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Tumor detection of ^{18}F-PSMA-1007 in the prostate gland in patients with prostate cancer using prostatectomy specimens as reference method

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ABSTRACT

Prostate-specific membrane antigen (PSMA) radiopharmaceuticals used with positron emission tomography/computed tomography (PET-CT) are a promising tool for managing patients with prostate cancer. This study aimed to determine the accuracy of ^{18}F-PSMA-1007 PET-CT for detecting tumors in the prostate gland using radical prostatectomy (RP) specimens as a reference method and to determine whether a correlation exists between ^{18}F-PSMA-1007 uptake and the International Society of Urological Pathology (ISUP) grade and prostate specific antigen (PSA) levels at diagnosis. **Methods:** Thirty-nine patients referred for ^{18}F-PSMA-1007 PET-CT for initial staging and who underwent RP within four months were retrospectively included. Uptake of ^{18}F-PSMA-1007 indicative of cancer was assessed and maximum standardized uptake values (SUVmax) and total lesion uptake (TLU) were calculated for the index tumor. Histopathology was assessed from RP specimens. True positive, false negative, and false positive lesions were calculated. **Results:** In 94.9% of patients, the index tumor was correctly identified with PET. SUVmax was significantly higher in the tumors vs normal prostate tissue, but no significant differences were found between different ISUP grades and SUVmax. There was a poor correlation between PSA at diagnosis and SUVmax (r=0.23) and moderate agreement between PSA at diagnosis and TLU (r=0.67). When all tumors (also non-index tumors) were considered, many small tumors (approx. 1-2 mm) were not detected with PET. **Conclusion:** ^{18}F-PSMA-1007 PET-CT performs well in correctly identifying the index tumor in patients with intermediate to high-risk prostate cancer. Approximately 5% of the index tumors were missed by PET, which agrees with previous studies.

Keywords: PET-CT; PSMA; prostate; histopathology; Gleason score

INTRODUCTION

Prostate cancer remains one of the most common malignancies affecting men worldwide (*1,2*). The correct staging of this disease is important for treatment planning and prognostication. Positron emission tomography with computed tomography (PET-CT) is recommended for detecting sites of disease recurrence in patients with prostate cancer; this has particularly been the case since the introduction of prostate-specific membrane antigen (PSMA) ligands (*3*). PET-CT using PSMA-targeting radiopharmaceuticals could potentially be suitable for initial staging because it has a higher sensitivity and specificity for detection of lymph node metastases than conventional imaging modalities (*4-6*).

PSMA is a transmembrane protein often over-expressed in prostate cancer cells (*7*). It is also expressed in some other malignancies and benign tissues (*8*). Some studies indicate that PSMA expression is increased in more aggressive tumors and in castration-resistant prostate cancer (CRPC) (*9-11*). However, approximately 5-10% prostate cancer cells do not overexpress PSMA (*12*). PSMA ligands have been designed for radiolabeling with several radionuclides; ^{68}Ga is the most clinically common. ^{18}F-labelled PSMA agents offer advantages compared with ^{68}Ga-labelled ones with respect to image resolution and production amount. One promising ^{18}F-labelled PSMA radiotracers is ^{18}F-PSMA-1007 (*13*). Unlike ^{68}Ga-labelled radiopharmaceuticals, ^{18}F-PSMA-1007 is primarily eliminated via the hepatobiliary excretion route and therefore there is almost no bladder activity providing improved conditions for evaluation of the prostatic bed. Only a small number of studies have examined ^{18}F-PSMA-1007 PET-CT as a primary T staging modality (*14,15*); therefore further studies are warranted. Kuten et al (*15*) recently showed in a small study of intermediate- to high-risk prostate cancer patients that both ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 could identify dominant prostatic malignancies. In their study, ^{18}F-PSMA-1007 also detected some additional low-grade lesions.

