

Should 68Ga-PSMA PET/CT Replace CT and Bone Scan in Clinical Staging of High-risk Prostate Cancer?

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Abstract. *Background/Aim:* To evaluate the accuracy of 68Gallium prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) vs. CT combined with bone scan in the clinical staging of high-risk prostate cancer (PCa). *Patients and Methods:* From January 2020 to October 2021, 30 patients underwent clinical staging according to 68Ga-PSMA PET/CT, lung-abdominal CT and Technetium-99m bone scan. *Results:* 68Ga-PSMA PET/CT demonstrated a better accuracy in comparison with CT plus bone scan in the diagnosis of node metastases at definitive histology (76.9% vs. 46.1%; $p=0.001$). *Conclusion:* The 68Ga-PSMA PET/CT was more accurate than CT and bone scan in the staging of high-risk PCa, leading to a change in the therapeutic strategy in 10% of the cases.

Prostate cancer (PCa) treatment is changed following the opportunity to use a multidisciplinary approach also in men with locally advanced or oligometastatic disease. Although, diagnostic imaging with multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography/computed tomography (PET/CT) has improved the diagnostic accuracy for PCa staging, still today, international guidelines strongly recommend performing computed tomography (CT) combined with bone scan in men with intermediate- to high-risk PCa. However, it is noted that CT and bone scan lack sensitivity, therefore, there is a need for more effective imaging modalities that can be used in the diagnosis, risk assessment, staging, and follow-up of PCa. mpMRI provides valuable information regarding local staging, detection of intraprostate tumor, and especially extracapsular extension (1, 2) with an accuracy of 44-87% (3). Recently, 68Gallium prostate-specific

membrane antigen (PSMA) PET-CT was strongly suggested for its diagnostic accuracy in the case of early biochemical recurrence (4) and proposed as unique procedure also in the staging of high-risk prostate cancer.

The aim of this study was to prospectively evaluate the diagnostic accuracy of preoperative 68Ga-PSMA PET/CT vs. lung and abdomen CT combined with bone scan in the clinical staging of high-risk PCa.

Patients and Methods

From January 2020 to October 2021, 30 patients (median age=65 years; range=49-75 years) with high-risk PCa underwent clinical staging; their clinical parameters and biopsy findings (5) are listed in Table I. All the patients underwent Ga68-PSMA PET/CT (Figure 1), lung-abdominal CT and Technetium-99m ($^{99m}\text{Tc-MDP}$) bone scan; in addition, the mpMRI performed before prostate biopsy was used for local staging (6). PET/CT imaging was performed using a CT-integrated PET scanner Biograph 6 (Siemens, Knoxville, TN, USA) 60-90 min after the intravenous injection of 74-185 mBq mCi 68Ga-PSMA, which was prepared with a fully automated radiopharmaceutical synthesis device based on a modular concept (Eckert & Ziegler Eurotope, Berlin, Germany). The raw images were processed with appropriate iterative reconstruction techniques 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 presence of nodal enlargement, bone metastases, distant metastases and second cancer were evaluated. For statistical analysis the Student's *t*-test was used; a *p*-value <0.05 was considered statistically significant.

Results

In 29/30 (96.7%) patients, no visceral metastases were found; in 19/30 (63.3%) a nodal enlargement (>10 mm) suspicious for metastases was recorded, 11/30 (36.6%) had bone metastases and 1/30 (3.4%) had metastatic pancreatic cancer.

The accuracy of CT combined with bone scan, Ga68-PSMA PET/CT and mpMRI in the staging of high-risk PCa is reported in Table II. In detail, Ga68-PSMA PET/CT vs. lung-abdomen CT combined with bone scan demonstrated node enlargement

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and bone metastases in 26 (86.7%) vs. 13 (43.3%) cases and 11 (36.7%) vs. 5 (16.7%), respectively. Furthermore, Ga68-PSMA PET/CT changed the strategy of therapy in 3/30 (10%) cases for the presence of bone metastases in more than 3 sites (2 cases) and enlargement of distant nodes (1 case). However, CT scan allowed to detect one case (3.4%) of primitive metastatic pancreatic tumor that was missed by Ga68-PSMA PET/CT. mpMRI showed the presence of locally advanced PCa (extraprostatic extension) in 22/30 (73.3%) cases and local nodes enlargement in 12/30 (40%) cases; on the other hand, mpMRI missed 7 (23.3%) cases of distant nodes enlargement.

