

^{68}Ga -PSMA PET/CT Staging of Newly Diagnosed Intermediate- and High-Risk Prostate Cancer

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ABSTRACT: **Background:** ^{68}Ga -prostate-specific membrane antigen positron emission tomography/computerized tomography (^{68}Ga -PSMA PET/CT) is part of the initial workup of patients with intermediate and high-risk prostate cancer provided by the Israeli national health services.

Objectives: To assess the incidence of metastatic spread in consecutive patients with newly diagnosed cancer, and the potential added value of ^{68}Ga -PSMA PET/CT to the staging imaging algorithm.

Methods: Patients with newly diagnosed intermediate- and high-risk prostate cancer were referred for initial staging by ^{68}Ga -PSMA PET/CT between May 2016 and April 2017. Blood prostate-specific antigen (PSA) levels, clinical history, imaging reports and histopathological reports (including Gleason scores) were obtained. Maximal standardized uptake values (SUVmax) were determined for the primary lesions detected within the prostate.

Results: The study included 137 consecutive patients with intermediate- and high-risk disease who underwent ^{68}Ga -PSMA PET/CT staging. Of these, 75 had ^{68}Ga -PSMA uptake in both prostate lobes, 57 had unilateral uptake, and 5 patients had no uptake. SUVmax in the primary tumor correlated significantly with PSA levels. Thirty-five patients had increased uptake compatible with metastatic disease involving lymph nodes, bone, and viscera. Twenty-seven patients had available bone scintigraphy results: 18 (69%) of their 26 bone metastases detected by ^{68}Ga -PSMA PET/CT were missed on bone scintigraphy.

Conclusions: ^{68}Ga -PSMA PET/CT shows promise as a sole whole-body imaging modality for assessing the presence of soft tissue and bone metastases in the setting of prostate cancer.

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KEY WORDS: positron emission tomography/CT (PET/CT), ^{68}Ga -prostate-specific membrane antigen (PSMA), prostate-specific antigen (PSA), prostate cancer

High-risk patients are defined according to the D'Amico risk stratification [2]. According to the 2017 European Association of Urology guidelines, the initial workup of high-risk prostate cancer patients should include the following imaging modalities: pelvic magnetic resonance imaging (MRI), computerized tomography (CT), and bone scintigraphy (BS) [3]. Hovels et al. [4] reported a pooled sensitivity of 39–42% and a specificity of 82% for CT and MRI for the detection of lymph node metastases.

^{68}Ga -prostate-specific membrane antigen (PSMA) positron emission tomography/CT (PET/CT) has recently gained acceptance as a highly sensitive and specific imaging modality for evaluating the extent of disease in patients with prostate cancer [5]. ^{68}Ga -PSMA PET/CT utilizes low-molecular-weight ligands for human PSMA radiolabeled with ^{68}Ga (^{68}Ga -PSMA-11, ^{68}Ga -PSMA-617 or ^{68}Ga -PSMA-I&T) [6] that bind to the extracellular part of the PSMA receptor and are then internalized into the prostate cancer cell. Several ^{18}F -labeled PSMA ligands are also available [7].

A few publications introduced PET/MRI with ^{68}Ga -PSMA as an imaging modality with the potential of improving localization of primary prostate disease in a “one-stop shop” examination [8,9]. PSMA is a transmembrane protein with an extracellular portion expressed on the surface of prostate tumor cells at all tumor stages. It is located in the cytosol in normal prostate cells and switches to a membrane-bound protein in prostate cancer, thereby increasing its expression in prostate cancer cells [6,10–12]. PSMA expression increases further with prostate cancer stage and grade, in castration-resistant prostate cancer and under androgen-deprivation therapy (ADT) [6].

Most reports on the role of ^{68}Ga -PSMA PET/CT in patients with prostate cancer address its use in the setting of biochemical recurrence, although ^{68}Ga -PSMA PET/CT was also shown to be superior to conventional imaging for the detection of metastases for initial staging at primary diagnosis [13–17]. Based on this growing body of evidence to support the advantages of ^{68}Ga -PSMA PET/CT, the Israel Ministry of Health added it to the national list of health services (“the health basket”) in January 2016. The imaging modality is provided without cost for primary staging of prostate cancer in patients with inter-

Prostate cancer is the most common malignancy among men in developed countries, including Israel where it is the fourth leading cause of death from malignant disease [1].

mediate- and high-risk disease and for restaging patients with biochemical failure.

