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ORIGINAL PAPER

PSMA PET/CT in the diagnosis of prostate cancer: Why and when?

Pietro Pepe [1], Ludovica Pepe [2], Daniele Cignoli [3], Marco Roscigno [3, 4]

[1] Urology Unit, Cannizzaro Hospital, Catania, Italy;
[2] Pathology Unit, Policlinico G. Martino University of Messina, Messina, Italy;
[3] Department of Urology, ASST Papa Giovanni XXIII, Bergamo, Italy;
[4] Milano-Bicocca University, International School of Medicine, Milano, Italy.

Summary ***Prostate-specific membrane antigen (PSMA) is expressed in most primitive and metastatic prostate cancer (PCa), and PSMA inhibitors conjugated with the radionuclides Gallium 68 (68Ga) and fluoride 18 (18F) have been evaluated to detect PCa; moreover, tumour uptake, which represents PSMA expression, is highly correlated with the aggressiveness of the primary prostatic tumour. PSMA positron emission tomography/computed tomography (PET/CT) demonstrated to be sensitive for the detection of primary prostatic lesions, regional lymphadenopathy and clinical metastases in case of biochemical recurrence. In this respect, PSMA PET/CT has been evaluated in men enrolled in clinical trials candidate to initial or repeat prostate biopsy especially in the presence of clinical high risk for PCa, Active Surveillance (AS) and/or in case of negative histology of Prostate Imaging Reporting and Data System (PI-RADS score) 4-5 targeted biopsy. Although many experimental studies reported a superimposable detection rate for PCa of PSMA PET/CT vs. mpMRI targeted biopsy, still today, the use of PSMA PET/CT is experimental and had some limitations: cost, availability, patient characteristics, local expertise and false negative rate. Although prospective and randomized studies are awaited, including a greater number of patients, PSMA PET/CT evaluation could be proposed in the presence of claustrophobia, cardiac pacemaker and severe obesity especially in men at high risk for PCa.***

KEY WORDS: *Targeted prostate biopsy; PSMA PET/CT; mpMRI vs. PSMA PCa diagnosis; PSMA PET/CT targeted biopsy; PSMA false negative rate*

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INTRODUCTION

Prostate-specific membrane antigen (PSMA) is expressed in most primitive and metastatic *prostate cancer* (PCa) (1, 2), and PSMA inhibitors conjugated with the radionuclides *Gallium 68* (68Ga) and *fluoride 18* (18F) have been evaluated for the diagnosis of PCa (3-6); morever, tumour uptake, which represents PSMA expression, is highly correlated with the aggressiveness of the primary prostatic tumour (7-9). PSMA *positron emission tomography/computed tomography* (PET/CT) demonstrated to be sensitive for the detection of primary prostatic lesions, regional lymphadenopathy (10) and clinical metastases in case of biochemical recurrence (11, 12). In this respect, PSMA PET/CT has been evaluated in clinical trials in men candidate to initial or repeat prostate biopsy especially in the presence of clinical high risk for PCa, in men during Active Surveillance and/or in case of negative histology of *Prostate Imaging Reporting and Data System* (PI-RADS score) 4-5 targeted biopsy.

MATERIALS AND METHODS

Literature search strategy

This review examines the role of PSMA PET/CT in the diagnosis and management of PCa, focusing on why and when it should be used. A comprehensive literature search was conducted using electronic databases such as *PubMed*, *Scopus*, and *Web of Science*. The review was performed following the *preferred items for systematic reviews and meta-analysis* (PRISMA) reporting guidelines from 2014 to February 2025 (Figure 1).

Search terms

The search strategy included terms such as "*PSMA PET/CT*", "*prostate cancer*", "*PCa diagnosis*", "*targeted biopsy*", and "*multiparametric MRI*".

Inclusion criteria

Articles were included if they discussed PSMA PET/CT in the context of prostate cancer diagnosis, compared it with other imaging modalities, or explored its use in different patient cohorts.

Exclusion criteria

Articles not in English, case reports, conference papers, and studies focusing exclusively on treatment rather than diagnosis were excluded.

