A prospective study of cancer detection rates following early repeat imaging and biopsy of PI-RADS 4 and 5 regions of interest exhibiting no clinically significant prostate cancer on prior biopsy

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Cite as: Becher E, Wysock JS, Taneja SS, et al. A prospective study of cancer detection rates following early repeat imaging and biopsy of PI-RADS 4 and 5 regions of interest exhibiting no clinically significant prostate cancer on prior biopsy. *Can Urol Assoc J* 2022 July 21; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.7843

Published online July 21, 2022

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ABSTRACT

Introduction: We aimed to determine cancer detection rates following early repeat multiparametric magnetic resonance imaging (mpMRI) and biopsy of Prostate Imaging-Reporting and Data System (PI-RADS), v2.1 4 and 5 regions of interest (ROI) exhibiting no clinically significant prostate cancer (csPCa) on prior biopsy and to identify predictors for these missed csPCa.

KEY MESSAGES

- PI-RADS 4/5 ROI that are not found to harbor significant prostate cancer upon initial biopsy should be promptly re-evaluated.
- Only men exhibiting downgrading to PI-RADS 2 can safely avoid a repeat biopsy.
- Only PSA was found to be a predictor of finding clinically significant prostate cancer upon repeat biopsy.

Methods: Between January 2019 and August 2020, 36 men with 38 PI-RADS 4 or 5 ROI with no evidence of csPCa (defined as Gleason grade group [GGG] >1) on prior MRI fusion target biopsy (MRFTB) + systematic biopsy (SB) were invited to participate in the present prospective study. All men underwent repeat mpMRI and persistent PI-RADS >2 ROI were advised to undergo repeat MRFTB+SB. Cancer detection rates of any and csPCa were determined. Relative risk was calculated to analyze association of baseline variables with the finding of csPCa on repeat biopsy.

Results: Of the 38 initial PI-RADS 4 and 5 ROI, on followup mpMRI, 14 were downgraded to PI-RADS 1/2 and, per protocol, did not undergo repeat biopsy and; eight (33%), 12 (50%), and

four (17%) were PI-RADS 3, 4, and 5 respectively. Of these 24 persistently suspicious mpMRI ROI, 20 (83%) underwent repeat biopsy and six (30%), six (30%), and eight (40%) were benign, GGG 1, and GGG >1, respectively. Only prostate-specific antigen ≥10 ng/mL was a predictor for missed csPCa.
Conclusions: Our prospective study supports a recommendation for early repeat mpMRI of all PI-RADS 4 or 5 ROI exhibiting no csPCa, with repeat MRFTB + SB of persistent PI-RADS >2 ROI .

INTRODUCTION

A limitation of PSA screening coupled with trans-rectal ultrasound guided random systematic biopsy (SB) is its low specificity for detection of clinically significant prostate cancer (csPCa) which leads to unnecessary biopsies and over-detection and treatment of low-risk disease [1,2]. There is an emerging consensus that multi-parametric MRI (mpMRI) addresses some of these limitations of PSA screening since the positive predictive value of mpMRI is directly proportional to the Prostate Imaging-Reporting and Data System (PI-RADS) scores of the regions of interest (ROI) [3-5]. Other studies have demonstrated that the detection rate of csPCa is significantly improved by the implementation of mpMRI and MRI / ultrasound fusion target biopsy (MRFTB) [6-8]. Therefore, mpMRI is recommended prior to performing prostate biopsy when the technology is available [9].

The optimal biopsy strategy remains controversial [10]. At our institution, virtually all men undergo a mpMRI prior to prostate biopsy [11]. Our standard biopsy protocol consists of performing both MRFTB together with a 12 core SB. Our published cancer detection rates for csPCa defined as Gleason grade group (GGG) > 1) for PI-RADS 3, 4 and 5 ROI is 23%, 73% and 88%, respectively [11]. A recent meta-analysis found that the PPV of PI-RADS 4 & 5 ROI for detection of csPCa was 40 and 69%, respectively with higher rates in biopsy naïve patients (13). There is no consensus how to manage PI-RADS 4 and 5 lesions that do not yield csPCa following prostate biopsy.