The current study was aimed at assessing the incidence of metastatic spread in patients with newly diagnosed intermediate and high-risk prostate cancer, and addressing the potential added value of ⁶⁸Ga-PSMA PET/CT in the staging imaging algorithm.

PATIENTS AND METHODS

STUDY POPULATION

Between May 2016 and April 2017, a total of 137 consecutive patients with newly diagnosed intermediate- and high-risk prostate cancer were referred to the Department of Nuclear Medicine at Tel Aviv Sourasky Medical Center for initial staging by means of ⁶⁸Ga-PSMA PET/CT. Patients with Gleason score ≥ 6 and prostate-specific antigen (PSA) ≥ 10, or patients with Gleason score ≥ 7 were included. The referring physicians were either oncologists or urologists. None of the patients had received previous treatment, including ADT.

PSA values, Gleason scores, relevant clinical history, and any other available imaging reports were obtained from each patient prior to their undergoing the PET/CT study. Each patient’s medical file was retrospectively reviewed for missing clinical data. Patient characteristics are summarized in Table 1.

METHODS

⁶⁸Ga-PSMA PET/CT imaging was performed according to the institute’s protocol, which is in accordance with international guidelines [18]. ⁶⁸Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[⁶⁸Ga(HBED-CC)]) was used as the PSMA ligand. ⁶⁸Ga-PSMA-11 was injected intravenously as a bolus at a dose of 148–166.5 MBq (4–4.5 mci) 45–100 min before image acquisition. The patients were instructed to void immediately prior to study initiation. PET/CT scans were performed starting from the tip of the skull to mid-thigh using the Discovery 690 PET/CT system (GE Healthcare, USA). First, a diagnostic CT (reference mAs, 200–240, 120 kV) was performed, followed by a PET scan with an acquisition time of 4 minutes per bed position. PET images were reconstructed by means of an ordered-subsets expectation maximization algorithm. CT

data were used for attenuation correction. The studies were read on a XELERIS workstation (GE Healthcare) equipped with fusion software that enables the display of PET images (with and without attenuation correction), CT images, and the fused data of both modalities. Maximal standardized uptake values (SUV) were obtained for the primary lesions detected within the prostate using 1 cm volume-of-interest (VOI) sphere. Lesions with perceptible uptake above background were considered positive.

The institutional human research ethics committee approved the application of the imaging findings in patients with newly diagnosed prostate cancer for the purpose of this report.

DATA ANALYSIS

Statistical assessment (Spearman correlation coefficient) was done using the SPSS version 21.0 software (IBM Corp., Armonk, NY, USA) with a significance considered at *P* = 0.05.

RESULTS

A total of 137 consecutive patients with intermediate- and high-risk disease were analyzed [Table 1]. Of these 137 patients, 75 (55%) had pathological ⁶⁸Ga-PSMA uptake in both prostate lobes; 57 (42%) had unilateral disease, and 5 (3%) had no pathologic ⁶⁸Ga-PSMA uptake. Sixteen patients (11.6%) had increased uptake in the seminal vesicles. In addition to the primary tumor sites, 35 patients (25.5%) had non-physiologic sites of increased ⁶⁸Ga-PSMA uptake outside the prostate gland compliant with metastatic disease, including lymph nodes, bone and viscera. Twenty-eight patients (20%) had increased uptake in their lymph nodes, of whom 9 had increased uptake outside the pelvis (i.e., nodes located cranial to the bifurcation of the common iliac vessels). Fifteen patients (10.9%) had increased uptake in bones, and one (0.7%) had increased uptake in the lung nodules. Figure 1 illustrates ⁶⁸Ga-PSMA uptake in primary and secondary tumor sites in two patients.

Maximal SUV of the primary lesion in the prostate (prostate cancer SUVmax) ranged between 0.88 and 38 with a mean of 8.54 ± 5.21 [Table 2]. SUVmax correlated with the PSA values (Spearman, *r* = 0.319, *P* < 0.01) [Figure 2]. Notably, there were no significant correlations between prostate cancer SUVmax and Gleason score or the presence of metastatic disease. Five patients had no increased uptake in their prostate. These patients might have prostate cancer with no expression of PSMA; however, post-surgical pathology findings were unavailable to confirm that possibility.