Study screening

Titles and abstracts retrieved from the initial search were screened for relevance by two independent reviewers. Full-text articles were then assessed for eligibility.

Data synthesis

Findings from the included studies were synthesized nar-

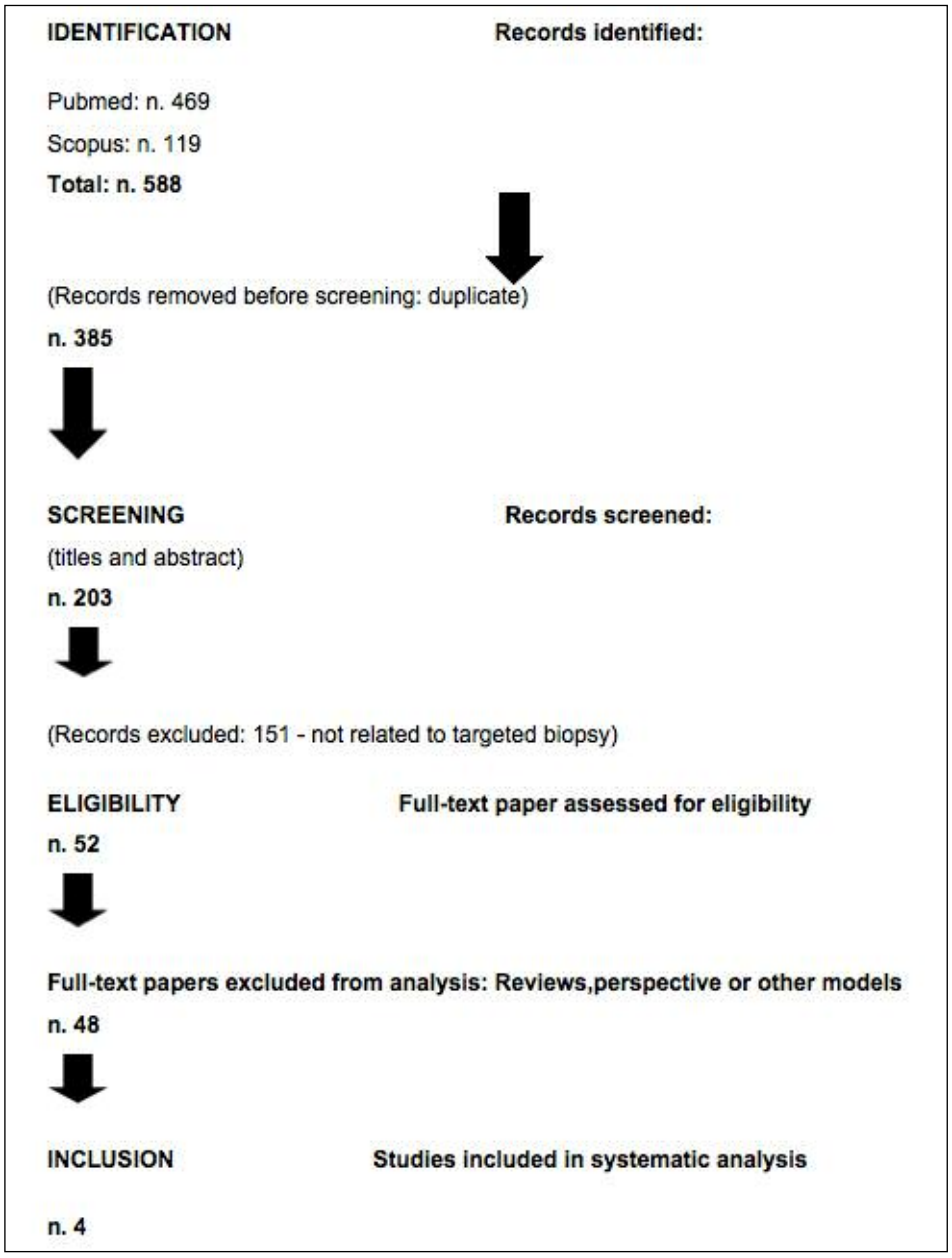


Figure 1.
Flow chart of the study selection process.

ratively, given the diversity of methodologies and outcomes. The review summarizes emerging trends, potential benefits, limitations of PSMA PET/CT, and its comparative accuracy with mpMRI.