Among the 30 men with PCa, 16 (53.3%) underwent external radiotherapy combined with LHRH agonist therapy, 13 (43.3%) underwent retropubic radical prostatectomy (RRP) plus extended lymphadenectomy and one (3.4%) was submitted to hormonal therapy (LHRH antagonist) because of the presence of primitive metastatic pancreatic cancer. In the 13/30 (43.3%) men submitted to RRP, definitive specimen showed a pT3aN0 (0/18) in 1 case, pT3a N+ (2/20) in 3 cases, pT3bN0 (0/17) in 2 cases and pT3bN+ (8/23) in 7 cases; the concordance between Ga68-PSMA PET/CT vs. lung-abdomen CT in the diagnosis of nodes metastases was confirmed by definitive histology in 10/13 (76.9%) vs. 6/13 (46.1%) cases ($p=0.001$), respectively.

Discussion

The PSMA is a cell surface protein and an important target for diagnostic and therapeutic use (7). Today, there are many radio-labeled PSMA derivatives developed for the diagnosis, staging and treatment of PCa by targeting PSMA in nuclear medicine applications (7, 8). Ga68-PET/CT is now an established imaging technique that has been developed in response to inadequacies in standard of care imaging modalities to improve the detection of metastatic disease in prostate cancer, particularly in the setting of disease recurrence (9).

The gold standard for the clinical staging of high-risk PCa is CT and bone scan; however, the best way to evaluate lymph nodes (LN) status remains surgery. Recently, the European Association of Urology (EAU) guidelines recommended CT or MRI in men with intermediate and high-risk PCa to evaluate lymph node status awaiting randomized controlled trials results before putting the PSMA PET/CT result into the decision-making process of the treatment (10). Abdollah *et al.* (11) reported that removal of a minimum of 20 pelvic nodes provided 90% real nodes staging; Hövels *et al.* (12) demonstrated a sensitivity of 42% and 39% for CT and MRI in LN staging with a specificity of 82% for both procedures; however, these imaging methods only provide morphological data and assess nodes metastasis based on the size of the LN. Guntelkin *et al.* (13), in 28 patients with intermediate-high-risk groups submitted to extended pelvic lymphadenectomy, demonstrated that 68Ga-PSMA PET/CT

Table I. Clinical parameters and biopsy findings in 30 patients with high-risk prostate cancer.

Clinical and biopsy findings	Number of patients
Grade Group 4 (Gleason score 8)	20 (66.7%)
Grade Group 5 (Gleason score 9)	10 (33.3%)
Median PSA ng/ml (range)	19 (4.3-92)
Clinical T1c stage	11(36.7%)
Clinical T2 stage	13 (43.3%)
Clinical T3 stage	6 (20%)
Median TPC (range)	45% (30-75)
Initial biopsy	27 (90%)
Repeat biopsy	3 (10%)
Median GPC (range)	80% (60-100%)

PSA: Prostate specific antigen; TPC: total percentage of cancer; GPC: greatest percentage of cancer.

scan had an accuracy of 89.3%, whereas Maurer *et al.* (14) reported an accuracy of 65.9%. sensitivity, 98.9% specificity, and 88.5% accuracy in detecting nodes metastases. Sprute *et al.* (15) reported in the analysis of all malignant nodes of 96 patients submitted to extended lymphadenectomy a sensitivity and specificity on lesion-based analysis of 71.2 and 99.5%, respectively. Szigeti *et al.* (16) compared Ga-PSMA-11 PET/CT findings with mpMRI in the detection of locoregional lymph node metastases in men submitted to surgery showing a detection rate for metastases in 60% vs. 50% of the cases, respectively. Hofman *et al.* (17) in 339 men with high-risk PCa demonstrated that Ga68-PSMA PET/CT had a 27% greater accuracy than conventional imaging (CT and bone scan); in detail, subgroup analyses also showed the superiority of GaPSMA PET/CT for patients with pelvic nodal metastases (91% vs. 59%), and distant metastases (95 vs. 74%) showing that first-line conventional imaging conferred management change less frequently (15% vs. 28%) and had more equivocal findings (23% vs. 7%) than 68Ga-PSMA PET/CT.

In our series, Ga68-PSMA PET/CT outperformed lung-abdomen CT combined with bone scan in diagnosing nodes enlargement and bone metastases. In detail, Ga68-PSMA PET/CT demonstrated a better concordance in the diagnosis of nodes metastases in comparison with CT plus bone scan at definitive histology (76.9% vs. 46.1%; $p=0.001$), respectively. Finally, Ga68-PSMA PET/CT changed the strategy of therapy in 3/30 (10%) cases because of the presence of bone metastases in more than 3 sites (2 cases) and enlargement of distant nodes (1 case). However, CT scan allowed the detection of one case (3.4%) of primitive metastatic pancreatic tumor that was missed by Ga68-PSMA PET/CT.

There are some limitations to our study. First, the number of patients evaluated was low. Second, the revision of Ga68-PSMA PET/CT imaging by a radiologist, probably, would have allowed the detection of primitive pancreatic cancer.

