



Axumin (^{18}F -Fluciclovine) PET imaging in men exhibiting no clinically significant cancer on initial negative biopsy of PI-RADS 4 and 5 regions of interest

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Abstract

Purpose The objective of the study was to determine whether Axumin (^{18}F -Fluciclovine) PET/MRI informs the decision to perform an early repeat biopsy of PI-RADS 4/5 region of interest (ROI) exhibiting no clinically significant prostate cancer (csPCa) on initial biopsy.

Methods This prospective study enrolled men with at least one PI-RADS 4/5 ROI on multi-parametric MRI and no csPCa on prior biopsy defined as Gleason grade group (GGG) > 1. All men underwent an Axumin PET/MRI and only-persistent PI-RADS > 2 ROI were advised to undergo a repeat biopsy. A PET cancer suspicion score (PETCSS) was internally developed to stratify PET avid lesions according to their suspicion of harboring csPCa.

The sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of the PETCSS for predicting csPCa were assessed. Relative risk was calculated to analyze the association of baseline variables with csPCa on repeat biopsy.

Results Thirty-eight ROI on 36 enrolled men were analyzed. Fourteen (36.8%) were downgraded to PI-RADS 1/2 and were not subjected to repeat biopsy. Thirteen (92.9%) of these downgraded scans also exhibited low-risk PETCSS. Overall, 18/22 (81.2%) subjects underwent a repeat per protocol biopsy. Of the 20 ROI subjected to repeat biopsy, eight (40%) were found to harbour csPCa.

The sensitivity, specificity, PPV and NPV of the PETCSS were 50, 50, 40, and 60%, respectively. No predictor of csPCa was found in the risk analysis.

Conclusion Our pilot study showed that both MRI and PET sequences have limited performance for identifying those persistently suspicious PI-RADS 4/5 ROI that are found to harbor csPCa on repeat biopsy.

Keywords Prostate cancer · Positron emission tomography · Multiparametric magnetic resonance imaging · PI-RADS

Introduction

A limitation of prostate-specific antigen (PSA) screening for prostate cancer is its lack of specificity for detecting clinically significant prostate cancer (csPCa) resulting in high rates of unnecessary biopsy and over-treatment of low-risk disease [1]. The PROMIS trial demonstrated excellent

performance of mpMRI for identifying csPCa [2]. At our institution, all men without contraindications are advised to undergo a mpMRI prior to prostate biopsy. We and others have shown that cancer detection rates of csPCa are directly proportional to the prostate imaging reporting and data system (PI-RADS) v2.1 score [3–5]. Our published cancer detection rates for csPCa defined as Gleason Grade Group (GGG) > 1 disease for PI-RADS 3, 4 and 5 region of interest (ROI) is 23, 73, and 88%, respectively [5]. Therefore, we routinely recommend initial biopsy for all PI-RADS 3–5 ROI. There is increasing evidence that MRI-targeted biopsy alone fails to detect csPCA in some PI-RADS 4 and 5 ROI [6–9].

The potential of Axumin (^{18}F -Fluciclovine (anti-1-amino-3- ^{18}F fluorocyclobutane-1-carboxylic acid)) for detecting

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prostate cancer was first recognized over a decade ago [10]. Ghafoor et al. [11] recently published a comprehensive review showing that the ligands ^{68}Ga -PSMA-11; ^{18}F -DCF-PyL-PSMA; ^{18}F -DFCBC-PSMA, and ^{18}F -PSMA-1007 improve localization of local, nodal and systemic disease recurrence following primary treatment. PET imaging with ^{18}F -Fluciclovine is currently approved and widely used for this indication [10, 12, 13]. Ghafoor et al. [11] did not reference any studies showing whether PET imaging aids in the identification of patients who require repeat imaging and biopsy following an initial negative prostate biopsy. We chose to investigate ^{18}F -Fluciclovine over PSMA since at the time the study was initiated PET-PSMA was not commercially available in the United States.

The objective of the present study was to determine whether Axumin (^{18}F -Fluciclovine) PET/MRI informs decisions on whether to perform early repeat prostate biopsy of PI-RADS 4 and 5 ROI exhibiting no csPCa on initial biopsy who have persistent suspicious mpMRI ROI for csPCa.