This study tested the accuracy of ^{18}F-PSMA-1007 PET-CT for detecting cancer in the prostate gland using radical prostatectomy (RP) specimens as the reference method. We then determined if there was a correlation between the uptake of ^{18}F-PSMA-1007 and the International Society of Urological Pathology (ISUP) grades and PSA at diagnosis.

MATERIALS AND METHODS

Patients

From September 2019 to July 2020, 700 patients with biochemical recurrence after curative treatment or with newly diagnosed intermediate or high risk prostate cancer were examined by ^{18}F-PSMA-1007 PET-CT at Skåne University Hospital in Malmö or Lund and retrospectively included. In this cohort, 42 patients underwent radical prostatectomy for localized disease. One patient was excluded due to a long time period between the PET-CT and the surgery; two others were due to previous brachytherapy leaving 39 patients—all were admitted for initial staging and with a time from PET-CT to surgery not exceeding four months for the final analyses. This study was approved by the Regional Ethical Review Board at Lund University (#2016/417 and #2018/753) and was performed in accordance with the Declaration of Helsinki. All patients signed a written informed consent.

PET-CT

Four Discovery MI (GE Healthcare, Milwaukee, WI, USA) PET-CT systems were used for image acquisition. Imaging was performed 120 min after radiotracer administration. The patients were scanned from the mid-thigh to the base of the skull. The mean (± standard deviation, SD) administered ^{18}F-PSMA-1007 activity was 4.0 ± 0.4 MBq/kg (range 3.7-6.7) while the mean

accumulation time was 120 ± 6 min (range 115-153 min). The PET images were reconstructed using Q.Clear (GE Healthcare, Milwaukee, WI, USA) including the time-of-flight and point spread function modelling with a 256 x 256 matrix (pixel size 2.7 x 2.7 mm^2, slice thickness 2.8 mm). Images were acquired for 2-4 min/bed (4 min/bed when the protocol was set up); this speed was later optimized to 2 min/bed position (15). The regularization factor, β, in the Q.Clear reconstruction algorithm was 500 when images were acquired with 4 min/bed (2 patients), 600 when images were acquired with 3 min/bed (12 patients), and 800 for images acquired with 2 min/bed (25 patients). The β values for the different acquisition times were chosen to obtain a similar noise level in the images (*16*).

CT images were acquired for attenuation correction of the PET images and anatomic correlation. A diagnostic CT with intravenous and oral contrast was performed. The tube current modulation was applied by adjusting the tube current for each individual with a noise index of 37.5 and a tube voltage of 100 kV. The slice thickness was 0.625 mm. The CT used for attenuation correction was acquired in the late venous phase. An adaptive statistical iterative reconstruction technique was applied.

Image analysis

All PET-CT images were subjected to image analysis with commercially available Hermes software (Hermes Medical Solutions, Sweden) by one experienced nuclear medicine physician (ET). Only the patient's age and indication for the examination was known to the physician when analyzing the images. Suspected tumors in the prostate gland were characterized by maximum standardized uptake value (SUVmax), tumor volume, and tumor lesion uptake (TLU) calculated as SUVmean x tumor volume. These metrics were calculated by placing an automatically drawn VOI with a fixed threshold of 41% of tumor SUVmax around the suspected tumor. For some lesions

with relatively low SUV, the automatically drawn VOI failed, and a manual VOI was then drawn instead. The nuclear medicine physician marked the lesion regarded as index lesion.

Histopathology

A second evaluation was performed by one of the authors (AS) in addition to the routine clinical evaluation of prostatectomy specimens. All slides from the RP specimens were annotated and evaluated using the digital pathology system Sectra Digital Pathology solution (Sectra Medical, Linköping, Sweden). Every tumor focus was annotated with the Gleason score, ISUP grade, and the tumor localization. The index tumor was defined as the area where the tumor showed its largest tumor dimension (*17*). No major differences between the initial reported diagnosis of Gleason score and the review were found.