The objective of our prospective study is to determine whether early repeat mpMRI and selective re-biopsy of PI-RADS 4 and 5 ROI exhibiting no csPCa should be routinely performed. A secondary objective is to identify predictors of missed csPCa in this cohort.

METHODS

Between January 2019 and August 2020, consecutive men with at least one PI-RADS 4 or 5 ROI and no evidence of csPCa following MRFTB + SB were invited to participate in the present prospective IRB (study number 018-0060 clinicaltrials.gov #NCT03635866). Men were eligible for the present study if the enrollment biopsy showing no csPCa was performed within a year of signing informed consent.

All mpMRI were performed per protocol [12] and interpreted by board certified radiologists uniformly reporting PI-RADS scores. The site(s) and maximal axial length(s) of all ROI were recorded. The mpMRI ROI were segmented by the radiologists using the Profuse platform. Our standard prostate biopsy protocol adopted by 4 uro-oncologists (HL, ST, JW, WH) utilizes the Artemis platform to target 4 tissue cores into the MRI ROI and 12 SB using the Artemis computer generated template [12]. The individual core lengths, length of cancer per core and length of Gleason pattern 4 and 5 disease per core were entered into the database.
All men enrolled with a persistent PI-RADS > 2 MRI ROI on study mpMRI were advised to undergo repeat biopsy in order to determine rates of csPCa missed by initial biopsy. The repeat biopsy was performed using our standard targeted biopsy protocol and mandating only SB ipsilateral to the MRI ROI. The systematic cores ipsilateral to the lesion were taken to correct for co-registration error during the fusion. Scans showing downgrading of the original PI-RADS 4/5 ROI to PI-RADS 1 or 2 were blindly re-interpreted by a different uro-radiologist experienced in prostate MRI interpretation to account for inter-reader variability.
The repeat biopsy was interpreted to show csPCa if the targeted or ipsilateral SB showed any Gleason pattern 4 disease.

Difference between PSA changes in the patients with down-graded scans versus thosw with persistently suspicious ROI was done through chi square test. Relative risk was calculated to analyze the association of baseline variables with the finding of csPCa on repeat biopsy on the subjects who underwent repeat biopsy. Variables analyzed were baseline GGG of initial biopsy, baseline PSA, PSA density, maximum axial diameter, and anatomical location (peripheral zone (PZ) and transition zone (TZ)). All data was stored on a REDCap based database and analyzed using SPSS v. 25.

RESULTS

Thirty-six men meeting eligibility criteria signed informed consent to participate in the present study and underwent a repeat protocol mpMRI. Two men presented with two PI-RADS 4 ROI at baseline, therefore 38 ROI were analyzed on a per-lesion basis.

Relevant baseline demographic characteristics, and initial mpMRI findings and biopsy outcomes of the 36 men enrolled in the study are shown in Table 1.

All 36 men underwent a repeat MRI (Table 2). Fourteen of the MRI ROI were downgraded to PI-RADS 1 or 2 and were not subjected to a repeat biopsy. Of the 24 persistent suspicious MRI ROI, eight (33%), 12 (50%) and 4 (17%) were PI-RADS 3, 4 and 5 respectively. Twenty of these 24 ROI were subjected to repeat per protocol biopsy.
The GGG of the cancers detected on repeat biopsy are shown in Table 2. Of the 20 ROI biopsied, six (30%), six (30%), and eight (40%) were benign, GGG1 and GGG >1, respectively.

There were no statistically significant differences between PSA changes in those patients whose mpMRI presented downgrading versus those who had persistently suspicious scans

(p=0.248). Only PSA ≥10 ng/mL was found to have a significant association with detection of csPCa on repeat biopsy (Table 3).

