and are not available worldwide [8].

We evaluated the role of mpMRI in predicting TRUS-Bx without the use of fusion software (visual estimation) in early risk stratification of patients on AS. To our knowledge, the present study describes the largest prospectively collected data report on visual-estimation-guided biopsy that strictly followed the Standards of Reporting for MRI-targeted Biopsy Studies (START) guidelines.

**Patients and Methods**

The patients were prospectively enrolled for AS in our programme between March 2014 and January 2016. Upon receiving approval from our Institutional Review Board, a single-arm prospective cohort study was initiated and included patients with low-risk, low-grade, localised prostate cancer. It was required for the patients to have had a standard biopsy (SBx) taken a maximum of 6 months before referral to our institution with at least 12-core samplings, clinical stage T1c–T2a cancer, Gleason score ≤6, serum PSA level of ≤10 ng/mL, no more than three positive cores on the entry biopsy, and all biopsy cores had to have <50% involvement. Eligible candidates had to have a life-expectancy of ≥5 years. An experienced prostate cancer pathologist from our institution reviewed all initial SBxs to confirm eligibility criteria. Patients were excluded from the protocol if they were previously submitted to any kind of prostate surgery, hormonal treatment, or if they had contraindications to undergo mpMRI or TRUS-guided prostate biopsy (TRUS-Bx).

Patients underwent mpMRI after ≥6 weeks of the initial SBx to minimise artefacts. A single radiologist with >10 years of experience in mpMRI, without previous knowledge of the initial SBx, evaluated all images using axial-oblique, fast spin-echo T2-weighted, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE)-MRI on a 16-channel cardiac surface external phased-array coil 3.0-T MRI system (Signa HDx 3T; GE Healthcare, Milwaukee, WI, USA) with standard widespread recommendations for image acquisition [9]. The validated Prostate Imaging Reporting and Data System (PI-RADS) version 1 was used to define CSRs [10]. Every CSR was scored on an overall point scale of 1–5 based on T2-weighted, DWI, and DCE-MRI sequences. The 5-point scale was defined as a/an (i) highly unlikely, (ii) unlikely, (iii) indeterminate, (iv) likely and (v) highly likely presence of clinically significant prostate cancer. Subsequently, an individual overall score was assigned to each patient based on the highest lesion score. Localisation of CSRs was reported and considered for CBx with TRUS visual estimation by a single radiologist using a loaded biopsy gun and 18-G needles up to 90 days after of the initial mpMRI study. Every man underwent sampling of 12 systematic sites, independent of mpMRI results. MRI images were then considered and appeared on the screen adjacent to the ultrasound, allowing real-time visual estimation comparison of methods and zones of interest. Every lesion with grade ≥2 scores on mpMRI underwent at least two targeted biopsies with one core obtained at approximately every 4 mm along the longest axis of the target. Patients with only grade 1 lesions had at least two additional random fragments retrieved so that the total number of fragments was not different between patients with and without suspicious lesions. Each fragment was then properly identified using number, prostate localisation, and whether it was guided or randomly retrieved. The primary study outcome was reclassification on CBx. Reclassification occurred if the CBx established significant cancer and was defined as any fragment with Gleason ≥7, more than three fragments positive for prostate cancer, or a highest tumour volume in any core of >50%. The same experienced urological pathologist, blinded to the initial SBx results, reviewed all CBx materials independently. Our report is consistent with previously reported and recommended START guidelines [8].
Patient demographic data were reported using descriptive statistics. The performance of mpMRI for predicting disease that was upgraded on CBx was assessed by determining sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We further identified any clinical parameters (based on clinical relevance) to include in the analysis such as patient age, PSA level, PSA density (PSAD), number of positive cores in the initial SBx, and mpMRI grade. Univariate and multivariate logistic regressions were performed to study all relationships between those selected variables and reclassifications associated with an upgrade on CBx. Two different analyses were done, one including all the patients irrespective of their PSAD to study it as an independent predictor for reclassification and another analysis only including patients with PSAD of $<0.15$ ng/mL/mL. As the likelihood of upgrading is similar between lesions classified as PI-RADS 1, 2, or 3 and between those classified as grades 4 and 5 we combined participants in two different groups for the purpose of comparison [4]. Consistent with START guidelines, we performed cross-tabulation of insignificant and significant cancer detection by targeted vs systematic biopsies in patients who underwent each biopsy type. A biostatistician using Stata version 11 performed all calculations. The threshold for statistical significance was set at $P < 0.05$.