Statistical analysis

Patient demographics were analyzed descriptively. For analysis of tumor localization, each prostate was divided into three axial levels (base, mid, apex) and divided at each level into eight segments (ventral, dorsal, peripheral left and right, central left and right) (*18*). For PET-CT and histopathology, the data for each patient were reported on a print of the 24-segment scheme where the tumors were marked by the nuclear medicine physician and the pathologist in a blinded fashion (not being aware of the marking of the other modality). Agreement of the PET-CT with histopathology was considered if the same segment was marked or if there was a discrepancy of up to 1 segment in any direction. True positive, false positive, and false-negative lesions were calculated. Since many of the patients had multi-focal tumors, the analyses were performed both for only the index tumor and for all tumors. Associations between the ISUP grade and SUVmax of the index tumor were evaluated using the Kruskal-Wallis test with a Mann-Whitney U test as the

post-hoc test. Bonferroni correction for multiple comparisons was applied, and adjusted p-values are shown in the manuscript. Correlation between PSA at diagnosis and SUVmax and TLU in the index tumor were analyzed with Spearman correlation. A significance level of p=0.05 was applied. Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY).

RESULTS

Patients

All 39 patients were admitted to PET-CT for initial staging. The patient characteristics are shown in Table 1. Four of the patients were on medication related to benign prostate hyperplasia (one alpha blocker, three hormonal therapy), but no other prostate-related medication was used.

Uptake of PET-tracer in index tumors

An index tumor was identified in RP specimens in all 41 patients. The ISUP grade varied between 2 and 5 with 5 being the most common (Table 1). In 37 of 39 patients (94.9%), the same lesion was also found by PET. In all of these cases, the nuclear medicine physician had marked the lesion as index lesion. Only in two patients (5.4%) was the index tumor not detected by PET (not marked as suspicious tumor by the nuclear medicine physician). The median SUVmax for the index tumor was 20.1 (range 3.7-61.7) whereas SUVmax was 3.7 (range 2.4-12.4) in surrounding prostate tissue (without pathology proven tumor). The SUVmax in surrounding prostate tissue in the two patients with index tumors not detected by PET was 8.3 (second highest among all patients) and 3.9, respectively. The median TLU in the index tumor was 13.6 (range 1.5-191.8). See details in Table 2. The ISUP grade was 3 and 4 in the two patients where PET did not detect the index tumor; they were 35 x 19 mm and 7 x 9 mm, respectively.

A comparison between different ISUP grades and SUVmax for all index tumors and adjacent normal prostate tissue is shown in Fig 1. There was an overall statistically significant difference ($p<0.0001$, Kruskal-Wallis test). The post-hoc analysis showed a significant difference between normal prostate tissue and ISUP grade 2 ($p=0.026$), ISUP grade 3 ($p=0.001$), ISUP grade 4 ($p=0.001$), and ISUP grade 5 ($p<0.001$); no other comparisons were statistically significant. No statistically significant differences were found ($p=0.18$ and $p=0.31$, respectively; Kruskal-Wallis test) when analyzing only the different ISUP grades regarding SUVmax or TLU. The correlation between PSA at diagnosis and SUVmax in index tumor was poor ($r=0.23$, $p=0.17$) and between PSA at diagnosis and TLU in index tumor was moderate ($r=0.67$, $p<0.0001$), Fig. 2.

Fig. 3 shows one patient where the PET and histopathology were in good agreement regarding the index tumor. Fig. 4 shows one patient where the tumor was detected at histopathology and was not visualized on PET. Fig. 5 shows one patient with a false positive uptake on PET.

PET in all lesions

In total, 118 tumors (in 39 patients) were detected by histopathology, and 62 tumors (in 39 patients) were detected by PET. Here, 55 of the 118 tumors (46.6%) were classified as true PET positive whereas the remaining 63 tumors were false negative on PET. Among the 63 false PET-negative lesions, 39 (61.9%) were very small (approx. 1-2 mm), and two (3.2%) were large (7 x 9 mm and 35 x 19 mm; the two index tumors described above). Seven of 118 lesions (5.9%) detected by PET were false positives based on pathology review. In these lesions, median SUVmax was 11.4 (range 6.5 to 13.3) and TLU 4.9 (range 4.2-9.5); thus slightly lower compared with true positive lesions. No aberrant findings on histopathology were seen in areas with false-positive 18F-PSMA-1007 uptake.