Methods

Study design

This pilot study was designed to determine the utility of Axumin (^{18}F -Fluciclovine) PET/MRI to inform decision whether to perform early re-biopsy in men with mpMRI PI-RADS 4 or 5 ROI without csPCa on initial prostate biopsy. Men with a mpMRI showing at least one PI-RADS 4 or 5 ROI and no finding of csPCa (defined as Gleason grade group (GGG) > 1) on initial biopsy were eligible for the study. The interval between initial biopsy and signing of informed consent had to be less than one year. The study was approved by the institution IRB under protocol s18-00,601.

All baseline and study mpMRI were interpreted by board-certified radiologists trained to uniformly report according to PI-RADS v2.1 criteria. The anatomical location and maximal axial length of the ROI were recorded. The ROI for the baseline study mpMRI was 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 mpMRI ROI and 12 systematic biopsies (SB) using the Artemis™ computer-generated template [14]. The baseline individual core lengths, length of cancer and percent Gleason pattern 4 disease was entered into the database. All men underwent an ^{18}F -Fluciclovine PET MRI. Both the initial MRI and the PET-MRI were multiparametric.

Axumin (^{18}F -Fluciclovine) PET/MRI technique

See supplementary material.

PET interpretation

An experienced nuclear medicine physician interpreted the PET images, using the StarVIBE and HASTE MRI sequences for anatomic localization. The PET/MRI images were interpreted using a fusion viewer (MIM version 6.9, MIM Software). Comparison was made with the prior diagnostic prostate MRI to localize the previously seen PI-RADS 4/5 ROI, however, the nuclear medicine physician was blinded to the follow-up mpMRI acquired at the same time as the PET. Unlike the PI-RADS scoring system, there is no standardized PET scoring system for assessing the probability of prostate cancer. Therefore, a scoring system was developed to qualitatively rate the likelihood of prostate cancer based on the Blue Earth Diagnostics interpretation training document for Axumin [15]. For each of the previously seen PI-RADS 4/5 ROI, a qualitative visual uptake intensity score was assigned with relative uptake in the lesions compared to uptake background uptake within the prostate gland/blood pool and the marrow uptake, with the L3 vertebral body as the reference standard. Lesions that were less than 10 mm in the greatest dimension with any uptake greater than the background prostate/blood pool were assigned PET cancer suspicion score (PETCSS) 3 as volume averaging may cause relatively lower intensity of tracer uptake (Supplementary Table 1).

Follow-up biopsy

Only persistent PI-RADS > 2 MRI ROI were segmented by the radiologists using the Profuse software and were subjected to early repeat MRFTB independent of the PET findings. The repeat biopsy was also performed using our standard biopsy protocol [14].

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PETCSS for predicting csPCa was determined for the entire cohort and those with persistent PI-RADS > 2 ROI.

Detailed information related to baseline demographics, mpMRI ROI and biopsy outcomes were recorded prospectively and entered into a REDCap (v8.10.8 Vanderbilt University, Nashville, TN, USA) database. 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 PSA, PSA density, maximum axial diameter, anatomical location (peripheral zone (PZ) and transition zone

(TZ)), and PETCSS. Data was analyzed on SPSS® v25 (IBM, Amonk, NY, USA).

Results

Thirty-six men signed informed consent and were enrolled in the study. Two subjects had 2 PI-RADS 4 ROI on their baseline mpMRI, therefore, 38 ROI on 36 men were analyzed. Relevant baseline demographic characteristics, mpMRI findings and initial biopsy outcomes of the 36 subjects and their 38 ROI are shown in (Table 1).

All 36 subjects underwent an Axumin (¹⁸F-Fluciclovine) PET/MRI. Fourteen of the 38 (36.8%) mpMRI ROI were downgraded to PI-RADS 1 or 2 ROI and were not subjected to a repeat biopsy. Of these 14 downgraded mpMRI ROI, 13 (92.9%) also had low-risk PETCSS. 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. Of the 24 persistent suspicious ROI identified in 22 subjects, 8 (33.3%), 12(50%) and 4 (16.7%) were PI-RADS 3, 4, and 5 respectively (Table 2). The PETCSS was 1, 2, or 3 in 11 (45.8%), 1 (4.2%), and 12 (50%) ROI, respectively. Overall, 18 of the 22 (81.8%) subjects with persistent mpMRI lesions underwent a repeat per protocol biopsy. Of the 20 ROI subjected to repeat biopsies, six