Risk of Bias
The risk of bias assessment for each study has been reported in Figure 2; all the selected studies had low risk of bias.

PSMA PET/CT and prostate biopsy: Why?
Although mpMRI has improved diagnostic accuracy of systematic prostate biopsy in the diagnosis of csPCa, about 15-20% of PCa could be missed by mpMRI targeted biopsy (13, 14), therefore targeted cores should always be combined with systematic or perilesional biopsies as recently suggested by EAU guidelines (15). PSMA is overexpressed in most primitive and metastatic PCa; moreover, tumour PSMA uptake, is highly correlated with the aggressiveness of the primary prostatic tumour (16) (Table 1). PSMA PET/CT demonstrated to be sensitive also for the detection of primary prostatic lesions especially in men at high risk for PCa (17). The presence of focal uptake on PSMA-PET/CT, Standardised Uptake value (SUVmax), and the maximal dimensions of PET-avid lesions have been correlated with the presence of csPCa. There is a range of proposed SUVmax cutoffs to detect csPCa (18, 19) and its value is highly correlated with ISUP Grade Group PCa (20). *Kalapara et al.* (21) compared the accuracy of 68Ga-PSMA PET/CT with mpMRI in 205 men who underwent radical prostatectomy and showed a diagnostic accuracy of 96% for the detection of csPCa. *Pepe et al.* (18) in 160 men demonstrated that a SUVmax of 8 diagnosed a csPCa in 98% of