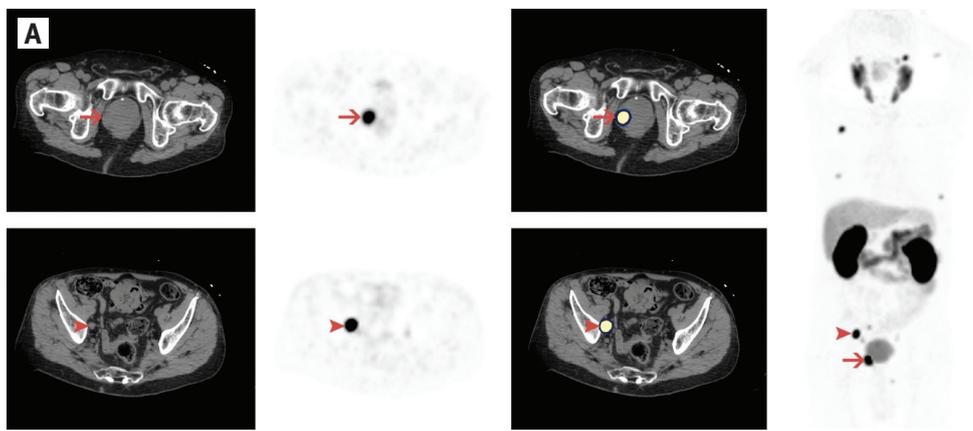
Results of a contemporaneous bone scintigraphy were available for 27 patients, with a mean interval between the BS and PET/CT studies of 2.2 months. A total of 26 positive bone lesions were identified on PSMA PET in 15 of 27 patients (11%), and only 8 of 26 (31%) of those PET

Table 1. Patient characteristics (n=137)

Age (yr)	Mean ± SD 68.5 ± 6.8	
PSA (ng/ml)	Median (IQR) 11.3 (6.8–22.2)	
Gleason score (n)	6	16
	7	66
	8	36
	9–10	19

Figure 1. ⁶⁸Ga-PSMA PET/CT of two patients with metastatic prostate cancer

[A] A 69-year-old high-risk patient (Gleason 8, PSA 52.64) with extensive bone metastases and a metastatic external iliac lymph node. Top row (from left to right): trans-axial CT, PET, and fusion images of PSMA uptake in the primary tumor site in the prostate (arrow), located to the lateral right mid-gland, SUVmax 35. Bottom row (from left to right): trans-axial CT, PET, and fusion images of a PSMA uptake in a metastatic external iliac lymph node (0.8*1.2 cm, arrowhead). Right: Maximum intensity image (mip) showing the extent of disease, including primary prostate malignancy, bone, and lymph node metastases. This patient was treated with hormonal therapy and docetaxel.



[B] A 69-year-old high-risk patient (Gleason 9, PSA 46.3) with extensive lymphatic and skeletal metastatic disease. Top row (from left to right): trans-axial CT, PET, and fusion images of PSMA uptake in the entire prostate gland (maximal SUV 17.4) and in a blastic lesion in the left pubic bone (arrow). Bottom row (from left to right): trans-axial CT, PET, and fusion images of PSMA uptake in L1 vertebral body and pedicle, with extension of disease into the spinal canal (arrowhead). Right: maximum intensity image (mip) showing the extent of disease. This patient was treated with radiation therapy to the L1 vertebra in addition to hormonal therapy and docetaxel

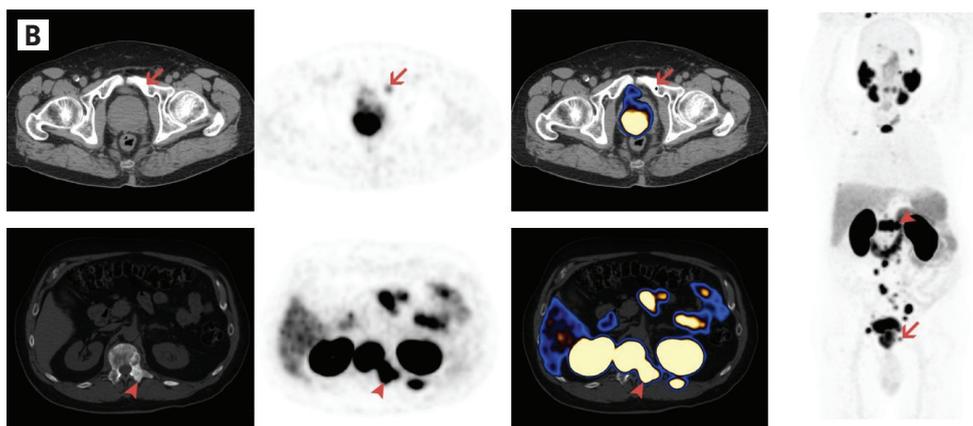


Figure 2. Correlation between prostate cancer SUVmax and PSA. SUVmax values were plotted against PSA values