Table 1 Baseline characteristics

Age, years ^a	66 (62–72)
Serum PSA, ng/mL ^a	5.60 (4.44–7.84)
PSA density ^a	0.11 (0.09–0.16)
Ethnicity ^a	
Caucasian	25 (69)
African American	3 (9)
Hispanic	3 (9)
Other	5 (12)
MRI ROI	
Maximum axial diameter	10 (7–14)
Location	
Peripheral zone	28 (74)
Transition zone	10 (26)
Baseline biopsy results	
Benign	23
GG 1 disease < 6 mm	11
GG 1 disease ≥ 6 mm	2
Median time to repeat biopsy, months	12 (8–14)

Continuous variables are displayed as median (IQR). Categorical variables are displayed as *n* (%)

^aNumber of subjects, *N* = 36

Table 2 Repeat MRI and biopsy outcomes (*N* = 38)

Follow-up MRI	
PI-RADS score	
1	7 (18)
2	7 (18)
3	8 (21)
4	12 (32)
5	4 (11)
Follow-up biopsy	
PI-RADS score of ROI undergoing repeat biopsy (<i>N</i> = 20)	
3	5 (25)
4	11 (55)
5	4 (20)
Gleason grade group (GGG)	
Benign	
1	7 (35)
2	6 (30)
3	6 (30)
4 and 5	1 (5)
	0

Continuous variables are displayed as median (IQR). Categorical variables are displayed as *n* (%)

(30%), six (30%), and eight (40%) were benign, GGG1 and GGG > 1, respectively.

The sensitivity, specificity, PPV and NPV of the PETCSS to predict csPCa following repeat biopsy is shown in Supplementary Table 2. Since there was only one PETCSS of 2, it was grouped together with group 1 (low risk).

Table 3 Predictors of clinically significant prostate cancer (csPCa) following early repeat biopsy of persistently suspicious mpMRI ROI

	<i>n</i>	RR csPCa
Baseline PSA		
≥ 10 ng/mL	2	0.846 (0.671–1.067)
< 10 ng/mL	16	
PSA density		
≥ 0.15	10	1.154 (0.339–3.992)
< 0.15	8	
Baseline maximum axial diameter of ROI		
≥ 10 mm	9	1.346 (0.411–4.406)
< 10 mm	9	
Lesion location		
PZ	13	1.282 (0.591–2.783)
TZ	5	
PET score		
3	9	0.481 (0.213–1.087)
1 and 2	9	

Relative risk was calculated to determine factors predicting csPCa following early re-biopsy of the 20 ROI (Table 3). No predictor of csPCa was found in this analysis.

Discussion

mpMRI is widely used to inform decisions on whether to perform a prostate biopsy in men presenting with an elevated serum PSA [16, 17]. At our institution, over 95% undergo a pre-biopsy mpMRI [5]. We have also reported very low rates of csPCa following prostate biopsy in men with PI-RADS 1 scores [5]. Based on these cancer detection rates, we rarely perform a prostate biopsy of men with low suspicion PI-RADS 1 or 2 ROI.

PI-RADS 4 and 5 ROI are characterized as highly suspicious for csPCa [4]. Therefore, it is in this group where legitimate concern exists for false negative biopsies. Several retrospective studies recommend early re-imaging following a negative mpMRI guided biopsy of PI-RADS 4 or 5 ROI providing the repeat mpMRI remains suspicious for csPCa [6, 7]. Our observation that ipsilateral SB increases detection of csPCa missed by MR targeted biopsy suggests the real potential for false negative MRFTB due to mis-registration [18]. There is no consensus definition for csPCa. Ahmed et.al reported on the utility of mpMRI to detect csPCa using several definitions. The definition chosen for the present study was $G/G > 1$ since its sensitivity was intermediate among the proposed definition [2].

We have previously reported that many ROI that are negative on biopsy show downgrading of the PI-RADS ROI on follow-up mpMRI [19, 20]. In the present study, 14 of the 38 initial mpMRI ROI were downgraded to a PI-RADS 1 or 2 lesion. Since the risk of identifying csPCa following repeat mpMRI of PI-RADS 4 or 5 lesions downgraded to PI-RADS 1 and 2 has been reported to be 0 [6], we are justified in not recommending repeat biopsy if the repeat mpMRI showed downgrading to PI-RADS 1 and 2.