Results

In all, 145 men were consecutively enrolled in our programme between March 2014 and January 2016. Eight patients were initially excluded (three due to previous hormonal therapy, three because of TURP, and two because of another concomitant metastatic malignancy). A single pathologist at our institution reviewed the remaining 137 patients who had their SBx performed in an outpatient setting. There were 32 patients (23%) that did not meet our inclusion criteria because they were classified as having significant cancer and were referred to active treatment, leaving 105 patients for final analysis (Fig. 1).

Descriptive characteristics of all 105 patients submitted to mpMRI and subsequent CBx are depicted in Table 1. There were 42 (40%) patients classified with grades 1, 2, or 3 lesions on mpMRI, while 63 (60%) patients had grades 4 or 5 lesions. There were no discernible targets in 18 patients (PI-RADS grade 1) who underwent at least two additional random samplings, separate from the 12 standard fragments on CBx. Overall, 87 patients underwent visual-estimation TRUS-Bx. A median (interquartile range [IQR]) of 15 (14–18) fragments were sampled at CBx and consisted of 12 systematic fragments, between two and six guided fragments in those with identifiable lesions (PI-RADS 2, 3, 4 and 5), and between two and four random fragments in those patients without identifiable lesions.

Three patients needed to be readmitted after TRUS-Bx. One had urinary retention with clots, managed conservatively with bladder irrigation. The other two patients developed acute prostatitis and required i.v. antibiotics.

Among the 63 patients with a high suspicion for a significant cancer on mpMRI (PI-RADS 4 or 5), 54 (85.71%) were...
reclassified on CBx. Among the 42 patients with low suspicion for significant cancer (PI-RADS 1, 2, or 3), only four (9.5%) were reclassified (Fig. 1). Reclassification among patients with PI-RADS 1, 2, 3, 4, and 5 was 0%, 93.13%, 74.5%, and 100%, respectively. Of note, no patients with PI-RADS score of 1 were upgraded on CBx and all those harbouring PI-RADS 5 lesions were reclassified to a higher-grade disease on CBx (Table 2). Overall, mpMRI sensitivity, specificity, PPV, and NPV for predicting reclassification on CBx were 92.5%, 76%, 81%, and 90.5%, respectively. Of the men that were reclassified, 47 (44.8%) were upgraded because of Gleason score ≥7 and 11 (10.4%) because of three or more positive fragments with >50% involvement of each fragment (Table 3). In the univariate analysis, only the number of positive cores on initial biopsy ($P = 0.013$), PSAD ($P = 0.005$), and mpMRI suspicious for high-grade disease ($P = 0.001$) were predictive for reclassification on CBx. However, in the multivariate analysis, only PSAD ($P = 0.005$) and mpMRI suspicious for high-grade disease ($P = 0.001$) remained significant for prediction of reclassification.

A separate analysis was performed including only patients with a PSAD of $<0.15$ ng/mL/mL. A total of 84 patients were included and the reclassification rate among patients with PI-RADS 1, 2, 3, 4, and 5 was 0% (0/17), 9.1% (1/11), 11.1% (1/9), 73% (27/37) and 100% (10/10), respectively. Overall, mpMRI sensitivity, specificity, PPV, and NPV for predicting reclassification on CBx were 94.8%, 77.7%, 78.7%, and 94.5%, respectively. Similarly to the investigation considering the entire cohort, in the multivariate analysis, only PSAD ($P = 0.014$) and mpMRI suspicious for high-grade disease ($P = 0.001$) remained significant for prediction of reclassification.

Patients with PI-RADS 3 who were not reclassified had a median (IQR) prostate volume of $52.5 (31–110)$ mL and a median (IQR) PSA of $0.1 (0.09–0.28)$ ng/mL/mL. Their median (IQR) lesion size was $5 (4–13)$ mm; three (3/10) lesions were located in the anterior quadrant and one (1/10) in the transition zone.