DISCUSSION

In this study, we compared the uptake of ^{18}F-PSMA-1007 with the histopathology of RP, in patients with intermediate to high-risk prostate cancer. In the vast majority of patients, the index tumor was correctly identified with PET. SUVmax was higher in the tumors vs normal prostate tissue, but no correlations between ISUP grade and SUVmax or between ISUP grade and TLU were found. There was poor correlation between PSA at diagnosis and SUVmax and a moderate agreement between PSA at diagnosis and TLU of the index tumors. When all tumors were considered, many small tumors (approx. 1 mm) were not detected with PET. Although only 39 patients were included, this is the largest study to date comparing ^{18}F-PSMA-1007 and prostatectomy specimens in patients with intermediate to high-risk prostate cancer. Being able to correctly identify the index lesion could possibly be of interest to help targeted biopsies or to enable focal dose escalation during primary curative radiotherapy (*19*).

Prostate cancer cells typically show increased expression of PSMA. Benign prostatic tissue also expresses PSMA but with lower intensity compared to prostate cancer cells. However, PSMA is not as specific as the name implies. Many other conditions than prostate cancer can over-express PSMA (*8*). In our study, we found a small number of false-positive uptakes of ^{18}F-PSMA-1007. It has also been found that not all prostate cancer cells over-express PSMA. Maurer et al. (*4*) observed that 8% of index tumors in 130 patients with intermediate to high-risk prostate cancer showed no or only a slight increase in ^{68}Ga-PSMA-11 uptake. This has been confirmed by Budäus et al. (*12*). In our study, only ~5% of the index tumors were not visualized by PET. When regarding all tumors, a considerably higher proportion of tumors were missed by PET with the vast majority being very small tumors, which can be expected to not show up on PET due to limited spatial resolution and partial volume effect.

To the best of our knowledge, there is only one previous study comparing ^{18}F-PSMA-1007 uptake and prostatectomy specimens. Kesh et al. (*14*) studied ten patients with biopsy-confirmed

high-risk prostate patients. ^{18}F-PSMA-1007 detected the index tumor correctly in all patients but missed two non-index lesions. ^{18}F-PSMA-1007 PET-CT showed three false-positive lesions. Similar results have been shown for a small study population using ^{68}Ga-PSMA-11 (*20,21*).

A previous study compared ^{68}Ga-PSMA-11 with transrectal ultrasound biopsies from 90 patients (*9*). 91.1% of the patients demonstrated high uptake in the index tumor that exceeded the physiologic tracer uptake in normal prostate tissue (median SUVmax 12.5 vs 3.9). In their analysis, there was a moderate correlation between PSA and SUVmax (r=0.51) and a significantly higher SUVmax in tumors with a Gleason score >7 compared with tumors with Gleason score of 3+3, 3+4, and 4+3. It remains unknown whether the different results obtained from the study by Uprimny et al. regarding correlation with SUVmax and PSA as well as increasing SUVmax with worse Gleason score or ISUP grade can be attributed to different radiopharmaceuticals used, differences in the study population, or the lower number of patients included in our study. We found a better correlation between PSA and TLU than PSA and SUVmax. TLU also considers the size of the tumor and is a better measure of tumor burden than SUVmax.

Some studies exist comparing multi-parametric magnetic resonance imaging (MRI) and PSMA PET-CT (*22-24*). The combination has been shown to have higher sensitivity and specificity than either MRI or ^{68}Ga-PSMA-11 imaging alone for detecting intraprostatic tumors. PSMA PET could offer improved specificity while MRI offers improves tumor localization.