The present study represents a pilot investigation whether Axumin (^{18}F -Fluciclovine) PET/MRI informs the decision for repeat early biopsy in men with PI-RADS 4 and 5 MRI ROI with no evidence of csPCa who have persistent suspicious MRI ROI. We did not perform a prostate biopsy in 14 subjects whose MRI ROI were downgraded to PI-RADS 1 or 2. Of these 14 PI-RADS 4 or 5 ROI showing PI-RADS down-grading, 13 exhibited PETCSS of 1 which shows excellent concordance between low suspicion for cancer based on mpMRI and PET scoring.

A ^{18}F -Fluciclovine PET/MRI includes both a mpMRI and PET imaging. Therefore, the utility of PET imaging must add to information gleaned from the mpMRI. We assumed a repeat biopsy was not justified in cases where the PI-RADS 4 or 5 ROI was downgraded to PI-RADS 1 or 2. Our present

study shows excellent concordance between downgrading of suspicious ROI based on mpMRI and PET imaging. If we assume the 13 low-risk PETSS would have yielded negative biopsy since all these ROI were downgraded on MRI, then the sensitivity, specificity, negative predictive value and positive predictive value of PET imaging for csPCa would be 50, 73, 82 and 36%, respectively. Over half of the cases with persistent suspicious mpMRI ROI showed no evidence of csPCa on early repeat biopsy. The objective of the present study was to determine if the addition of PET imaging would inform the decision on who with persistent suspicious PI-RADS ROI should undergo early re-biopsy. There is ample evidence that downgrading of the PI-RADS 4 or 5 ROI is associated with an extremely low risk of csPCa so there is no role for PET imaging in informing whether these men should undergo repeat biopsy. The performance of PET imaging in the subset of subjects with persistently suspicious PI-RADS 4 or 5 is not adequate to inform the decision on who with persistent suspicious PI-RADS ROI should undergo re-biopsy. No variable was found to carry a significant association with the finding of csPCa upon repeat biopsy in this pilot study.

There are several studies reporting good performance of PET to identify sites of prostate cancer in men with high-risk disease undergoing radical prostatectomy [12, 13, 21–24]. There is no consensus on whether PET imaging is superior to mpMRI alone. These localization studies are not relevant to a screening cohort or men with possible missed cancers following mpMRI targeted biopsy.

There are several strengths of the present study. To our knowledge, it is the first prospective investigation evaluating the utility of PET imaging for informing decision for early repeat prostate biopsy of persistently suspicious mpMRI ROI. All subjects enrolled in the study underwent a uniform initial and repeat biopsy protocol. Experienced radiologists and nuclear medicine physicians reviewed the mpMRI and PET images, respectively and experienced uro-oncologists performed the biopsies. Despite the fact the enrollment period was during the peak of the COVID-19 pandemic, our compliance with protocol for repeat early biopsy was over 80%.

There are several limitations to acknowledge. The sample size is small and the number undergoing repeat early biopsy is even lower because of PI-RADS down-grading. Unlike mpMRI, there is no standardized or validated grading system for assessing PET ROI. For the purposes of the present study, we developed a PETCSS, but this score requires validation.

Conclusion

The overall 21% rate of csPCa justifies early re-assessment of all men with initial PI-RADS 4 or 5 ROI exhibiting no cancer on initial biopsy. If repeat biopsy is performed only

on persistent suspicious PI-RADS > 2 ROI, then the cancer detection rate of csPCa increases to 44%. The objective of the present study was to determine whether Axumin (^{18}F -Fluciclovine) PET/MRI informs decisions on who with persistently suspicious mpMRI should undergo a repeat biopsy. Our pilot study failed to support this indication for Axumin (^{18}F -Fluciclovine) PET/MRI despite its overall favorable NPV in the entire cohort.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00345-022-04172-3>.

Author contributions EB: statistical analysis, protocol development, manuscript writing. SK: PETCSS development and internal validation. JW: data collection. ST: data collection, manuscript oversight. WH: data collection. HL: protocol development, manuscript writing.

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Declarations

Conflict of interest The authors does not present any conflict of interest relevant to the study.

Ethical approval All participants in the study signed an informed consent. This study was approved by NYU Langone Health IRB under study number 018–00601 and carried out in accordance with the Declaration of Helsinki.

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