68Ga-PSMA-11 PET/MR detects local recurrence occult on mpMRI in prostate cancer patients after HIFU

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Short running title: PSMA PET/MR for recurrent PCA after HIFU
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**ABSTRACT**

High-intensity focused ultrasound (HIFU) is a promising new modality for the treatment of localized prostate cancer (PCa). Follow up of patients is recommended with biopsies and multiparametric MRI (mpMRI). However, mpMRI in the postinterventional setting is often false negative. It was our aim to investigate if the new tracer targeting the prostate specific membrane antigen (\(^{68}\text{Ga-PSMA-11}\)) could be used to localize recurrent disease with PET/MR in patients with discrepant findings between mpMRI and template biopsies.

**Methods:** Interim analysis of the first ten patients scanned between 09/2016-05/2018 with positive template biopsy and negative mpMRI after HIFU from an ongoing clinical trial (NCT02265159). All patients underwent a \(^{68}\text{Ga-PSMA-11}\) PET/MRI within 3 months. Four prostatic quadrants were defined and for every quadrant suspicion for recurrence was rated on a 5 point Likert scale from definitely no recurrence (1) to highly suspicious for recurrence (5), with (4) used as cut off for suspected disease based on PET/MRI by one blinded reader. \(^{68}\text{Ga-PSMA-11}\) uptake of suspicious lesions and background areas was measured with the maximum standardized uptake value (SUV\(_{\text{max}}\)). The apparent diffusion coefficient (ADC) values of lesions and background was given for each segment. PET/MRI scans were compared with the template biopsy results including corresponding Gleason Scores (GS), number of positive cores and tumor length.

**Results:** The quadrant-based sensitivity, specificity, positive and negative predictive value for PET/MRI was 55%, 100%, 100% and 85%, respectively. Patient based, PET/MRI was negative in four cases with GS3+4 and a tumor length between 0.1-3mm. All tumor lesions with GS4+3 or higher were detected on PET/MRI.

**Conclusion:** Our preliminary results indicate that \(^{68}\text{Ga-PSMA-11}\)-PET/MR has the potential to localize PCa recurrence after HIFU occult on mpMRI.
Keywords: prostate specific membrane antigen, magnetic resonance imaging, template biopsy, high-intensity focused ultrasound.
INTRODUCTION

Focal treatment of the prostate with high-intensity focused ultrasound (HIFU) is a promising new modality for the treatment of localized prostate cancer (PCa). With limited side effects such as urinary incontinence and erectile dysfunction, disease control after one treatment can be reached in about 81-92% of the patients (1). There is currently no validated method for monitor treatment success. Based on consensus meetings, follow up of patients to rule out persistence or recurrence is recommended with biopsies, prostate specific antigen (PSA) and multiparametric MRI (mpMRI) (2,3). Prostate biopsies remain the most accurate option to monitor patients after focal HIFU (4). However, tissue sampling is an invasive procedure associated with significant morbidity (5). The non-invasive diagnostic tests PSA and mpMRI could not show sufficient sensitivity and specificity in order to replace follow-up biopsies.

However, mpMRI is often difficult to interpret due to signal alterations of the treated prostate. Early work on MRI appearance of the prostate after HIFU showed, focal high signal on T1-weighted images, most likely representing interstitial hemorrhages and a dark central zone on T2-weighted images representing the central necrosis (6). The same authors suggested later that dynamic contrast enhancement can increase the detection of local recurrence after HIFU (2). But still, the post interventional changes, especially the focal hemorrhages can limit the interpretation of mpMRI for prostate (7).