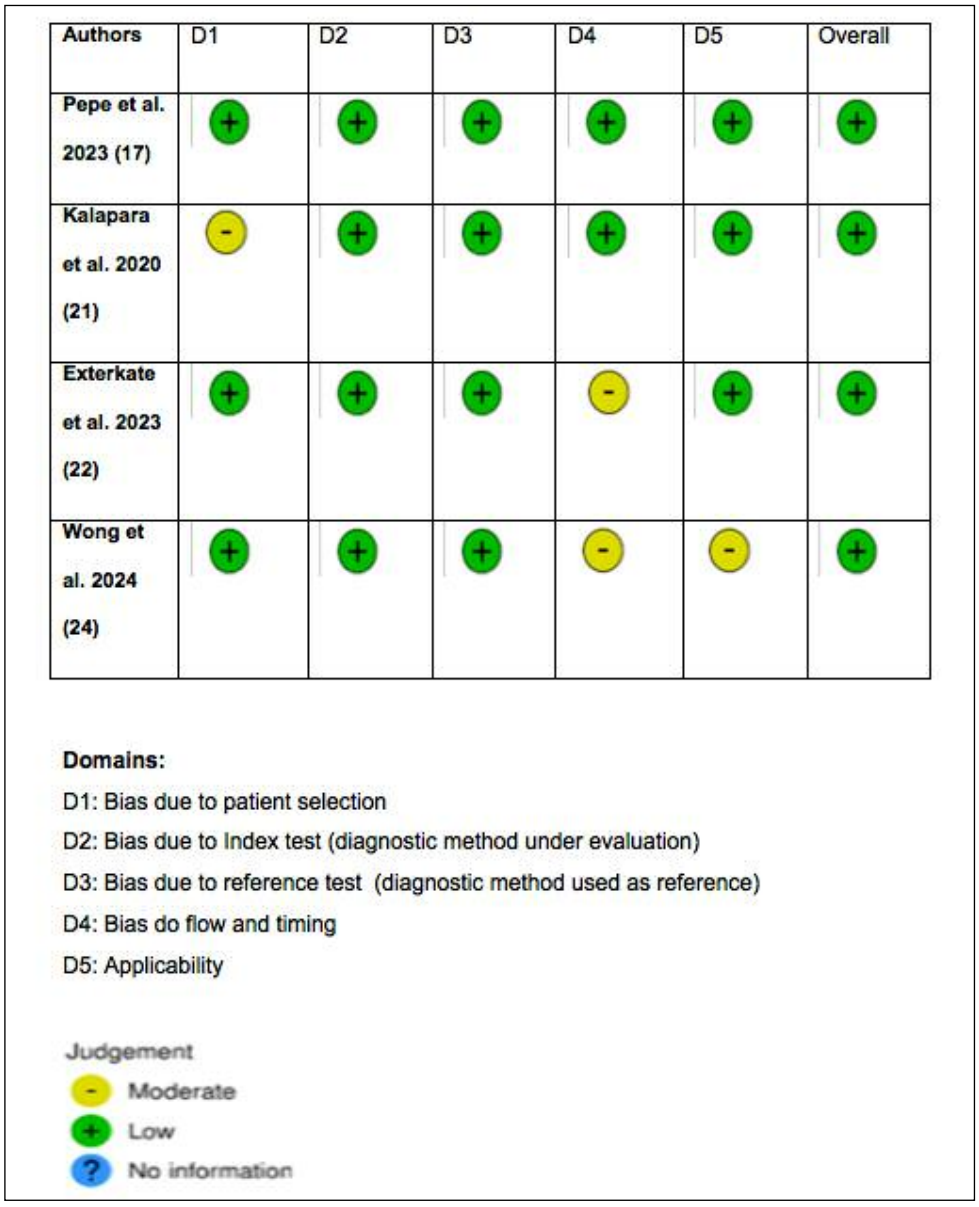


Figure 2.
Risk of bias domains.

Table 1.
Overview of the most relevant studies, included in the review, comparing PSMA PET/CT to mpMRI in the diagnosi of PCa.

Study	Imaging modalities compared		n° of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%	Diagnostic accuracy (%)	Key findings & conclusions
Pepe et al. 2023 (16)	68Ga-PSMA PET/CT vs. mpMRI, in patients with clinical parameters high risk for PCa		125	100% vs. 90.9%	80.3% vs. 78.9%	87.9% vs. 78.9%	100% vs. 84.9%	92% vs. 86.2%	68Ga-PSMA PET/CT demonstrated comparable accuracy and sensitivity with mpMRI in detecting significant prostate cancer.
Kalapara et al. 2020 (20)	68Ga-PSMA PET/CT vs. mpMRI	overall PCa csPCa	205 133	- -	- -	- -	- -	91% vs. 89% 96% vs. 91%	PSMA PET/CT showed superior accuracy and sensitivity in detection and localization of prostate cancer compared to mpMRI and pathology.
Exterkate et al. 2023 (21)	18F-PSMA-1007 PET/CT vs. mpMRI	overall PCa csPCa	129 96	85% vs. 62% 95% vs. 73%	- -	- -	- -	- -	18F-PSMA PET/CT had higher per-lesion sensitivity and specificity for localization and staging compared to mpMRI.
Wong et al. 2024 (23)	18F-PSMA PET/CT vs. mpMRI	overall PCa csPCa	184 84	73.8% vs. 78.4% 77.1% vs. 87.3%	52.1% vs. 72.6% 47.2% vs. 57.3%	- -	57.2% vs. 68.8% 70.2% vs. 81.2%	63% vs. 76% 62% vs. 72%	PSMA PET/CT showed high correlation with MRI for diagnosing and localizing prostate cancer; showed potential as a diagnostic tool.

