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ORIGINAL PAPER

PSMA PET/CT in diagnosing and staging high grade prostate cancer: Accuracy and cost-effectiveness

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Summary ***Introduction: To evaluate accuracy and cost-effectiveness of prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) as single procedure in diagnosing and staging high grade prostate cancer (PCa).***
Materials and Methods: From June 2022 to December 2025, 330 men (median age: 65 years) underwent transperineal prostate biopsy for the suspicion of high grade PCa (PSA > 20 ng/ml and/or suspicious digital rectal examination). All the patients underwent PSMA PET/CT targeted biopsy of intraprostatic lesions suspicious for PCa (Standard Uptake Value > 8) combined with extended prostate biopsy.
Results: Median PSA was 30.5 ng/ml (range: 20-785 ng/ml) and 135/330 (41%) men had positive DRE; a csPCa was found in 325/330 (98.5%) patients and 297/325 (91.4%) had a Gleason score > 8/ISUP Grade Group > 4. Clinical staging by PSMA PET/CT demonstrated: 130 (40%) cT2PCa vs. 195 (60%) cT3PCa cases; in detail, 95/325 (29.2%) had positive nodes, 60 (18.5%) bone metastases and 40 (12.3%) multiple metastases. The overall reimbursement for diagnosing PCa in the 330 patients submitted to prostate biopsy was 471,883,5 €.; using PSMA PET/CT without MRI the cost of this latter procedure could be spared for a total of 71,016 €.
Conclusions: PSMA PET/CT as a single imaging procedure demonstrated an high accuracy in diagnosing and staging high grade PCa, moreover, improved cost-effectiveness and allowed to start quickly therapy.

KEY WORDS: PSMA PET/CT; Prostate cancer; PSMA PET/CT cost-effectiveness; High grade PCa.

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INTRODUCTION

Although the risk of overdiagnosis and overtreatment for *prostate cancer* (PCa) based on PSA screening (1, 2) has been reduced using *multiparametric magnetic resonance imaging* (mpMRI) (3), genetic markers (4, 5), risk calculator (6) or Active Surveillance protocols (7), still today, the risk of overtreatment remains not negligible (8). On the other hand, annually about 7% of men with a new diagnosis of PCa are metastatic therefore the necessity to improve detection and staging of these cases to perform quickly the best treatment for each patient. In this respect, *prostate-specific membrane antigen* (PSMA) *positron emission tomography/computed tomography* (PET/CT) demonstrated a better accuracy than conventional imaging (abdominal and lung computed tomography combined with bone scan) in the staging of high risk PCa, combined with a high accuracy also in the PCa diagnosis resulting to be not inferior to mpMRI (9-15). The opportunity to perform only PSMA PET/CT for diagnosing and staging high risk PCa could be useful to omit mpMRI before biopsy improving time for diagnosis and optimizing also spending review (16-18). PSMA inhibitors conjugated with the radionuclides Gallium 68 (68Ga) and Fluoride 18 (18F) have been evaluated for the diagnosis of PCa (10) and tumour uptake, which represents PSMA expression, is highly correlated with the aggressiveness of the primary prostatic tumour (16); moreover, PSMA PET/CT demonstrated to be accurate for the detection of lymphadenopathy (18) and clinical metastases in case of biochemical recurrence (19). In addition, PSMA PET/CT has been evaluated in many clinical trials in men submitted to initial or repeated prostate biopsy, during Active Surveillance (20-22) and/or in case of negative histology of mpMRI *Prostate Imaging Reporting and Data System* (PI-RADS score) 4-5 targeted biopsy (23).
In this study, the cost-effectiveness of PSMA PET/CT as single procedure for diagnosis and staging of high grade prostate cancer (PSA > 20 ng/ml and/or positive digital rectal examination) has been prospectively evaluated.

PATIENTS AND METHODS

From June 2022 to December 2025, 330 men (median age: 65 years; range: 51-88 years) underwent transperineal prostate biopsy for the suspicion of high grade cancer (PSA > 20 ng/ml and/or abnormal DRE) (24, 25). All the patients were included in a clinical trial and written consent was obtained before the procedure: mpMRI was omitted and the patients performed only PSMA PET/CT (*Biograph 6; Siemens, Knoxville, TN, USA*). The PSMA PET/CT intraprostatic lesions suspicious for csPCa were submitted to cognitive targeted biopsies (TPBx: 4 cores) plus extended prostate biopsy (EPBx: median 12 cores; range: 10-16 cores); moreover, in the presence of confirmed csPCa PSMA PET/CT imaging examination was used for staging PCa (26). The prostate biopsy was performed transperineally using a GE Logiq P6 ecograph

(*General Electric; Milwaukee, WI, USA*) supplied with a biplanar trans-rectal probe (5-7.5 MHz) using a tru-cut 18gauge needle (*Bard; Covington, GA, USA*) under sedation and antibiotic prophylaxis (27). The lesions of PSMA PET/TC characterized by a Standard Uptake Value (SUVmax) > 8 suspicious for PCa underwent targeted cores (17); 18-F PSMA 1007 (150 cases) or 68Ga PSMA 11 (180 cases) was administered to patients via an intravenous bolus and scans were acquired in 3-dimensional mode with an acquisition time of 3 min per bed position. Images were 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. The location of focal uptake on PSMA PET/TC, three-dimensional size, and standardised uptake value (SUVmax) values were reported on a per-lesion basis with a sextant scheme (apex, midgland, and base, each split into left and right) (28,29). Two specialists in nuclear medicine blinded to pre-imaging clinical parameters evaluated PSMA PET/CT data separately and independently; in the presence of equivocal PSMA PET/CT of confirmed high grade PCa a *flourodeoxyglucose* (FDG) PET/CT was performed for clinical staging.