The novel positron emission tomography (PET) tracer targeting the prostate specific membrane antigen (PSMA) labeled with Gallium 68 (68Ga-PSMA-11) is primarily used for the detection of recurrent PCa (8,9). The major benefit of 68Ga-PSMA-11 is a significantly improved sensitivity(10), with a high reliability and robust interreader agreement (11,12). First investigations showed that 68Ga-PSMA-11 can also be used to improve local staging of PCa (13,14), corresponding to the initial results on immunohistochemistry showing a low PSMA expression on the cell membrane in normal prostate tissue but high membranous expression on PCa (15).
The effect of focal HIFU on PSMA expression is unknown. Until now, only one case report describing a successful re-HIFU based on a positive Choline PET/MRI has been published (16). However, the limited specificity of Choline in the prostate limits the confidence in Choline PET/MR as a tool for reevaluation after HIFU, since not only prostate cancer but also benign prostate hyperplasia is known to have intense Choline uptake. $^{68}$Ga-PSMA-11 does not have increased uptake in benign prostate hyperplasia and might be superior for the detection of local recurrence after HIFU.

Therefore, we investigate if $^{68}$Ga-PSMA-11 PET/MRI could be used to localize biopsy proven recurrent disease after HIFU therapy in patients with negative mpMRI.
MATERIALS AND METHODS

Patients

We performed an interim analysis of the first 10 patients prospectively investigated between December 2016 and March 2018 from an ongoing prospective single-arm clinical trial (NCT02265159). All patients underwent curatively intended focal HIFU therapy for a Gleason score (GS) 6-7 prostate cancer. Patients were included and referred for a $^{68}$Ga-PSMA-11 PET/MRI scan of the pelvis if there was a biopsy proven significant prostate cancer on transperineal follow-up template biopsy, not detected on clinical routine mpMRI. The maximum time interval accepted between biopsy and mpMRI was 3 months. PCa was defined as clinically significant in the presence of any Gleason 4 pattern (GS ≥ 3+4).

Template biopsy of the prostate

Systematic transperineal template mapping fusion biopsies were performed by experienced urologists in all patients after 6, 12 and 36 months after initial HIFU therapy. Patients were positioned in dorsal lithotomy position. As an antibiotic prophylaxis all patients received 80mg Gentamycin intravenously prior biopsy. Fusion of live-TRUS and mpMRI was performed by using the BiopSee® biopsy system (Medcom, Darmstadt, Germany) to allow later reconstruction of the histology. Systematic biopsy cores were taken from all 20 predefined Barzell zones leading to organ coverage of approximately 95% (17). For comparison to the PSMA PET/MRI results the biopsy cores were grouped into 4 quadrants right anterior (RA), left anterior (LA), right posterior (RP) and left posterior (LP).

$^{68}$Ga-PSMA-11 PET/MRI

All patients underwent a pelvic PET/MRI on a dedicated hybrid scanner (SIGNA PET/MR, GE Healthcare, Waukesha, WI, USA) 60 minutes after injection of 85 MBq $^{68}$Ga-PSMA-11 (range 82-89 MBq). The protocol included specific sequences covering the pelvis, including a high
resolution T1-weighted LAVA-FLEX sequence, T2-weighted fast recovery fast spin-echo sequence in three planes and diffusion weighted images as previously published (18). The PET frame time over the prostate was 15 minutes, this allowed us to lower the injected dose to 85 MBq $^{68}$Ga-PSMA-11, with excellent image quality. To rule out lymph nodes or distant metastasis, one more partial body frame with 4 minutes frame time was performed up to the renal vessels. To reduce $^{68}$Ga-PSMA-11 activity in the bladder, furosemide was injected intravenously 30 minutes prior to the $^{68}$Ga-PSMA-11 injection. Volumes of interest (VOI) were placed over the entire PSMA-positive lesion tumor. $^{68}$Ga-PSMA-11 uptake was quantified with the maximum standardized uptake value ($SUV_{max}$), furthermore PSMA uptake in normal prostate tissue was measured.