A total of 25.5% (12/47) of the patients with PI-RADS 4 lesions were not reclassified. In two of them the lesion was located in the anterior quadrant of the prostate and one had a lesion in the transitional zone. The median (IQR) size of their prostates was $81 (43–145)$ mL, median (IQR) size of the lesions was $10 (6–13)$ mm, and the median (IQR) PSA was $0.07 (0.06–0.16)$ ng/mL/mL.

Overall, 87 patients underwent each type of prostate biopsy, systematic and targeted. The mpMRI identified significant nodules away from the regions of previous positive fragments in 46 of them. Cross-tabulation of insignificant and significant cancer was performed according to START guidelines (Table 4). Cancer detection rates for significant cancer with systematic and targeted CBx were 39/87 (44.8%) and 49/87 (56.3%), respectively. Systematic and targeted biopsies were concordant in 34 cases of significant cancer. Targeted biopsy detected significant cancer in 15 patients that SBx classified as ‘no cancer’ (4) and ‘insignificant cancer’ (11)
Discussion

Multiple criteria have been used to define low-risk prostate cancer since Epstein et al. [11] noted that certain biopsy characteristics (no Gleason 4 component, no more than two cores involved, and no core with >50% involvement) can predict low-risk findings in radical prostatectomy specimens. Recently, many groups have added PSAD, with an upper limit of 0.15–0.20 ng/mL/mL, as an additional criterion because they found a higher rate of disease reclassification after definitive treatment of patients with prostate cancer [12]. Likewise, most centres that follow patients in AS set a limit of a maximum two positive fragments with <50% of involvement of each individual core [1]. Two important exceptions are the groups from Memorial Sloan-Kettering Cancer Center who admitted patients with up to three involved cores, and Toronto who admitted patients with Gleason scores up to 7 and with PSA levels up to 15 ng/mL [2,13].

We decided to do two separate analyses to evaluate the interrelationship of PSAD and mpMRI findings on disease reclassification. The first included all patients, irrespective of their PSADs, and showed that both PSAD and mpMRI are independent predictors of disease reclassification on CBx. A second analysis was done, excluding patients with PSAD of >0.15 ng/mL/mL, because we recognise that including patients with a high PSAD could have eventually overestimated the utility of visual-estimation TRUS-Bx. We found again that both PSAD and mpMRI were independent predictors for disease reclassification but, more importantly, did not see significant changes in disease reclassification rates, except for patients with PI-RADS 2, whose rate dropped from 23.1% to 9.1%. Likewise, there were no significant changes in sensitivity, specificity, PPV and NPV of the mpMRI in predicting reclassification on CBx.

We admitted patients with up to three positive cores involved with cancer and 76.2% of our patients had two or three positive fragments on initial biopsy. Interestingly, in the univariate analysis, the number of positive cores was predictive of upgrading on CBx but it did not remain a significant factor in the multivariate analysis after considering PI-RADS score and PSAD together. Even though it is still a controversial subject, we believe that based on our present results, we should not withhold AS from patients with more than two positive fragments. There is always going to be a trade-off between missing eligible patients for AS when using stricter criteria and offering AS to patients who harbour higher risk disease when using broadened parameters.

MRI has been used as a tool to better stratify patients considered for AS [6]. Cumulative data from previous studies showed that almost 73% of patients who underwent radical prostatectomy for low-risk disease had abnormal preoperative mpMRI images [14–16]. Also, 51% of the patients with a visible lesion on preoperative mpMRI had upgrading in the final specimen compared to only 13% of those with a normal preoperative mpMRI [14–16].

The first studies to evaluate the accuracy of mpMRI to predict the results of CBx only included patients submitted to SBx without any method to guide biopsies towards CSRs [17,18]. Overall, mpMRI accuracy to predict upgrading ranged from 15% to 32% and discouraged most urologists from considering it a useful tool to predict reclassification [4]. Margel et al. [19] reported for the first time the use of a cognitive estimative method to target CSRs using TRUS on previous mpMRI images. They showed a reclassification rate of 47% with a PPV and NPV of 83% and 81%, respectively. Unfortunately, they only included 60 patients and no accurate mpMRI reading method was used [4,19].