One limitation of our study is the retrospective design and the limited number of patients. Another limitation is the nature of the study cohort where the distribution of included patients was skewed towards high risk because this is the main indication for performing a PET-CT in our county. No immunostaining of PSMA expression was performed for the prostatectomy specimens. Another limitation is the challenging task of comparing PET-CT and prostatectomy specimens and difficulties to transfer both modalities into the 24-segment prostate model. Therefore, no calculations of sensitivity, specificity, and positive/negative predictive values were performed

because we believe the sources of error were large and would lead to unreliable values. Finally, only one nuclear medicine physician and one pathologist made the respective evaluations.

CONCLUSION

^{18}F-PSMA-1007 PET-CT nicely identifies the index tumors in patients with intermediate- to high-risk prostate cancer using prostatectomy specimens as the reference method. Approx. 5% of the index tumors were missed by PET, which agrees with previous findings. Small-sized non-index tumors were often missed by PET.

ABBREVIATIONS

ISUP: International Society of Urological Pathology; MRI: magnetic resonance imaging; PET-CT: positron emission tomography with computed tomography; PSA: prostate specific antigen; PSMA: prostate-specific membrane antigen; ROI: region of interest; RP: radical prostatectomy; SD: standard deviation; SUV: standardized uptake value; VOI: volume of interest

DISCLOSURE

The Knut and Alice Wallenberg foundation, the Medical Faculty at Lund University, Region Skåne and the Swedish Prostate Cancer foundation are acknowledged for their generous financial support. The authors declare that they have no conflict of interest. These studies were approved by the Regional Ethical Review Board (#2016/417 and #2018/753) and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

ACKNOWLEDGMENTS

The staff of Clinical Physiology and Nuclear Medicine at Skåne University Hospital who performed the image examinations are greatly appreciated.

KEY POINTS

Question: What is the accuracy of ^{18}F-PSMA-1007 PET-CT for detecting cancer in the prostate gland, using radical prostatectomy (RP) specimens as the reference method?

Pertinent findings: In this retrospective study, we found that ^{18}F-PSMA-1007 PET-CT performs well at identifying the index tumor in patients with intermediate- to high-risk prostate cancer using prostatectomy specimens as the reference method. Small-sized non-index tumors were often missed by PET.

Implications for patient care: The results indicate that ^{18}F-PSMA-1007 PET-CT is a reliable method for detecting prostate cancer.

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TABLES

Table 1. Patient characteristics.

Parameter	**Mean ± SD (range)**	
Age	65 ± 5.6 (53-76)	
BMI	26.9 ± 3.2 (19.3-34.4)	
Days from PET to surgery	53 ± 22 (11-105)	
PSA at diagnosis	**n**	
<10	21	
10-19.9	9	
≥20	9	
ISUP grade	*At diagnosis*	*In RP specimens*
1	1	0
2	4	6
3	13	10
4	11	9
5	11	14
missing	1	0
T stage	*Clinical*	*In RP specimens*
T1	16	0
T2	20	20
T3	3	19

Table 2. SUVmax and TLU for different ISUP grades for the 37 index tumors also identified by PET. SUVmax for normal prostate tissue are calculated for all 39 patients.

		SUVmax		TLU	
	N	**Median**	**Range**	**Median**	**Range**
Normal prostate	39	3.7	2.4-12.4	-	-
ISUP 2	6	14.5	7.9-20.9	22.2	3.7-95.2
ISUP 3	9	25.2	3.7-39.7	5.6	1.5-101.9
ISUP 4	8	19.5	8.6-31.7	12.3	7.1-58.6
ISUP 5	14	33.0	7.6-61.7	38.8	2.4-191.8