**Multiparametric MRI**

MRI was performed on a 3T MRI system (Skyra, SIEMENS Healthcare, Erlangen, Germany). For signal reception a 18-channel phased-array receiver coil was used. The protocol and the sequence parameters were in concordance with the current international prostate MR guidelines (19). Transverse diffusion-weighted echo-planar imaging images (DWI), based on dynamic parallel transmit technology, utilizing selective excitation for depiction of a reduced field-of-view (FOV) were acquired with identical orientation and at identical locations as the T2w images with the following acquisition parameters: TR/TE, 5000/75 ms; in-plane resolution, 0.7 x 0.7 mm; slice thickness, 3 mm; b-values, 100/600/1000 s/mm$^2$. Dynamic contrast enhanced images were acquired using the following parameters: TR/TE, 5-6.3/1.8 ms; in-plane resolution, 1 x 0.6 mm; temporal resolution, <8 s. All scans were technically adequate; no patients were excluded from further analysis.

**Image analysis**

Two readers one with 10 years and one with two years of experience in urogenital imaging, blinded for the biopsy results read the PET/MRI images. The prostate was subdivided into 8
segments: right anterior base (RAB), left anterior base (LAB), right posterior base (RPB) and left posterior base (LPB), with corresponding segments at the apex (RAA, LAA, RPA and LPA). For every segment suspicion for recurrence was rated on a 5 point Likert scale from no recurrence (1) to highly suspicious for recurrence (5), with (4) used as cut off for suspected recurrence. For quantitative analysis images were directly compared with the biopsy results and for every PCa lesion with GS>3+3 the corresponding SUV\textsubscript{max} and apparent diffusion coefficient (ADC) values were assessed for the corresponding region.

For every lesion the modified GS according to the WHO 2016 classification (20), number of positive cores and the maximum cancer core length in mm was recorded. To compare the total tumor burden with the corresponding quantitative \textsuperscript{68}Ga-PSMA-11 PET/MR and mpMRI metrics the cancer volume was estimated by multiplication of the number of positive cores and maximum core length in mm (MCL).

Patients were included in the presence of any Gleason 4 pattern, however additional definitions of clinical significance based on the definition of Ahmed et al used in the PROMIS trial, were applied to improve the comparability with published literature (GS ≥4+3 or a maximum cancer core length of 6 mm or longer) (21).

**Statistical analysis**

Statistical analyses were performed using SPSS statistics software version 23 (IBM, Armonk, USA). The eight segments form the qualitative image analysis were aggregated into quadrants by summarizing corresponding locations from the base and the apex as previously reported (22). Interreader agreement was assessed with weighted kappa. Sensitivity and specificity was calculated quadrant based, after dichotomization of both imaging and pathology data and summarizing the imaging results for apex and base. Pathology was considered positive for significant cancer harboring a GS > 3+3, and imaging read out was considered positive for a Score 4-5. Descriptive analyses were used to display patient data as mean and range. The
correlation between estimated tumor volume and $SUV_{\text{max}}$ and ADC values was assessed with 2-tailed Pearson correlation test. A p-value $< 0.05$ was considered statistically significant.
RESULTS

The median age was 68 years (range 59-74). The median time between focal HIFU and positive transperineal template biopsy was 15 months (range 6-35 months), the median time interval between mpMRI and $^{68}$Ga-PSMA-11 PET/MRI was 2 months (range 0-3 months). All routine read out of mpMRI were negative for recurrent disease. In 6 patients GS 3+4 lesions were detected, 3 patients had GS 4+3 disease and one patient GS 4+4. Patient characteristics are given in a table (Table 1).

Patient based analysis

For 6 of 10 patients the $^{68}$Ga-PSMA-11 PET/MRI was positive, with complete agreement for both readers. No false positive lesions were seen on $^{68}$Ga-PSMA-11 PET/MRI. Five of the lesions were given a Likert score of 5 (highly suspicious for recurrence) and in one case a score of 4 (probably recurrence) was given. No patient had suspicious lesions outside the prostate.