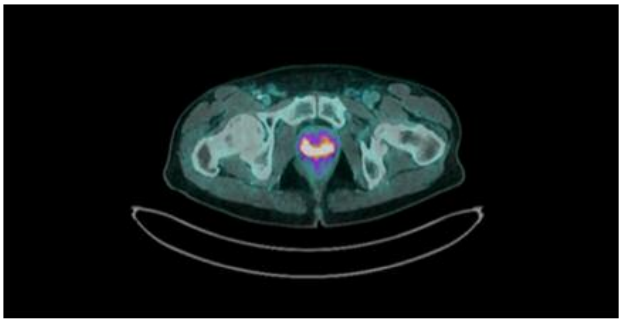
the cases with a false positive rate of 4.8%; on the contrary, only 12% of men with a ISUP GG2/Gleason score 3 + 4 had a SUVmax below 8. *Exterkate et al.* (22) compared PSMA PET/CT *vs.* mpMRI accuracy in detecting PCa in 80 men submitted to radical prostatectomy: per-lesion sensitivity for localisation of overall PCa and csPCa was 85% *vs.* 62% and 95% *vs.* 73%, respectively. *Demirci et al.* (18) in 141 patients submitted to radical prostatectomy showed that the SUVmax values were significantly higher in high-risk patients compared those in low-risk patients (18.9 ± 12.1 *vs.*7.16 ± 6.2).

PSMA PET/MRI, combining the advantages of mpMRI and PSMA PET, is a promising modality for guiding biopsy with demonstrated feasibility (23). The PEDAL study (24, 25) showed that multiparametric MRI outperformed PSMA PET/CT in identification of prostate cancer, although the distinction was not notable when detecting csPCa; moreover, the synergy of mpMRI and PSMA-PET/CT demonstrated enhanced sensitivity and negative predictive value (24, 25).

PSMA PET/CT targeted biopsy: how?

PSMA PET/CT imaging is performed using a CT-integrated PET scanner; PSMA is administered to patients via an intravenous bolus and the PET acquisition start at a mean of 58 ± 12 min (range, 50-81 min) afterward. Scans are acquired in 3-dimensional mode with an acquisition time of 3 min per bed position and a low dose unenhanced CT scan is performed from the skull base to the middle of the thigh. Images are processed to obtain PET, CT, and PET-CT fusion sections in the axial, coronal, and sagittal planes with a thickness of approximately 0.5 ~ cm by two experienced nuclear medicine specialists. The location of focal uptake on PSMA PET/TC, three-dimensional size, and SUVmax values are reported (Figure 3) on a per-lesion basis with a sextant scheme (apex, midgland, and base, each split into left and right). There is a range of proposed cutoffs to detect csPCa from SUVmax 3.15 to SUVmax 9.1 (21, 26, 27); 68Ga or 18F PSMA-PET/CT index lesions showed by the SUVmax cut-off are submitted to targeted cores (four cores) always combined with extended systematic prostate biopsy. The procedure could be performed by transrectal or transperineal approach using a tru-cut 18-16 Gauge needle under sedation and/or local anesthesia and antibiotic prophylaxis; however, the transperineal way is recommended to reduce risk of sepsis and increase detection rate of anterior zone PCa (28, 29). PSMA PET/CT images should be evaluated together the nuclear medicine specialist to improve the accuracy of targeted biopsy because the procedure is usually performed by cognitive approach and the urologists often are not confident with prostatic PSMA PET/CT images used for targeted biopsy.

Figure 3.
Patient with prostate cancer Grade Group 3/Gleason score 4 + 3 and PSA 19 ng/ml: intraprostatic SUVmax equal to 16.



The focal uptake on PSMA-PET/CT, SUVmax, and the maximal dimensions of PET-avid lesions have been correlated with the presence of csPCa (22-24); Emmett et al. (7) suggested a 5-point PRIMARY score to optimize the accuracy of PSMA PET/CT for csPCa; a 5-level PRIMARY score was assigned on the basis of analysis of the central read: no pattern (score of 1), diffuse *transition zone* (TZ) or central zone (not focal) (score of 2), focal TZ (score of 3), focal *peripheral zone* (PZ) (score of 4), or an SUVmax of at least 12 (score of 5). The Primary study demonstrated a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of csPCa in the presence of a PRIMARY score > 3 (high-risk patterns) equal to 88%, 64%, 76%, and 81%, respectively.

PSMA targeted biopsy: When?