FIGURES

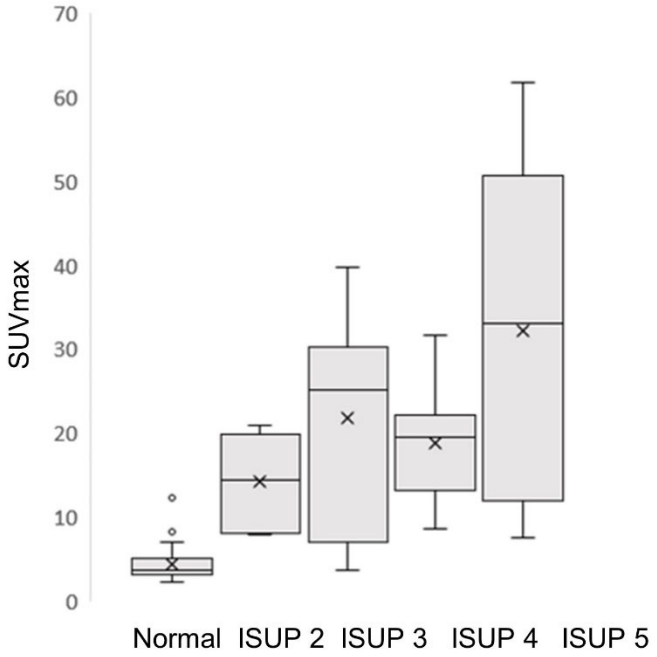

Figure 1. Histograms for SUVmax of normal prostate tissue and the ISUP grades for the index tumors.

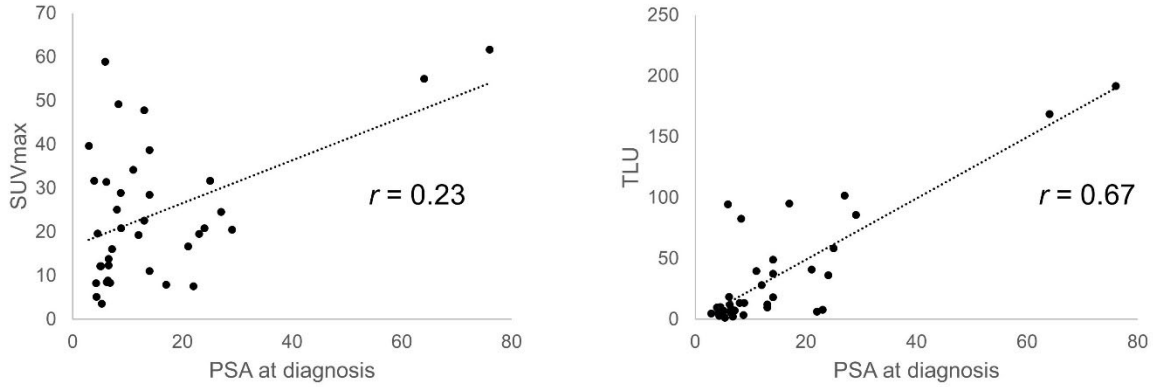

Figure 2. Correlation between PSA at diagnosis and SUVmax of the index tumor (left) and between PSA at diagnosis and TLU of the index tumor (right).