Quadrant based lesion detection on $^{68}$Ga-PSMA-11 PET

The quadrant-based sensitivity, specificity, positive and negative predictive value for $^{68}$Ga-PSMA-11 PET/MRI was 55%, 100%, 100% and 85%, respectively. The weighted interreader agreement for the 5 point scale was $\kappa = 0.78$ (CI 0.68-0.94). Six suspicious lesions were seen on $^{68}$Ga-PSMA-11 PET/MRI by both readers, all corresponding to the quadrant positive for PCa on template biopsy. Four lesions were not detected on $^{68}$Ga-PSMA-11 PET/MRI in the blinded read out. All lesions negative on PET had a GS 3+4 disease with only one core positive and a maximum core length of less than 4 mm. After dichotomization, there was full agreement between both readers. By reader one only one segment was labeled undetermined on $^{68}$Ga-PSMA-11 PET/MRI (Likert score 3), negative on pathology (Table 2).

Illustration of two lesions, one positive (Fig. 1) and one negative (Fig. 2) on $^{68}$Ga-PSMA-11 PET/MRI.
Correlation of $^{68}$Ga-PSMA-11 PET uptake and diffusion restriction with tumor burden

According to the definition of significant cancer used in the PROMIS trial by Ahmed et al (defined as a Gleason ≥4+3 or more, or a maximum cancer core length of 6 mm or more) (21) only 3 patients had clinically significant tumor, all were positive on $^{68}$Ga-PSMA-11 PET with a mean SUV$_{\text{max}}$ 8.4.

If any Gleason pattern 4 is considered clinically significant, the median uptake on $^{68}$Ga-PSMA-11 PET positive cancer lesions was SUV$_{\text{max}}$ 8.6 (range from 4.6 – 12.1, Table 3).

Higher estimated tumor volume (defined as the number of positive biopsies multiplied by maximum core length) and higher GS were associated with $^{68}$Ga-PSMA-11 uptake measured as SUV$_{\text{max}}$ or Tumor to background ratio (Fig. 3). There was a significant correlation between estimated tumor volume and SUV$_{\text{max}}$ (0.674, p<0.001).

The median maximum $^{68}$Ga-PSMA-11 uptake in the negative segments was SUV$_{\text{max}}$ 3.5 (range from 2.2 – 5.8). High $^{68}$Ga-PSMA-11 accumulation (SUV$_{\text{max}}$ > 4) was observed in 7 segments in the posterior base, corresponding to increased activity in the central zone and not rated as suspicious for recurrence.

Comparing the ADC values with the estimated tumor volume and GS, there was no association between lower ADC values and higher GS or estimated tumor volume (Fig. 4). There was no significant correlation between estimated tumor volume and ADC values (0.040, p=0.808). ADC values were slightly lower in segments positive for PCa mean 1059±560 x 10$^{-6}$ mm$^2$/s (range 131-1811), compared to cancer negative segments with a mean ADC 1174±390 x 10$^{-6}$ mm$^2$/s (range 445-2078).
DISCUSSION

Our study shows that in 6 out of 10 patients 68Ga-PSMA-11PET/MRI detected recurrent disease not seen on clinical routine mpMRI. Furthermore, PSMA accumulation in true positive lesions had a high tumor to background ratio and correlated significantly with the total tumor burden, while ADC values did not show a significant negative correlation with tumor burden.

These results stand in contrast to the previously published excellent results for mpMRI to detect recurrent disease after HIFU therapy with sensitivities ranging from 94-97% (2,23). However, all previously published studies used transrectal biopsies with or without MRI guiding as a reference standard. In the study published by Lotte et al. 24 of 98 patients were excluded, because they did not undergo any biopsy, probably due to a negative mpMRI (23). The use of mpMRI to guide biopsy gained wide acceptance and is ideally performed in patients without previous intervention. After a previous biopsy the PICTURE study in 249 patients showed that using a Likert Score of 3 as a cut off, the sensitivity for mpMRI is very high (97%), to the price of a very low specificity of 22% (24), reflecting the potential false positive findings in the prostate after interventions (7).

Furthermore, these results for the accuracy of mpMRI to detect clinical significant cancer were based on the definition according to Ahmed et al: with a GS ≥ 4+3 and/or a maximum cancer core length of ≥ 6 mm (21,25). Applying the same threshold to our study only three patients had significant tumor on template biopsy, 68Ga-PSMA-11 PET/MR was positive in all three cases, while mpMRI was not able to detect those lesions.