Marliere et al. [20] and Hu et al. [21] separately reported their experience with the mpMRI as a predictor of CBx using a fusion-guided biopsy and different available software. Both authors included a 5-point scale to grade the probability of high-risk disease on mpMRI, but only Hu et al. [21] followed START guidelines [8]. In the study by Marliere et al. [20], the reclassification rate among patients with a positive mpMRI was 79%, whereas Hu et al. [21] reported a much lower rate of only 38% of the patients being reclassified [4]. This difference most likely occurred because Hu et al. [21] considered every patient with ≥2 points on a 5-point scale positive. It is well known that grades 4 and 5 are predictive of a higher risk disease, so including patients with grades 2 and 3 among those considered having a positive mpMRI study might have lowered their reclassification rate [9]. As only PI-RADS grades 4 and 5 mpMRI were considered positive in our present study, our rate of positive mpMRI before CBx was only 60%, which is much lower than the abovementioned studies. However, our reclassification rate among those with a positive study was 85%, which is among the highest in previously published studies (Fig. 1).

Before our report, only Hu et al. [21] previously described the reclassification rate divided by image graded scores, but they used the University of California Los Angeles (UCLA) scoring system, which weights diffusion differently from the PI-RADS in the final score. Surprisingly, 19.5% (22/113) of their patients had no targets on mpMRI, grade 1 UCLA score [21]. In our present series, 17% (18/105) of our patients were classified as PI-RADS 1. We hypothesise that our high rate of PI-RADS 1 lesions occurred because those patients belonged to a highly selected low-risk subpopulation in our study.
Among all 18 patients with PI-RADS grade 1, 16 had only up to two fragments with Gleason 6 prostate cancer on admission biopsy and all of them had a PSAD of <0.15 ng/mL/mL. Therefore, it is more common to find uniform signal intensity and no diffusion abnormalities in this low-grade, low-volume disease group of patients.

Reclassification rates for low-suspicious lesions on mpMRI vary extensively in the literature [7,19–21]. Hu et al. [21] previously reported a reclassification rate of 29% for patients with UCLA score of 2 on mpMRI. On the other hand, Hoeks et al. [7] described a NPV of 84% for the detection of cancer when grouping patients with PI-RADS 1 and 2. For patients with PI-RADS 2 lesions, we targeted those linear, wedge shaped hypointensities on T2-weighted images and indistinct hypointensities on DWI, even with the difficulty in establishing margins. Among 13 patients with PI-RADS 2, three were reclassified as having higher-grade prostate cancer in our present series. We believe our rate of reclassification was high among PI-RADS 2 patients because of initially not restricting PSAD to 0.15 ng/mL/mL as an inclusion criterion. After excluding patients with PSAD of >0.15 ng/mL/mL, only one of 11 patients was reclassified within this group.

We reported one of the lowest reclassification rates among PI-RADS 3 patients, compared to previously reported studies [7,19–21]. Among 11 patients with PI-RADS 3, four had either anterior quadrant or transition zone disease in our present series. Also, the median size of the lesions was only 5 mm. Altogether, those reasons might have accounted for our low rate of diagnosis of higher-grade disease with visual-estimation TRUS-Bx in this subpopulation. On the other hand, our reclassification rate for PI-RADS 4 disease is among the highest reported in the literature and it did not change significantly when we only analysed those patients with a PSAD of <0.15 ng/mL/mL [7,19–21]. Interestingly, three out of the 12 PI-RADS 4 not reclassified patients had either anterior quadrant or transition zone disease. Most of them had small lesions (<10 mm), large prostate volumes (median of 81 mL) and low PSADs. The combination of large prostate volumes with low-volume of disease might have accounted for the difficulties we encountered targeting those patients’ lesions with visual-estimation TRUS-Bx.