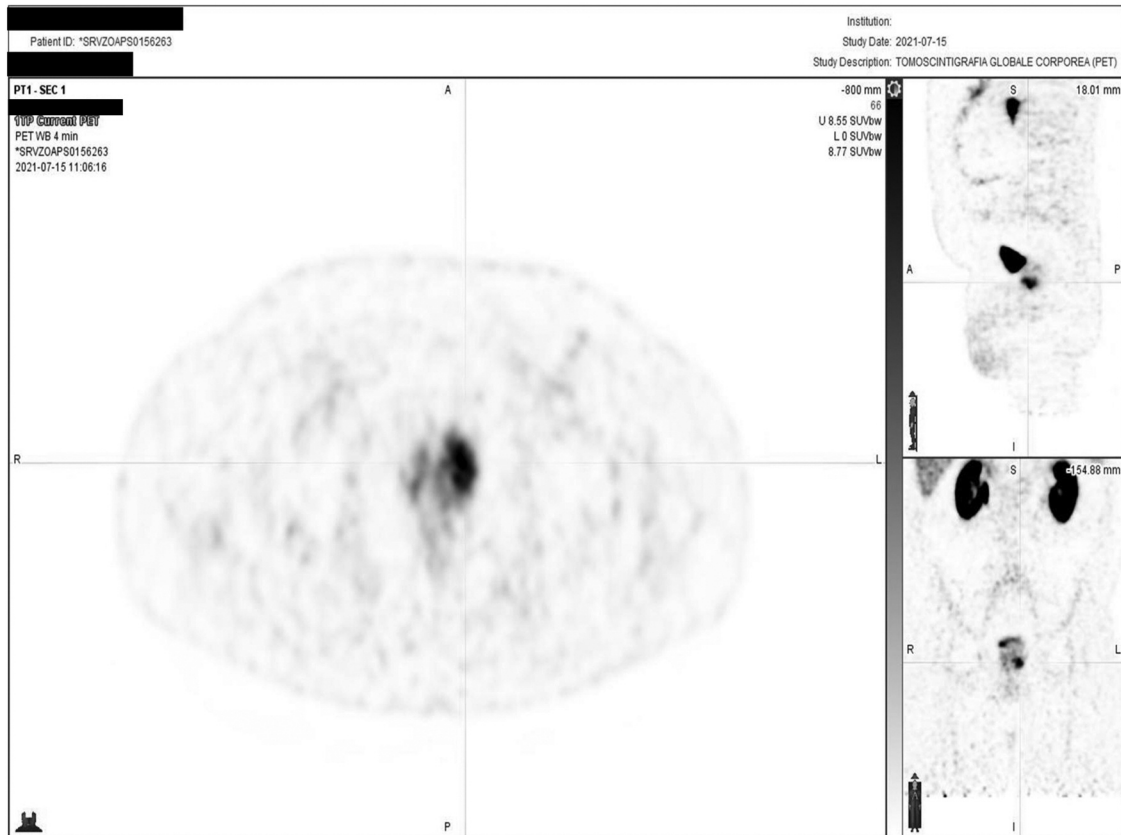


Figure 1. Preoperative Ga68-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography: presence of highly suspicious area of prostate cancer in the left lobe of the prostate gland (axial, sagittal and coronal evaluation).

Table II. Clinical staging of men with high-risk prostate cancer performed by lung-abdomen CT, Ga68-PSMA PET/CT, and mpMRI.

Clinical stadiation 30 patients	CT	Bone scan	Ga69 PSMA PET/CT	mpMRI
Locally advanced PCa (extraprostatic extension)	12 (40%)	-	16 (53.3%)	22 (73.3%)
Regional nodes enlargement	8 (26.7%)	-	19 (63.3%)	12 (40%)
Distant nodes enlargement	5 (16.7%)	-	7 (23.3%)	-
Bone metastases (<3 sites)	3 (10%)	4 (13.3%)	8 (26.7%)	3 (10%)
Bone metastases (>3 sites)	-	1 (3.4%)	3 (10%)	1 (3.4%)
Distant visceral metastases	1 (3.4%)	-	-	-
Pancreatic cancer	1 (3.4%)	-	-	-

PSMA: Prostate-specific membrane antigen; CT: computed tomography; PET: positron emission tomography; Pca: prostate cancer; mpMRI: multiparametric magnetic resonance imaging.

Third, mpMRI may be useful only for local staging because a whole-body MRI should be performed for total body clinical staging. Finally, a greater number of men prospectively submitted to radical prostatectomy should be evaluated to compare preoperative 68Ga-PSMA PET/CT results with definitive histology specimens.

In conclusion, 68Ga-PSMA PET/CT scan demonstrated better accuracy in the diagnosis of nodes and bone

metastases in comparison with lung-abdomen CT combined with bone scan. These results indicate that 68Ga-PSMA PET/CT might become the standard imaging method for high-risk PCa staging (18).

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

The Authors contributed equally to all aspects of this study.

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