In the setting of focal therapy not only detection, but also accurate delineation of the tumor is crucial for potential retreatment. In a recent analysis of 625 consecutive patients undergoing HIFU therapy, a high failure free 5 year survival of 88% was achieved. Even patients with a high risk tumor according to D’Amico classification did not need a salvage therapy or show any metastasis 5 years after HIFU (26). In this multicenter study only 222 of 625 patients
underwent biopsies after HIFU, and PSA rise was not considered an endpoint for failure free survival. The authors do not state if mpMRI was performed routinely, but in 121 of the patients a repeat HIFU was performed (26). The optimal surveillance after focal prostate therapy is still controversial. A recently published meta-analysis and consensus publication suggests that mpMRI should be performed at 3–6 months (with targeted biopsy of the treated zone and any suspicious lesion seen on mpMRI), at 12–24 months and at 5 years. Additionally, a systematic biopsy should be performed at 12–24 months and again at 5 years (4). The sensitivity of mpMRI for the detection of clinically relevant cancer in comparison to template biopsies was based on studies in man without any focal treatment (27-29). Indeed, little is known about the sensitivity of mpMRI especially, early after HIFU when post interventional changes are still present. The consensus recommendations published in 2013 state that mpMRI is the technique of choice for follow-up of focal ablation. Early publications of mpMRI after HIFU published extensive signal alterations after 3 and 6 months, with low signal on T2-weighted images and a substantial decrease in volume, but observed that contrast enhancement might correlated with residual disease (30). The most recent paper in 45 patients undergoing mpMRI and transrectal ultrasound (TRUS) guided biopsy after HIFU however, came to the conclusion, that dynamic contrast enhancement did not add any additional information compared to T2-weighted imaging and diffusion (23). However, this results need to be considered with caution, since many patients (24 of 98) with negative mpMRI were not considered for TRUS-guided biopsy within the study protocol.

The first results with a high detection of clinically significant cancer with PSMA PET/MR (13,14), have now been further supported with recent studies showing a good correlation between PSMA-upake and Gleason score or PSA values (31,32). However, not every prostate cancer has a high PSMA expression; in fact based on early immunohistochemistry work it is known that around 10% of the prostate cancers do not express PSMA (15,33). This finding is in concordance with present results from large studies with more than 100 patients for recurrent
prostate cancer, where PSMA-PET reaches detection rates for a PSA value above 2 ng/ml of 89%-97% (34). Therefore, in a small portion of about 10% of the patients, PSMA PET might be of limited use. For patients without PSMA expression, alternative tracers such as $^{68}$Ga-Bombesin, targeting the gastrin-releasing peptide receptor (GRPr) (35,36) could be investigated, for optimized personalized tumor detection and early therapy.

Our study has limitations, as it is a selected subgroup of patients with a positive biopsy but a negative clinical mpMRI after HIFU. With the present data it cannot be excluded, that in some cases the clinical mpMRI would be positive and PSMA-PET false negative, an overall sensitivity and specificity for both modalities after HIFU can therefore not be calculated. Given that patients within the HIFU study protocol already undergo multiple interventions and scans, it was the aim of this preliminary study to investigate if patients with discrepant findings between mpMRI and template biopsies could profit from the additional $^{68}$Ga-PSMA-11 PET/MRI to localize significant tumor. The promising results now will lead to a larger study investigating all patients with mpMRI and $^{68}$Ga-PSMA-11 PET/MRI before template biopsy to shed more light on the potential benefit of $^{68}$Ga-PSMA-11 PET/MRI to localize persistent or recurrent cancer in the prostate after focal therapy.