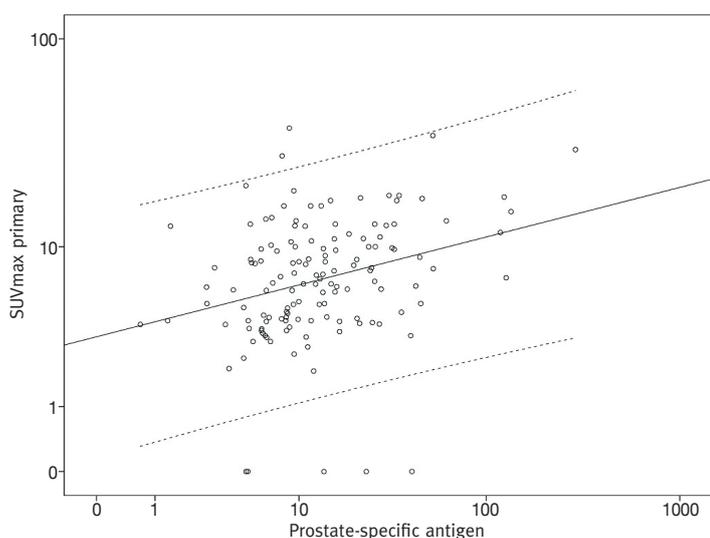


Table 2. ⁶⁸Ga-PSMA PET/CT measures

PCa SUVmax	Mean ± SD 8.5 ± 5.2	
Extent of uptake in prostate, n (%) (Total no. of patients, 137)	Bilateral	75 (55%)
	Unilateral	57 (42%)
	No uptake	5 (3%)
Seminal vesicles uptake, n (%)	16 (11.6%)	
Metastatic disease, n (%)	Total	35 (25.5%)
	Pelvic lymph nodes	26 (19%)
	Extra-pelvic lymph nodes	9 (6.5%)
	Bone	15 (11%)
	Viscera (lung)	1 (0.7%)

lesions were also evident on ^{99m}Tc-MDP BS. Of the 18/26 bone lesions (69%) detected solely by ⁶⁸Ga-PSMA PET, 4 were marrow-based lesions with normal bone morphology. Thirteen BS lesions showed no corresponding ⁶⁸Ga-PSMA uptake, and 9 of them were considered to be false-positive benign lesions based on correlation with CT and MRI findings.

DISCUSSION

In this study we evaluated the findings of ⁶⁸Ga-PSMA PET/CT studies undertaken in 137 consecutive patients with intermediate- and high-risk prostate cancer. PSMA PET detected metastases to the lymph nodes, viscera, and bone in 25.5% of patients. Importantly, more than two-thirds of the bone lesions identified on PET/CT were missed by standard bone scintigraphy.

⁶⁸Ga-PSMA PET/CT is gaining acceptance as a highly accurate imaging modality for primary staging of intermediate- and high-risk prostate cancer. Maurer et al. [13] retrospectively compared the performance of ⁶⁸Ga-PSMA PET/CT in staging 130 intermediate- to high-risk patients to that of conventional imaging modalities (i.e., CT, MRI) and found ⁶⁸Ga-PSMA PET/CT to be more sensitive, specific and accurate (65.9% vs. 43.9%, 98.9% vs. 85.4%, and 88.5% vs. 72.3%, respectively).

The present study evaluated the added value of ⁶⁸Ga-PSMA PET/CT in the initial staging of consecutive patients with newly diagnosed intermediate- or high-risk prostate cancer with the aim of assessing its potential role in defining the extent of disease. ⁶⁸Ga-PSMA PET/CT failed to identify the primary tumor site in 5 patients (3%), which is less than the 8.4% reported by Maurer et al. [13] and the 8.9% reported by Uprimny et al. [19]. The intensity of ⁶⁸Ga-PSMA PET/CT in the primary site (measured as SUV max) correlated with PSA levels, a finding that is compatible with those of Uprimny et al. [19] and Fendler et al. [17]. No significant correlation was found between SUVmax and the presence of metastatic disease or with Gleason score, in contrast to previously reported findings [19].