The use of PSMA PET/CT still today is experimental and should be reserved to men enrolled in clinical trials; awaiting the prospective and randomized studies could define the true role of PSMA in the diagnosis of PCa to guide targeted biopsy, many papers have been focused on the PSMA PET/CT accuracy in men with clinical high risk for PCa, enrolled in *Active Surveillance* (AS) protocols and in case of negative mpMRI/TRUS fusion biopsy of PIRADS score 5 lesions.

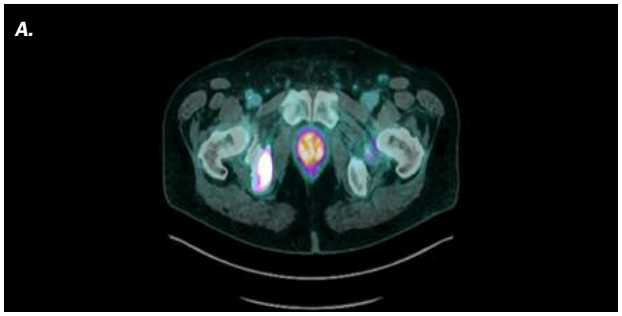
PSMA PET/CT: men with clinical high risk for PCa

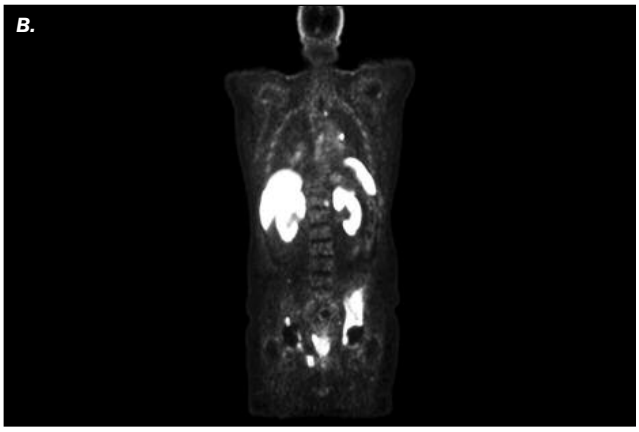
A PSMA PET/CT scan suspicious for PCa, as previously reported, results from a combination of factors, such as homogeneity and intensity of PSMA expression, tumor volume, and grade. The presence of focal uptake on PSMA-PET/CT, SUVmax, and the maximal dimensions of PET-avid lesions have been correlated with the presence of csPCa (22-24). The presence of high Primary score with elevated SUVmax values is highly correlated with the presence of advanced csPCa; these parameters are more evident in men with clinical high risk for csPCa (i.e., suspicion digital rectal examination "DRE", PSA values > 20 ng/ml), therefore, PSMA PET/CT evaluation could be proposed to perform diagnosis (targeted biopsy) and staging of confirmed PCa; at the same time, PSMA PET/CT improve cost-benefit ratio as a single procedure for the diagnosis and staging of high-risk PCa (Figure 4). *Pepe et al.* (17) in 125 men with median PSA of 35 (range 15-160 ng/ml and suspicion DRE in 56.2% of the cases demonstrated a diagnostic accuracy of PSMA PET/CT vs. MRI/TRUS fusion biopsy equal to 92.0 *vs.* 86.2%, respectively. *Bodar YJL et al.* (30) in 60 men with PSA values of 20-50 ng/ml demonstrated that PSMA-guided targeted biopsy identified 86.7% PCa and 100% of distant metastases.

PSMA PET/CT and Active Surveillance

AS is an alternative to radical treatment of low risk PCa, focusing on prevention of overtreatment (31, 32). The estimated risk-free treatment at 5, 10 and 15 years in men

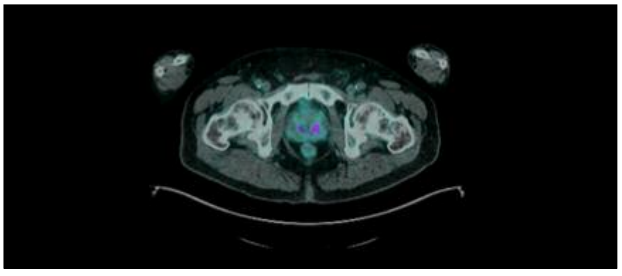
Figure 4.
Metastatic prostate cancer Grade Group 5/Gleason score 9 with PSA 80 ng/ml: intraprostatic SUVmax equal to 23 (a: axial scan); bone and nodes metastases (coronal scan).