CONCLUSION

Our preliminary results indicate that $^{68}$Ga-PSMA-11-PET/MR might detect local recurrence of PCa after HIFU that is not detected by mpMRI. $^{68}$Ga-PSMA-11 PET/MRI could be used to plan and target secondary HIFU to increase the rate of disease control for this promising new focal therapy.
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REFERENCES


FIGURE 1: First patient (HK06) with (A-C) axial slices of T2 weighted MRI, fused PSMA PET/MRI, and PSMA PET (window 1-8) with intense uptake in the left posterolateral peripheral zone, (D-E) the negative axial mpMRI (T2 weighted MRI and ADC map) and (F) the corresponding PDF from the BiopSee® system (Medcom) with the positive core biopsy (GS 4+3) labeled in blue in the PET positive area.
FIGURE 2: Second patient (HK09) with (A-C) axial slices of T2 weighted MRI, fused PSMA PET/MRI, and PSMA PET (window 1-8) without increased uptake, (D-E) negative axial mpMRI (T2 weighted MRI and ADC map) and (F) the PDF from the BiopSee® system (Medcom) with one positive core biopsy (GS 3+4) labeled in black.
FIGURE 3:

Scatter plot for estimated tumor volume (number of positive biopsies multiplied by maximum core length) and uptake on $^{68}$Ga-PSMA-11 PET ($\text{SUV}_{\text{max}}$) showing a significant correlation between the estimated tumor volume and $\text{SUV}_{\text{max}}$ ($r = 0.674$, $p<0.001$), as well as an association with higher Gleason Scores (GS) represented by colors and increased uptake on $^{68}$Ga-PSMA-11 PET.
FIGURE 4:

Scatter plot for estimated tumor volume (number of positive cores x maximum core length) and ADC values (x10^{-6} mm^2/s) from mpMRI, did not show a significant correlation with the estimated tumor volume (r = 0.040, p=0.808) and no association between higher GS and lower ADC values.
**TABLE 1**: Patient characteristics.

<table>
<thead>
<tr>
<th>Total – 10 patients</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>68 ± 4.3</td>
</tr>
<tr>
<td>Range</td>
<td>60-75</td>
</tr>
<tr>
<td><strong>PSA (pre HIFU)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.4 ± 3.5</td>
</tr>
<tr>
<td>Range</td>
<td>1.5 – 12.7</td>
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<tr>
<td><strong>Gleason score (pre HIFU)</strong></td>
<td></td>
</tr>
<tr>
<td>3+4</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>4+3</td>
<td>6 (60%)</td>
</tr>
<tr>
<td><strong>PSA (at scan)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.1 ± 2.2</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td><strong>Time between HIFU and recurrence</strong></td>
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<tr>
<td>Mean ± SD</td>
<td>15.8 ± 9.4</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td><strong>Gleason score (at scan on template biopsy)</strong></td>
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</tr>
<tr>
<td>3+4</td>
<td>6</td>
</tr>
<tr>
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<tr>
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**TABLE 2:** Segment based sensitivity and specificity.

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<th>TN</th>
<th>FP</th>
<th>FN</th>
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<th>Spec</th>
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<tr>
<td>PSMA PET/MRI (4/5)</td>
<td>6</td>
<td>29</td>
<td>0</td>
<td>5</td>
<td>55%</td>
<td>100%</td>
<td>100%</td>
<td>85%</td>
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<td>PSMA PET/MRI (3-5)</td>
<td>6</td>
<td>28</td>
<td>1</td>
<td>5</td>
<td>55%</td>
<td>97%</td>
<td>86%</td>
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*TP = true positive, TN = true negative, FP = false positive, FN = false negative, Sens = sensitivity, Spec = specificity, PPV = positive predict value, NPV = negative predict value*
<table>
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<tr>
<th>Patient</th>
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<th>Positive cores</th>
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<th>Clin sig Ca</th>
<th>$SUV_{\text{max}}$ Lesion TP</th>
<th>$SUV_{\text{max}}$ BG</th>
<th>Lesion/ BG</th>
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$MCL =$ maximum core length, $BG =$ background, $GS =$ Gleason score, $TP =$ true positive, $FP =$ false positive, $Pos$ cores = Number of positive biopsy cores, $Clin$ sig $Ca =$ clinical significant cancer according to Ahmed et al (21).