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ORIGINAL PAPER

# Targeted prostate biopsy: $^{68}$Ga-PSMA PET/CT vs. mpMRI in the diagnosis of prostate cancer

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**Summary** ***Introduction: To evaluate the diagnostic accuracy of $^{68}$Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) vs. multiparametric magnetic resonance imaging (mpMRI) targeted biopsy (TPBx) in the diagnosis of clinically significant prostate cancer (csPCa: Grade Group ≥ 2).***
***Materials and methods: From January 2021 to June 2022, 100 patients (median age: 66 years) with negative digital rectal examination underwent transperineal prostate biopsy for abnormal PSA values (median 7.5 ng/ml). Before prostate biopsy, all patients underwent mpMRI and $^{68}$Ga-PET/CT examinations and mpMRI (PI-RADS version 2 ≥ 3) or $^{68}$Ga-PET/CT index lesions suspicious for cancer (SUVmax > 5 g/ml) underwent cognitive targeted cores (mpMRI-TPBx and PSMA-TPBx: four cores) combined with extended systematic prostate biopsy (eSPBx: median 18 cores). The procedure was performed transperineally using a tru-cut 18-gauge needle under sedation and antibiotic prophylaxis.***
***Results: PCa was found in 58/100 (58.0%) men; in detail, 44/58 (75.9%) were csPCa; mpMRI and $^{68}$Ga-PSMA showed 66/100 (66%) and 62/100 (60%) lesions suspicious for PCa, respectively. $^{68}$Ga-PSMA-TPBx vs. mpMRI-TPBx vs. eSPBx diagnosed 42 (95.4%) vs. 36 (81.8%) vs. 30 (68.2%) csPCa, respectively; mpMRI-TPBx vs. $^{68}$Ga-PSMA-TPBx showed a diagnostic accuracy of 76.9% vs. 84.9% in diagnosing csPCa.***
***Conclusions: $^{68}$GaPSMA PET/CT TPBx demonstrated good accuracy in the diagnosis of csPCa, which was not inferior to mpMRI TPBx (84.9% vs. 76.9%) improving the detection rate for cancer of systematic biopsy.***

*KEY WORDS: Prostate cancer; $^{68}$Ga-PSMA PET/CT; mpMRI; Targeted prostate biopsy.*

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## INTRODUCTION

Although *multiparametric magnetic resonance imaging* (mpMRI) has improved diagnostic accuracy of systematic prostate biopsy in the diagnosis of *clinically significant prostate cancer* (csPCa), about 20-35% of PCa could be missed by mpMRI targeted biopsy (1). *Prostate-specific membrane antigen* (PSMA) is expressed in most primitive and metastatic PCa (2, 3), and PSMA inhibitors conjugated with the radionuclides Gallium 68 ($^{68}$Ga) and fluoride 18 (18F) have been evaluated in clinical practice for the diagnosis of PCa (4-6); morever, tumour uptake, which represents PSMA expression, is highly correlated with the aggressiveness of the primary prostatic tumour (7, 8). $^{68}$Ga-PSMA *positron emission tomography/computed tomography* (PET/CT) demonstrated to be sensitive for the detection of primary prostatic lesions, regional lymphadenopathy (9) and clinical metastases in case of biochemical recurrence (10, 11).
Our study prospectively compared the diagnostic accuracy of $^{68}$Ga-PSMA PET/CT vs. mpMRI targeted biopsy (TPBx) in the diagnosis of csPCa (grade group ≥ 2) (12).

## MATERIALS AND METHODS

From January 2021 to June 2022, 100 patients (median age: 66 years; range: 49-79 years) with negative digital rectal examination underwent repeated transperineal prostate biopsy for abnormal PSA values (median 7.5 ng/ml; range: 4.5-83 ng/ml) (13, 14). The study was approved by the *Ethics Committee of our Hospital*. All patients underwent prostate biopsy mpMRI and $^{68}$Ga-PET/CT imaging examinations; a 1.5 Tesla scanner equipped with surface 16 channels phased-array coil placed around the pelvic area with the patient in the supine position, multi-planar turbo spin-echo T2-weighted imaging, axial diffusion-weighted imaging, and *axial dynamic contrast* (ADC) enhanced MRI were performed for each patient (15). Two radiologists, blinded to pre-imaging clinical parameters, evaluated the MRI data separately and independently. PET/CT imaging was performed using a CT-integrated PET scanner (*Biograph 6; Siemens, Knoxville, TN, USA*). $^{68}$Ga-PSMA was prepared with a fully automated radiopharmaceutical synthesis device based on a modular concept (*Eckert & Ziegler Eurotope, Berlin, Germany*). $^{68}$Ga-PSMA-11 was given to patients via an intravenous bolus (mean, 144 ± 12 MBq; range, 122-188 MBq), and the PET acquisition was started at a mean of 58 ± 12 min (range, 50-81 min) afterward. Scans were acquired in 3-dimensional mode with an acquisition time of 3 min per bed position. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively using ordered-subsets expectation maximization (4 iterations, 8 subsets) followed by a post reconstruction smoothing gaussian filter (5 mm in full width at half maximum). For attenuation correction, a low dose unenhanced CT scan