Results

The median PSA was 30.5 ng/ml (range: 20-785 ng/ml) and 135/300 (41%) had positive DRE; none had significant complications from prostate biopsy that needed hospital admission. A csPCa was found in 325/330 (98.5%) patients, moreover, in the remaining 5/330 (1.5%) a granulomatous prostatitis was diagnosed. PSMA PET/CT demonstrated the presence of suspicious PCa in 327/330 (99.1%) men; median intraprostatic SUVmax was 24 (range: 10-96); the presence of metastases was found in 168/325 (51.7%) men: 95/325 (29.2%) had positive nodes, 60/325 (18.5%) bone metastases and 40/325 (12.3%) multiple metastases (Figure 1). In 3/330 (1%) men with PCa, PSMA PET/CT was equivocal and in all these cases a ductal adenocarcinoma was found. Clinical and biopsy parameters in men with PCa (31,32) are listed in Table 1.

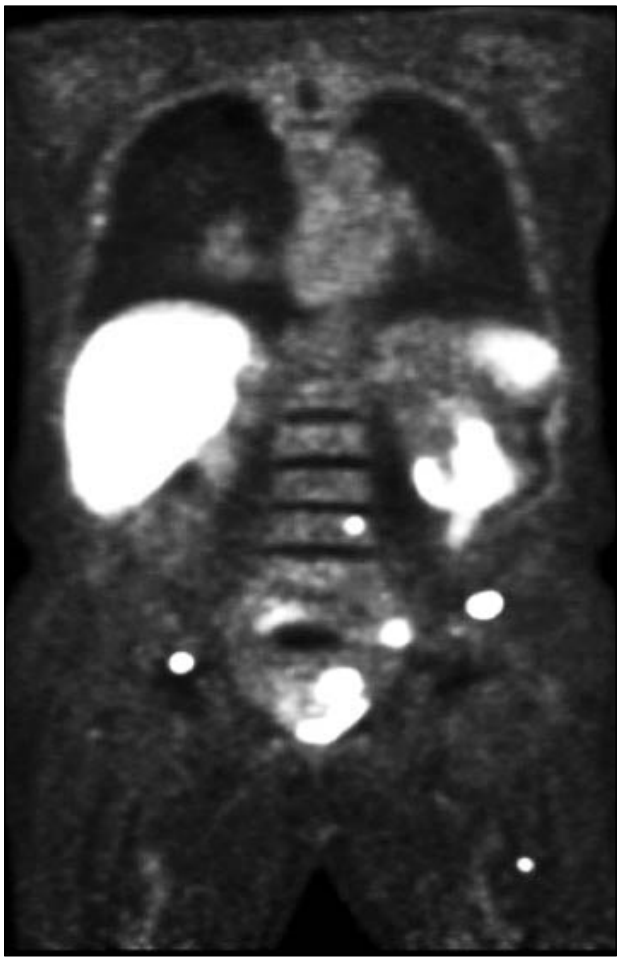
The reimbursement fares for each procedure used for diagnosing prostate cancer according to the regional public health system in Sicily (Italy) (30) are shown in Table 2; the overall reimbursement for diagnosing PCa in 330 patients submitted to prostate biopsy was 471,883,5 €. Using PSMA PET/CT without MRI the cost of this latter procedure could be spared for a total of 71,016 €. The

Table 1.
Clinical and biopsy findings of men with prostate cancer (PCa).

Clinical and biopsy parameters	No of cases
Suspicious DRE	135/325 (41.5%)
Median PSA ng/ml	30.5 (20-785)
PCa	325
Gleason score 4+3/ ISUPGG 3	25 (7.7%)
Gleason score 4+4/ISUPGG 4	64 (19.7%)
Gleason score 4+5/ISUPGG 5	171 (52.6%)
Gleason score 5+4/ISUPGG 5	59 (18%)
Gleason score 5+5/ISUPGG 5	3 (1%)
Ductal adenocarcinoma	3 (1%)
Number of positive cores	12 (4-20)
Positive TPBx	313 (96.3%)
Positive eTPBx	319 (98.1%)
Median GPC	80% (60-100)
Median TPC	45% (20-55%)
SUVmax (median)	27 (10-96)
Intraprostatic	27 (10-96)
Nodes	28 (9-41)
Bone	45 (15-96)

PDRE: digital rectal examination; GG: ISUP GG: International Society of Urological Pathology grade group; TPC: Total Percentage of Cancer; eTPBx: extended prostate biopsy; TPBx: targeted prostate biopsy; SUVmax: Standardized Uptake Value.