DISCUSSION

The csPCa detection rates following MRI targeted biopsy are directly proportional to the PI-RADS score [4,7,11,13]. At our institution, we routinely recommend biopsy for men with PI-RADS >2 ROI and only biopsy PI-RADS 1 and 2 ROI associated with other risk factors such as high PSA density, prominent family history, progressively rising PSA or elevated biomarkers such as 4KScore. Our csPCa detection rates for PI-RADS 3, 4, and 5 ROI is 23%, 73% and 88%, respectively [11]. These cancer detection rates are consistent with other large MRFTB experiences [14,15]. False negative targeted biopsies may occur due to co-registration errors [16-18]. Therefore, repeat imaging and biopsy has been recommended for PI-RADS 4 and 4 ROI that exhibit no csPCa on initial biopsy [19]. To our knowledge, we report the first prospective study examining "early " repeat biopsy of PI-RADS 4 or 5 ROI without evidence of csPCa on the initial MRI guided biopsy .

We have previously reported the early natural history of mpMRI ROI exhibiting no PCa on initial MRFTB + SB [20]. Of 51 ROI that were negative on initial biopsy and subjected to reflex repeat mpMRI within a year ,only 2 (3.9%) and none developed up-grading of PI-RADS score or significant growth of the ROI, respectively. Of the 13 (25.5%) cases that were initially PI-RADS 4, none showed up-grading or growth of the ROI. Therefore, growth or up-grading of MRI ROI in the short term will not inform who should undergo a repeat biopsy.

Ghavimi et al reported a retrospective study of men undergoing repeat mpMRI between 2008 to 2015 [21]. Of the 754 men in their database, only 83 underwent multiple mpMRI. The mean interval between mpMRI was 1.8 years. Of the 83 cases subjected to repeat mpMRI, 54 were on active surveillance with low-risk prostate cancer and 29 had no prior cancer. Since PI-RADS score of the index lesions rarely progressed, they recommended against short term mpMRI as an indicator of disease progression or false negative biopsy. Hauth et al retrospectively identified 72 cases of PI-RADS 4 ROI with a prior negative prostate biopsy [22]. The baseline PSA was 17.4 ng/ml which is very high for a prior negative biopsy cohort. Of these cases, only 26 (36%) underwent a repeat mpMRI which raises the concern for ascertainment bias. Repeat biopsies were recommended only for persistent PI-RADS 4 and 5 ROI. There was no standardized biopsy protocol. Overall, the natural history of the mpMRI ROI were: 2 (8%) resolved, 8 (31%) stabilized, and 16 (61%) progressed. The median time to repeat mpMRI was 17.6 months. The mean followup PSA was 21.4 ng/ml. Of the 24 persistent PI-RADS 4 or 5 ROI undergoing prostate biopsy, 18 (75%) were Gleason score 7 or 8 and six (25%) were benign. The authors recommended immediate repeat biopsy if a PI-RADS 4 ROI was negative on biopsy. Because of the extremely high baseline PSA levels, this recommendation cannot be extrapolated to all PI-RADS 4 ROI negative on prostate biopsy.

Kinnaird et al recently reported a retrospective study examining the natural history of a negative MRFTB[15]. Of the 2716 subjects in their MRFTB database, 733 (26.9%) had a negative initial biopsy and only 73 (9.9%) underwent a repeat biopsy. The repeat mpMRI showed PI-RADS <3 , 3 ,4 , or 5 in 20 (27.4%) , 24 (32.9%),16 (21.9%) , and 13 (17.8%), respectively. The median time from initial to follow up biopsy was 2.4 years and cancer was detected in only 17 (23%) cases. Only 28 of the initial 162 (17.3%) ROI showing PI-RADS 4 and 5 underwent a repeat MRI. Of the men with repeat PI-RADS<2, 3, 4, and 5 ROI, 0, 4 (17%), 6 (38%), and 5 (54%) exhibited csPCA defined as GGG > 1 on repeat biopsy. A limitation of this retrospective study is the percentage of men with PI-RADS 4 in the database who underwent a repeat mpMRI is very small and the indications for repeat mpMRI were not standardized.