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was performed from the skull base to the middle of the thigh. 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 by two experienced nuclear medicine specialists, who were blinded to the clinical data. The location of focal uptake on $^{68}$Ga-PSMA PET/TC (Figure 1), three-dimensional size, and standardised uptake value (SUVmax) values were reported on a per-lesion basis with a sexstant scheme (*apex, midgland, and base, each split into left and right*) (5). All mpMRI (*Prostate Imaging Reporting and Data System "PI-RADS" version 2 ≥ 3*) and $^{68}$GaPSMA-PET/CT (SUVmax > 5 g/ml) index lesions underwent targeted cores (mpMRI-TPBx and PSMA-TPBx: four cores) combined with extended systematic prostate biopsy (eSPBx: median 18 cores) (2, 14). The procedure was performed transperineally using a tru-cut 18-gauge needle (*Bard, Covington, GA, USA*) under sedation and antibiotic prophylaxis (17). Prostate-targeted cores were obtained using a *Hitachi 70 Arietta echograph* (*Chiba, Japan*) supplied by a bi-planar trans-rectal probe (14) by one urologist with 10 years of experience in cognitive targeted biopsy. Data were collected following START criteria (18).

## Results

PCa was found in 58/100 (58%) men; in detail, 44/100 (44%) were csPCa: 30/44 (75%) and 14 (25%) were located in the peripheral and anterior zones of the gland, respectively. Clinical parameters of men with PCa are reported in Table 1; in detail, mpMRI and $^{68}$Ga-PSMA showed 66/100 (66%) and 62/100 (60%) lesions suspicious for PCa, respectively. These were submitted to targeted cores combined with eSPBx. The diagnostic accuracy of mpMRI TPBx *vs.* $^{68}$Ga-PSMA TPBx is shown in Table 2. None of the patients had clinical complications following prostate biopsy (Dindo-Clavien grade1) (19). The average intraprostatic SUVmax was 8.5 g/ml (range = 4-49 g/ml) and the average maximal intraprostatic tumor dimension was 12 mm (range = 8-23 mm). $^{68}$Ga-PSMA-TPBx *vs.* mpMRI-TPBx *vs.* eSPBx missed 2 (4.5%) *vs.* 8 (18.2%) *vs.* 14 (31.8%) csPCa, respectively.

***Table 1.***
*Clinical parameters of 44 men with clinically significant prostate cancer (csPCa).*

| Clinical and biopsy findings | GG2 15 pz | GG3 11 pz | GG4 10 | GG5 8 |
|---|---|---|---|---|
| Initial biopsy | 9 | 6 | 6 | 6 |
| Repeated biopsy | 6 | 5 | 4 | 2 |
| Median PSA (range: 4.5-83 ng/ml) | 6.3 | 9.5 | 16 | 26 |
| Median GPC | 30% | 45% | 70% | 90% |
| Number of positive cores overall | 6 | 9 | 11 | 13 |
| mpMRI PI-RADS score ≥ 3 | 9 | 8 | 8 | 7 |
| $^{68}$Ga-PSMA PET/TC suspicious for PCa | 7 | 11 | 10 | 8 |

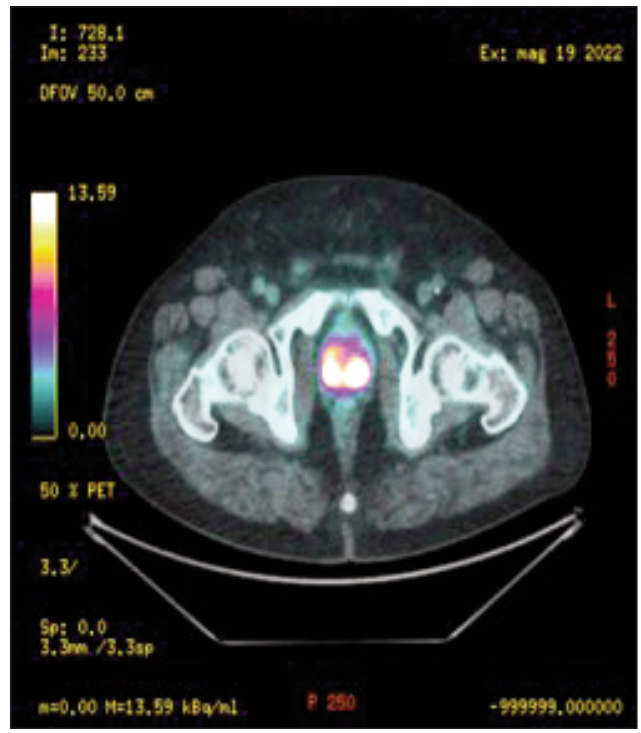
*GG: International Society of Urological Pathology Grade Group; mpMRI: multiparametric magnetic resonance imaging; PSA: Prostate specific antigen; GPC: Greatest percentage of cancer; PSMA: Prostate specific membrane antigen; PI-RADS: Prostate imaging reporting and data system; PET/TC: Positron emission tomography/computed tomography.*