Figure 1.
PSMA PET/CT in man with PSA value 115 ng/ml, positive digital rectal examination, prostate cancer Gleason score 4+5/ISUP Grade Group 5, multiple nodes and bone metastases.



ISUP: International Society of Urological Pathology.

Table 2.
Cost (€) of each diagnostic procedures used to perform prostate biopsy and clinical staging by public health regional tariff schedula (Sicily, Italy).

Diagnostic procedures	Regional catalogue	Cost (€)
Urological visit	89.01	17,90
PSA	90.56.9	3,95
Multiparametric MRI	88.95.5	215,20
Prostate biopsy	60.11	76,90
PSMA PET /CT	92.18.D	1.116,00
Cost for each patient		1429,95
Overall cost (330 patients)		471,883,5
Overall saving (330 patients)		71,016 (15%)

PSA: prostate specific antigen; MRI: magnetic resonance image; PSMA (prostate-specific membrane antigen) PET/CT (positron emission tomography/computed tomography).

economic impact on the cost "*out-of-pocket*" for private payers was also evaluated through market research from a regional survey in Sicily (Italy) by consulting five public and five private centers demonstrating that the cost for PSMA PET/CT ranges 1,000-1,500 € and for mpMRI 150-600 €. Another clinical and economic advantage was the opportunity to address mpMRI, and medical and paramedic work activity to others patients reducing time of their waiting list. In our clinical practice of about 500 prostate biopsy performed in a year, the time to diagnosis and staging decreased from a median of 90 (60-120) to 45 (30-60) days allowing to start therapy in advance especially in men with metastases.

Discussion

Recent clinical trials have reported encouraging results on the performance of PSMA PET/CT in diagnosing, staging and follow up of men with csPCa. Although, European Association of Urology guidelines (33) recommend PSMA PET/CT only for staging high risk PCa and/or PSA recurrence, PSMA is overexpressed in most primitive and metastatic PCa and the tumour PSMA uptake evaluated by SUVmax value, is highly correlated with the aggressiveness of the PCa (34).

The use of PSMA PET/CT for the initial diagnosis of PCa, still today, is experimental and should be reserved to men enrolled in clinical trials; awaiting 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. The presence of high "*Primary Score*" (16) 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 DRE, elevated PSA values), therefore, PSMA PET/CT evaluation could be proposed to perform targeted biopsy and whole body PCa evaluation improving the cost-benefit ratio as a single procedure for the diagnosis and staging of high-risk PCa. *Pepe et al.* (28) in 125 men with median PSA of 35 ng/ml and suspicion DRE in 56.2% of the cases reported a diagnostic accuracy of PSMA PET/CT *vs.* MRI/TRUS fusion biopsy equal to 92.0 *vs.* 86.2%, respectively. Bodar et al. (35) in 60 men with PSA values included between 20-50 ng/ml demonstrated that PSMA-guided targeted biopsy identified 86.7% PCa and 100% of distant metastases. Although, PSMA PET/CT is more accurate than conventional imaging (about 27% of the cases) (36) in PCa evaluation, 5-10% of primary PCa PSMA have low activity which evade detection by PSMA PET, mostly in high-grade and variant tumor types; in this respect, prostatic *ductal adenocarcinoma* (DAC), characterized by cancer involving ducts and/or acini usually associated with a high-grade Gleason score/ISUP Grade Group, large tumor volume, has a poor PSMA uptake compared with prominent FDG avidity, which would suggest that FDG PET/CT scans are necessary in diagnosing and staging DAC pattern (37).

Regarding our results some considerations should be made. Firstly, the diagnostic accuracy of PSMA PET/CT was evaluated using biopsy specimens and not in the entire prostate gland. Secondly, our protocol is based on a "*clinical trial*" approved in our hospital that need external validation (38-42), but economic and clinical advantages could be superimposable if adopted in others health systems.

In conclusion, PSMA PET/CT used to perform diagnosis and staging as a single imaging procedure in men at risk for high grade PCa improved cost-effectiveness reducing the costs, time to the diagnosis and staging allowing to start quickly therapy in men with high risk of metastases.

Declarations

Ethical approval and consent for participate: *Institutional review board and ethical com-mittee approval were granted the informed consent wasobtained from all individual partecipants included in the study.*

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 that support the findings of this study are available from the corresponding author upon reasonable request.*

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

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Authors' contributions: *Conceptualization, P.P., P.L., P.G.; Methodology, P.P., P.L., P.G.; Software, P.P., F.V., P.L., P.G.; Validation, P.P.; Formal Analysis, P.P., F.V., P.L., P.G.; Investigation, P.P., P.L., P.G.; Resources, P.P., P.L., P.G.; Data Curation, P.P., F.V., P.L., P.G.; Writing – Original Draft Preparation, P.P., P.L., P.G.; Writing – Review & Editing, P.P., P.L., P.G.; Visualization, P.P., P.L., P.G.; Supervision, P.P. Funding acquisition: None.*

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