enrolled in AS with GG1 PCa is equal to 76, 64, and 58% (33); although mpMRI is strongly recommended in the reevaluation of men in AS, still today, scheduled systematic repeated prostate biopsies are recommended in addition to targeted mpMRI/TRUS fusion biopsy (PI-RADS score > 3) to reduce the false negative rate for csPCa of mpMRI (34).
Recently, PSMA PET/CT accuracy has been evaluated in clinical trials in men enrolled in AS protocols (35, 36). In 220 men with intermediated-risk PCa enrolled in AS *Xue et al.* (37) demonstrated that a SUVmax of 5.4 may improve risk stratification for men with intermediate-risk prostate cancer to predicte pathological upgrading with a negative predictive value equal to 94%. *Pepe et al.* (3, 38, 39) evaluated 68Ga-PSMA PET/CT accuracy in the reevaluation of 40 men enrolled in AS protocol showing a diagnostic accuracy in the diagnosis of csPCa not inferior to mpMRI (83.3 *vs.* 70.2%). *Heetman et al.* (40) reported that PSMA PET/CT improved risk stratification in 9% of men who were upgraded to csPCA (*ISUP Grade Group* > 2) using a SUVmax cut-off equal to 4. Recently, Akcay et al. (41) and *Dondi et al.* (42) reported that PSMA PET/CT imaging is useful in distinguishing men for AS, potentially aiding in the identification of csPCa.
In definitive, still today, diagnostic imaging should not replace scheduled prostate biopsy in men enrolled in AS protocols, but it is mandatory to detect targeted lesions suspicious for csPCa; although, mpMRI is highly recommended, PSMA PET/CT represent an emergent diagnostic imaging that in selected cases could be used to evaluate men in AS (Figure 5). Although, the number of patients evaluated is very low and a SUVmax cut-off has not been defined, PSMA PET/TC evaluation could be proposed in men who cannot perfom mpMRI (i.e. severe obesity, claustrophobia or cardiac pacemaker).

Figure 5.
Patient enrolled in Active Surveillance protocol with prostate cancer Grade Group 1/Gleason score 6 and PSA 5.9 ng/m: intraprostatic SUVmax equal to 4.5.



PSMA PET/CT and negative biopsy in men with PI-RADS score 5 and equivocal PI-RADS score 3

The aggressiveness of csPCa is correlated with the mpMRI PI-RADS scores; in the presence of a suspicion area with PI-RADS score 5 ranges from 59.2 to 86% of the cases (43). The correlation of the PI-RADS score to the diagnosis of aggressiveness cancer has been well established; *Otti et al.* (44) showed in men with PI-RADS score 5 a detection rate for csPCa ranged from 59.2 to 86.7%, respectively (45). Therefore, a negative biopsy in men with PI-RADS score 5 need a close clinical follow up to avoid missing csPCa diagnosis. The use of PSA, *PSA density* (PSAD), risk calculator, urinary genetic tests (46-48), and the repetition of mpMRI allow to reduce the risk of harbouring a csPCa. In this respect, a second opinion regarding initial mpMRI (49) and histology evaluation should be performed to decrease the risk of false negative results. Recently, *Wong et al.* (50) in 29 men with PIRADS score 4-5 and negative biopsy histology reported that a SUVmax > 20 was correlated with the presence of csPCa. In 25 patients with PI-RADS score 5 and negative biopsy histology PSMA PET/CT evaluation, during follow up, showed SUVmax (median 7.5) values not suspicious for csPCa resulting in agreement with the mpMRI results (PIRADS score < 3) (51). In definitive, the strict clinical follow up of men with negative histology of PI-RADS score 5 lesions reduce the risk of missing csPCa especially if PSMA PET/CT evaluation is in agreement with the downgrading of mpMRI (PI-RADS score < 3) and favorable clinical parameters (PSA, PSAD).
Recently, PSMA PET/CT combined with PSA density has been suggested to evaluate equivocal PI-RADS score lesions to reduce the number of unnecessary biopsy and improve detection rate for csPCa (52, 53); *Privè et al.* (54) demonstrated in 26 men with PI-RADS 3 lesions a negative and positive predictive value of 93% and 27%, for ruling out or detecting csPCa.