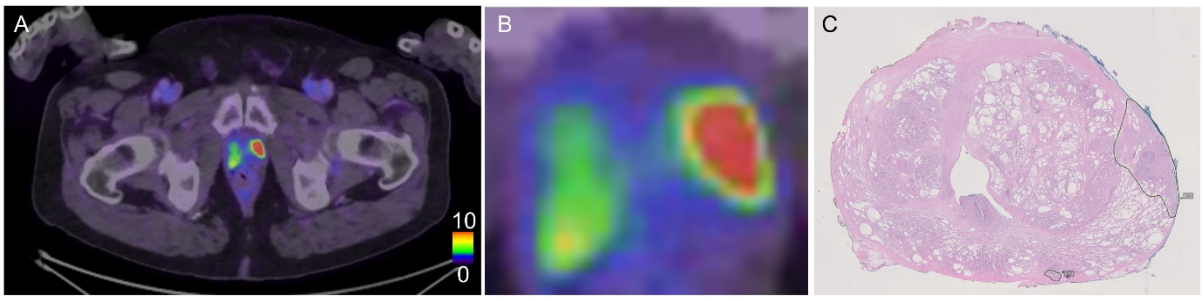

Figure 3. An example of one patient with a true positive tumor on PET. A: fused PET-CT image of the middle part of the prostate, B: zoomed fused PET-CT image of the prostate, C: the corresponding histopathology slice delineating a tumor in the left part of the prostate with a Gleason score 4+3. In C, a very small tumor can be seen in the dorsal left part not visualized on PET. The tracer uptake in the right prostate lobe is non-specific.

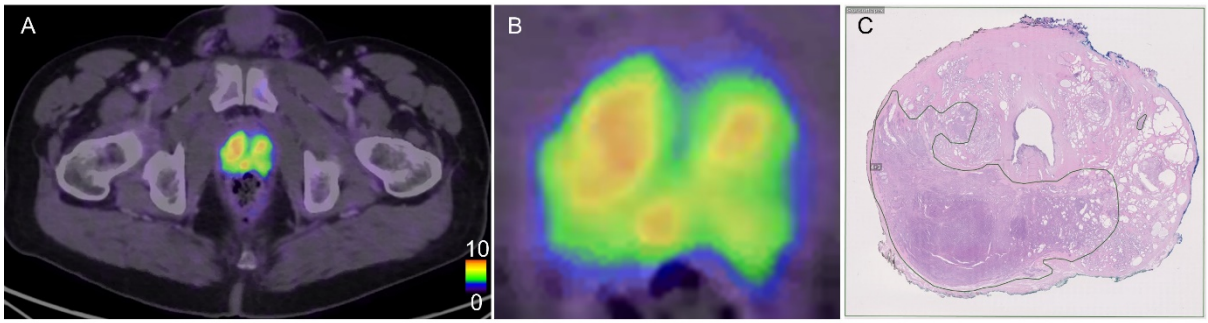

Figure 4. An example of one patient with a false negative tumor on PET. A: fused PET-CT image of the apical part of the prostate, B: zoomed fused PET-CT image of the prostate, C: the corresponding histopathology slice delineating a large tumor mainly located in the dorsal right part in the prostate with ISUP grade 3.

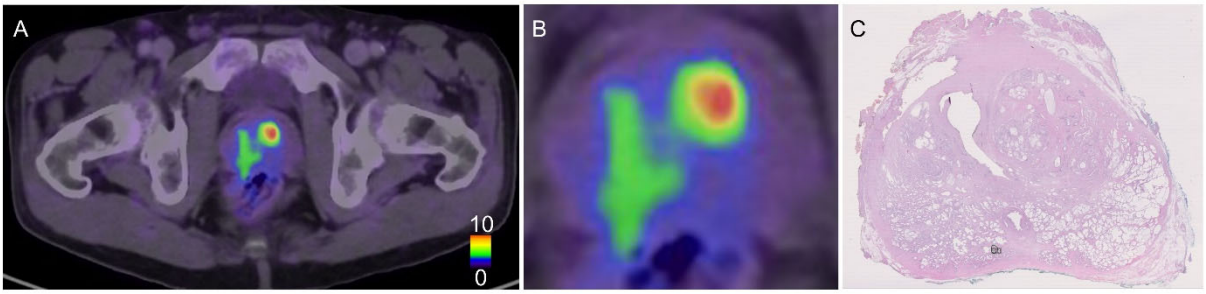

Figure 5. An example of one patient with a false positive uptake on PET in the ventral left part of the prostate. A: fused PET-CT image of the middle part of the prostate, B: zoomed fused PET-CT image of the prostate, C: the corresponding histopathology slice without a corresponding tumor. In C, we also see a very small tumor in the dorsal part not visualized on PET.

GRAPHICAL ABSTRACT