Metastatic disease was suggested on ⁶⁸Ga-PSMA PET/CT in 35 (25.5%) of our patients, reinforcing its value in the initial workup of intermediate- and high-risk patients. While there was no validating biopsy in these suspected metastatic lesions, we believe that this represents the routine clinical scenario where clinicians rely on PET findings and do not insist on invasive corroboration of the findings on imaging studies.

Our results support previous observations [20] that ⁶⁸Ga-PSMA PET/CT is superior to bone scintigraphy in detecting skeletal spread by its ability to identify lytic type metastases as well as marrow-based metastases. Moreover, BS is prone to false-positive uptake in benign lesions, while ⁶⁸Ga-PSMA PET is more specific. Therefore, it is suggested that routine BS can be omitted in most cases in the era of ⁶⁸Ga-PSMA PET/CT staging.

We are aware that our study may have some limitations related to its retrospective design and some unavoidable inherent biases due to missing data and subgroup analyses. Since the vast majority of our study patients underwent

radiation treatment and not definitive surgery, no histopathological data from radical prostatectomy specimens or lymphadenectomies were available as the gold standard. Moreover, no bone biopsies were performed.

CONCLUSIONS

The introduction of ⁶⁸Ga-PSMA PET/CT in the staging algorithm in routine practice in Israel allowed the assessment of the role of this modality in a retrospective study of consecutive patients with intermediate- or high-risk newly diagnosed prostate cancer. The results of this study show promise for ⁶⁸Ga-PSMA PET/CT as a sole whole-body imaging modality for assessing the presence of soft tissue and bone metastases.

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Capsule

Taking kidney fibrosis to TASC

The kidney, like other organs, has an inherent capacity to recover from acute injury; however, severe injury can lead to chronic kidney disease and fibrosis. **Canaud** and co-authors studied the maladaptive response to injury of kidney epithelial cells. The formation of target of rapamycin–autophagy spatial coupling compartments (TASCs) in cells was associated with cell-cycle arrest and fibrosis in human chronic kidney

disease. Furthermore, knocking out cyclin G1 prevented TASC formation and fibrosis in mouse models. These findings provide mechanistic insight into renal fibrosis and suggest a potential therapeutic target.

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Eitan Israeli

Capsule

L1 drives IFN in senescent cells and promotes age-associated inflammation

Retrotransposable elements are deleterious at many levels, and the failure of host surveillance systems for these elements can thus have negative consequences. However, the contribution of retrotransposon activity to ageing and age-associated diseases is not known. **De Cecco** et al. show that during cellular senescence, L1 (also known as LINE-1) retrotransposable elements become transcriptionally derepressed and activate a type-I interferon (IFN-I) response. The IFN-I response is a phenotype of late senescence and contributes to the maintenance of the senescence-associated secretory phenotype. The IFN-I response is triggered by cyto-

plasmic L1 cDNA, and is antagonized by inhibitors of the L1 reverse transcriptase. Treatment of aged mice with the nucleoside reverse transcriptase inhibitor lamivudine down-regulated IFN-I activation and age-associated inflammation (inflammaging) in several tissues. The authors propose that the activation of retrotransposons is an important component of sterile inflammation that is a hallmark of aging, and that L1 reverse transcriptase is a relevant target for the treatment of age-associated disorders.

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Capsule

Microbial network disturbances in relapsing refractory Crohn's disease

Inflammatory bowel diseases (IBD) can be broadly divided into Crohn's disease (CD) and ulcerative colitis (UC) from their clinical phenotypes. Over 150 host susceptibility genes have been described, although most overlap between CD, UC and their subtypes, and they do not adequately account for the overall incidence or the highly variable severity of disease. Replicating key findings between two long-term IBD cohorts, **Yilmaz** et al. defined distinct networks of taxa associations within intestinal biopsies of CD and UC patients. Disturbances in an association network containing taxa of

the Lachnospiraceae and Ruminococcaceae families, typically producing short chain fatty acids, characterize frequently relapsing disease and poor responses to treatment with anti-TNF α therapeutic antibodies. Alterations of taxa within this network also characterize risk of later disease recurrence of patients in remission after the active inflamed segment of CD has been surgically removed.

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