***Table 2.***
*Diagnostic accuracy of mpMRI-TPBx vs. $^{68}$Ga-PSMA-TPBx in the diagnosis of clinically significant prostate cancer (csPCa).*

| Number of csPCa (44 cases) | mpMRI TPBx 36 cases | 68Ga-PSMA PET/CT TPBx 42 cases |
|---|---|---|
| Sensitivity | 81.8% | 95.4% |
| Specificity | 71.8% | 80.0% |
| Positive predictive value | 54.5% | 73.4% |
| Negative predictive value | 87.5% | 96.5% |
| Diagnostic accuracy | 76.9% | 84.7% |

*PSMA: Prostate specific membrane antigen; mpMRI: multiparametric magnetic resonance imaging; PET/TC: Positron emission tomography/computed tomography; TPBx: targeted prostate biopsy.*

***Figure 1.***
*68Ga-prostate-specific membrane antigen (PSMA) PET/CT: presence of high suspicious area fo prostate cancer (SUVmax 20) in both lobe of the prostate (axial evaluation).*




## Discussion

To reduce the risk of overdiagnosis following screening protocols for PCa, mpMRI has been recommended to decrease the risk of overtreatment; on the other hand, systematic prostate biopsy should always be combined with mpMRI/TRUS fusion biopsy because of the false negative rate of mpMRI (PCa with low volume and grade group > 2) (20, 21). Recently, $^{68}$Ga-PSMA-PET/CT has been suggested to improve the clinical staging of high-risk PCa and disease recurrence (5, 10, 22); similarly, PSMA PET/CT has been proposed for the diagnosis of primary intraprostatic cancer. 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 (23-25). There is a range of proposed cut-offs to detect csPCa from SUVmax 3.15 to SUVmax 9.1 (26, 27); in addition, PSMA-PET/CT demonstrated high correlation between the ISUP grade group and SUVmax

and maximal dimension of the lesion. *Zhang et al.* (28) reported a higher detection rate for csPCa performing a single transgluteal PSMA PET/CT targeted core (SUVmax > 8) in comparison with systematic prostate biopsy (40 *vs.* 25% of the cases). *Liu et al.* (29), found 85.5% of csPCa (47/55 cases) performing PET/CT PSMA targeted cores; *Kalapara et al.* (30) compared the accuracy of $^{68}$Ga-PSMA PET/CT with mpMRI in 205 men who underwent radical prostatectomy and showed an accuracy of 96% *vs.* 91% for the detection of csPCa. *Xue et al.* showed that a SUVmax cut-off of 5.4 predicted pathological upgrading at definitive histology, showing 91% specificity and 94% negative predictive value (31). *Ferraro et al.* (32) in 49 men who underwent 68GaPSMA PET/MRI plus template biopsy demonstrated a diagnostic accuracy of PET/MRI targeted cores of 90% with only one false negative result. In definitive, the use of more parameters (i.e. genetic evaluation, diagnostic imaging, PSA density) (5, 33) included in risk calculator could better select men at risk for csPCa who should underwent prostate biopsy allowing to omit unnecessary procedures also in case of *Active Surveillance* (34) reducing complications rate (35).

In our series, among the 44/100 (44.0%) men with csPCa, mpMRI-TPBx *vs.* $^{68}$Ga-PSMA-TPBx showed a diagnostic accuracy of 76.9% *vs.* 84.9%; $^{68}$Ga-PSMA-TPBx *vs.* mpMRI-TPBx *vs.* eSPBx missed 2 (4.5%) *vs.* 8 (18.1%) *vs.* 14 (31.8%) csPCa, respectively. Although prospective and randomized studies are awaited, including a greater number of patients, $^{68}$Ga-PSMA PET/CT evaluation could be proposed in men with negative mpMRI or in the presence of claustrophobia, cardiac pacemaker and severe obesity.

Our study has some limitations. First, the number of patients evaluated was low. Second, the results should be evaluated in the entire prostate specimen and not in biopsy histology. Finally, a $^{68}$Ga-PSMA PET/TC fusion platform would increase the accuracy of targeted prostate biopsy.

## Conclusions

$^{68}$GaPSMA PET/CT TPBx demonstrated good accuracy in the diagnosis of csPCa, which was not inferior to mpMRI TPBx (76.9% *vs.* 84.9%) improving the detection rate for cancer of systematic biopsy.

## Authors' contributions

The Authors contributed equally to all aspects of this study.

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