Prostate biopsies at our institution are performed only by urologic oncologists experienced performing MRFTB using a standardized biopsy protocol [11]. All subjects with a PI-RADS 4 or 5 ROI with no cancer, or GGG 1 following MRFTB + SB were encouraged to enroll in the present prospective study. Since subjects underwent repeat mpMRI and biopsy within one year of the prior biopsy, we feel confident detection of csPCa is attributed to sampling error rather than progression of the disease.

Because of the previously reported null risk of csPCa following repeat biopsy of PI-RADS 4 ROI downgraded to PI-RADS 1 and 2 ROI [15], we did not perform a repeat biopsy on the 14 subjects whose ROI were downgraded to PI-RADS 1 or 2. Furthermore, these mpMRIs showing down-grading to PI-RADS 1 / 2 were blindly reviewed by a single uro-radiologist with vast experience in prostate MRI interpretation and there was 100% concordance with the initial interpretations, suggesting the down-grading was not attributed to inter-reader variability. We did encourage all other subjects to undergo repeat biopsy. Overall, 83% of subjects underwent a per protocol biopsy. Of the subjects undergoing repeat prostate biopsy, 30%, 30% and 40% were found to have no cancer, GGG 1 and GGG >1 cancer, respectively. We feel our 40% cancer detection rate of csPCa justifies a re-biopsy. Assuming a repeat biopsy of the 14 subjects with a PI-RADS 1 and 2 ROI would have yielded no csPCa, the sensitivity , specificity, NPV and PPV of repeat MRI for detecting csPCa would be 100%, 47%, 100%, and 33%, respectively. It is important to note, also, that there were no statistically significant changes in PSA between those patients with persistent PI-RADS 4/5 ROI and those who presented a down-grading to PI-RADS 1 or 2 on subsequent imaging. The 14 ROI that were found to harbor cancer on repeat biopsy corresponded to 14 different patients. Four of the six patients that were found to have GGG 1 disease chose to pursue active surveillance, while the remaining two patients chose to be treated with focal cryoablation. Out of the eight patients having been diagnosed with GGG ≥2 disease four were treated with focal cryoablation, while the other four chose to be treated with radical prostatectomy.

Relative risk was calculated for several baseline variables in order to identify predictors of csPCa on repeat biopsy. Only baseline PSA >10 ng/ml was a significant predictor of csPCa on repeat early biopsy. Meng et al failed to show an association association between benign

histological findings such as inflammation, high-grade prostate intraepithelial neoplasia, or atypical small acinar proliferation and csPCa following re-biopsy of a small group of men with no csPCa of PI-RADS 4 or 5 ROI [19].

There are several strengths of the present study. The major strength is it represents the only prospective study addressing management of PI-RADS 4 and 5 ROI, thereby minimizing ascertainment bias. All subjects enrolled in the study underwent standardized initial biopsy. The 36 subjects all underwent a repeat biopsy within a year suggesting we are assessing sampling error rather than the natural history of these ROI. A single group of experienced radiologists reviewed all studies. Despite enrollment occurred during the peak of the COVID-19 pandemic, we interpret our 83% compliance with protocol biopsy to be excellent.

The primary limitation of the present study is the relatively small sample size which we attribute to the 73% and 88% csPCa detection rates following initial biopsy of PI-RADS 4 and 5 ROI. Another limitation is that the study was carried out in a reference center for mpMRI and therefore the results may not be generalizable to community practice.

CONCLUSIONS

Our study provides compelling evidence that men with PI-RADS 4 or 5 ROI without csPCa on initial biopsy should undergo an early repeat mpMRI and all exhibiting persistent PI-RADS > 2 ROI should undergo repeat MRFTB + SB. Only baseline PSA was associated with detection of csPCa on repeat biopsy.

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