Including all patients, our reclassification rate was 55.2%, 44.8% because of Gleason ≥7 disease, and 10.41% because of a higher number of Gleason 6 disease on CBx (Table 3). This is comparable to what Lee et al. [22] found at the Cleveland Clinic on prostate specimens from patients submitted to radical prostatectomy for low-risk disease: 40% of their patients were upgraded for Gleason 7 and 8% had locally advanced disease. We hypothesise that our rate of reclassification was higher than previously reported because most of the patients had PI-RADS 4 or 5 and because we did not set an upper limit of PSAD as a criterion for enrollment. The sensitivity, specificity, and PPV and NPV values of mpMRI in predicting upgrade on CBx vary considerably in the literature [4]. Some groups had as low as 50% and others found 93% sensitivity [17,23]. The same is true for specificity, with values ranging from 42% to 95% [17,19]. In our present study, we found a very high sensitivity and NPV of 92.7% and 90.5%, respectively. We believe this is particularly important as most patients with low PI-RADS scores (1–3) may eventually be reassured that they have a very low chance of harbouring a higher risk disease. Among patients with PI-RADS 1–3 in our present series, only four cases were reclassified: two due to low-volume Gleason 7 disease and two due to a higher volume of Gleason 6 disease. On the other hand, our specificity and PPV were 71% and 86%, respectively. This is partially because a large proportion (25.5%) of our patients classified with PI-RADS grade 4 on mpMRI actually had low-risk disease on CBx (Table 2).

Although there are solid data comparing systematic SBx and targeted biopsy on patients with elevated PSA levels (prior negative or biopsy naïve patients), only limited prospective and randomised data comparing both techniques on patients enrolled in AS who already have a positive initial biopsy are available [24,25]. The best existing prospective trial included only 24 patients with prior positive biopsies enrolled in AS [25]. That study showed that targeted biopsy detected 75.0% of all clinically significant cancers and 86.4% of Gleason ≥7 cancers detected on SBx [25]. In accordance with START guidelines, we performed a cross-tabulation of the results of SBx and targeted biopsy on 87 patients submitted to both techniques. Overall, both types of biopsies were concordant in 39% (34/87) of cases. Targeted biopsy detected 91% (49/54) of clinical significant cancers whereas SBx only detected 72.2% (39/54) of such cases. A total of 15 of 87 (17%) patients would be misclassified if they were submitted to only SBx, whereas 5/87 (6%) would not have been classified as having high-risk disease if submitted to only targeted biopsy (Table 4).

Our present study has several limitations. We did a retrospective analysis of cases collected prospectively and not a prospective randomised trial comparing SBx and targeted biopsies. Despite having favourable results with a low reclassification rate among patients with PI-RADS grades 1–3, we were not able to report follow-up data, so we do not know how that group of patients is going to perform on subsequent biopsies. Furthermore, we did not have access to the final prostate specimens of most of our patients because only two patients with PI-RADS 1–3 requested to undergo surgery (because of patient desire) and ~60% of those with PI-RADS 4–5 that were upgraded had not undergone radical prostatectomy by the time of this analysis. We plan to report on these data in future studies.

Existing clinical criteria for AS groups patients with different risk classifications for prostate cancer [4]. Similarly to other...
authors, we have shown that reclassification rate on CBx among this patient population is high. Despite its limitations, mpMRI proved to be a useful tool to predict CBx results in our present series and we believe it should be investigated in further prospective studies together with novel molecular markers. Our present data suggest that we could possibly stop performing CBx in patients with PI-RADS 1 and 5, as most of them invariably either have low-risk disease on CBx or experience reclassification, respectively. However, our present results do not support the substitution of SBx when using visual estimation mpMRI-targeted biopsy. Many unanswered questions remain such as whether we should liberalise high-volume Gleason 6 disease and continue to follow these patients in AS when using mpMRI-fusion biopsy or if software-based fusion-biopsy is better than visual-estimation-guided biopsy in AS patients. Further prospective data comparing available standardised techniques with analysis of final prostate specimens will subsequently address these questions.

Acknowledgement
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Conflicts of Interest
None declared.

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Abbreviations: AS, active surveillance; CBx, confirmatory biopsy; CSR, cancer-suspicious region; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted imaging; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System; (P)(N)PV, (positive) (negative) predictive value; PSAD, PSA density; SBx, standard biopsy; START, Standards of Reporting for MRI-targeted Biopsy Studies; TRUS-Bx, TRUS-guided prostate biopsy; UCLA, University of California Los Angeles.