PSMA PET/CT: false negative rate

Although, PSMA PET/CT results about 27% more accurate than conventional imaging (55), 5-10% of primary

PCa PSMA have low activity which evade detection by PSMA PET, mostly in high-grade and variant tumor types (56-58). Prostatic *ductal adenocarcinoma* (DAC) is rare, aggressive, and characterized by cancer involving ducts and/or acini usually associated with a high-grade Gleason score/Grade Group, large tumor volume, and adverse prognostic parameters, including extraprostatic extension and seminal vesicle invasion.
Although mpMRI and PSMA PET/CT are provided of superimposable accuracy in the diagnosis of high risk PCa showing direct correlation between PI-RADS score and SUVmax values, in the presence of DAC only mpMRI (59) allows to perform diagnosis because PSMA PET/CT demonstrated a very limited diagnostic accuracy (60-62). In this respect, PSMA uptake has sometimes been poor compared with prominent 18-flourodeoxyglucose (F-18 FDG) avidity, which would suggest that FDG PET/CT scans are important in diagnosing and staging DAC pattern. The diagnostic utility of dual-tracer FDG/PSMA PET/CT for PCa may assist in characterizing high-risk disease during primary staging and restaging especially with concurrently negative PSMA PET. In conclusion, conventional imaging and PSMA PET/CT could result inadequate in the diagnosis and staging of DAC, the use of more imaging data including mpMRI and F-18 FDG could improve overall accuracy.

Conclusions

Although many studies have compared the accuracy of PSMA PET/CT with mpMRI targeted biopsy in the diagnosis of csPCa the use of PSMA PET/CT still today is experimental and had some limitations (63): cost, availability, patient characteristics, local expertise and false negative rate; moreover, the number of patients evaluated is very low and the use of a PSMA PET/TC fusion platform would increase the accuracy of targeted prostate biopsy.
Although prospective and randomized studies are awaited, including a greater number of patients, PSMA PET/CT evaluation could be proposed in the presence of claustrophobia, cardiac pacemaker and severe obesity especially in men at high risk for PCa.

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Declarations

Ethical statement: *Not applicable.*

Consent for publication: *All authors have read and approved the content and agree to submit for consideration for publication in the journal.*

Availability of data and material: *The data supporting the findings of this study are available from the corresponding authors upon reasonable request.*

Competing interests: *The authors declare that there is no conflict of interest.*

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Authors' contributions: *Conceptualization: P.P., R.M.; Investigation: P.P., R.M., P.L.,C.D.: Data curation: P.P., R.M., P.L.C.D.; Formal analysis: P.P., R.M., P.L.C.D; Methodology: P.P., R.M., P.L.C.D.; Resources: P.P., R.M., P.L.C.D.; Software: P.P., R.M., P.L.C.D.; Writing - original draft: P.P., R.M.; Writing - review & editing: P.P., R.M., P.L., C.D.*

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Correspondence

Pietro Pepe (Corresponding Author)
piepepe@hotmail.com
Urology Unit, Cannizzaro Hospital, via Messina 829, Catania, Italy

Ludovica Pepe
ludopepe97@gmail.com
Pathology Unit, Policlinico G. Martino University of Messina, Messina, Italy

Daniele Cignoli
urologia.segreteria@asst-pg23.it
Department of Urology, ASST Papa Giovanni XXIII, Bergamo, Italy

Marco Roscigno
roscigno.marco@gmail.com
Milano-Bicocca University, International School of Medicine, Milano, Italy