JMeXFRI

Journal of the Mexican Federation of Radiology and Imaging

Check for updates

FULL RESEARCH ARTICLE

The PROMISE-V2 PRIMARY score and SULmax [^{18}F]PSMA-1007 PET/CT in primary staging of prostate cancer

J. Antonio Serna-Macias[1,2], *M. Lourdes Garcia-Colmenero*[3*], *Emilly A. Cortes-Mancera*[4], *E. David Muñoz-Carpio*[5], *and Mixel Z. Baltierra-Hernandez*[5]

[1]*Postgraduate of High Specialty in Positron Emission Tomography/Computed Tomography, Universidad Nacional Autonoma de Mexico, Mexico City;* [2]*Radiology and Imaging Service, Hospital Angeles Pedregal, Mexico City;* [3]*Departamento de Imagen Molecular – PET/CT, CID Centro de Imagen y Diagnostico, Guadalajara, Jalisco;* [4]*Servicio de Medicina Nuclear, Hospital Central Sur de Alta Especialidad, Petroleos Mexicanos. Mexico City;* [5]*Departamento de Atencion a la Salud, Unidad Xochimilco, Universidad Autonoma Metropolitana. Mexico City. Mexico*

ABSTRACT

Introduction: The PRIMARY score of the PROMISE-V2 criteria for primary staging of prostate cancer (PCa) and its relationship with the maximum standardized uptake value normalized to lean body mass (SULmax) have not been evaluated. This study determined the relationship between the SULmax value in [^{18}F]PSMA-1007 PET/CT and the PROMISE-V2 PRIMARY score in patients with untreated PCa in primary staging. **Material and Methods:** This cross-sectional study included patients with PCa in primary staging. The SULmax value [^{18}F]PSMA-1007 PET/CT of the intraprostatic lesion was recorded, and the PRIMARY score was assessed based on the pattern of affected prostate zones (peripheral, transitional, or central) and the distribution of prostate-specific membrane antigen (PSMA) uptake (focal or diffuse). Lymph node (pelvic or extrapelvic) spread and metastasis (bone, lung, and/ or brain) were determined. **Results:** Fifty-five patients with PCa at primary staging were included. The SULmax value of an intraprostatic tumor in PRIMARY score 2 was 5.15 ± 0.54 g/mL; in PRIMARY score 3, 7.11 g/mL; in PRIMARY score 4, 8.31 ± 1.92 g/mL, and in PRIMARY score 5, 22.64 ± 7.77 ($p < 0.001$). The SULmax value of [^{18}F]PSMA increased in direct association with the PRIMARY score in cases with an intraprostatic tumor (11.49 ± 6.69 g/mL ($p < 0.001$) and an intraprostatic tumor + pelvic lymph nodes (15.17 ± 9.72 g/mL). In contrast, cases with extrapelvic lymph nodes or metastases (bone, brain, or lung) had lower SULmax values (12.43 ± 8.73 g/mL) ($p < 0.001$). **Conclusion**: Our study showed an association between the SULmax value and the PRIMARY score according to the affected anatomical zone, the expression patterns and a SULmax > 12 g/mL. The expression of PSMA uptake in the local tumor was highest in the pattern of focal involvement in the peripheral zone (PZ) as long as the disease was confined to the pelvis.

Keywords: *Prostate cancer. Prostate-specific membrane antigen. Positron emission tomography/computed tomography. SULmax value. PCa primary staging. Prostate cancer molecular imaging standardized evaluation.*

INTRODUCTION

Prostate cancer (PCa) is the second most common neoplasm in men[1,2]. At the time of diagnosis, 10 to 20% of patients have locally advanced disease and 8 to 35% distant metastatic disease[3]. Positron emission tomography/computed tomography (PET/CT) with prostate-specific membrane antigen (PSMA) is a hybrid imaging modality that detects and defines local and/or distant PCa and provides information on tumor biology, disease prognosis and treatment planning[4]. Intraprostatic tumors can be detected qualitatively by visual assessment of lesions based on their pattern and location or quantitatively by radiopharmaceutical uptake in a target lesion using the maximum standardized uptake value (SUVmax) and a comparison with normal tissue[5].

***Corresponding author:**
M. Lourdes Garcia-Colmenero
E-mail: lula.gacol@gmail.com

Received for publication: 10-06-2024
Accepted for publication: 12-09-2024
DOI: 10.24875/JMEXFRI.M24000091

Available online: 20-12-2024
J Mex Fed Radiol Imaging. 2024;3(4):243-255
www.JMeXFRI.com

2696-8444 / © 2024 Federación Mexicana de Radiología e Imagen, A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Several factors influence the SUVmax.[6] It is relatively higher in obese patients than thinner patients. One study found that SUV correction for lean body mass, known as the maximum standardized uptake value normalized to lean body mass (SULmax) radiotracer concentration, is a more appropriate quantitative method,[6] suggesting that SULmax is preferable to SUVmax for quantitative analysis[7]. Some authors[8-12] have analyzed the SUVmax according to the prostate zone, area, uptake pattern, and segmentation, similar to intraprostatic biopsy. It has also been described that a high SULmax value is related to the presence of metastases[10,11,13,14].

The PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation) criteria define guidelines for clinical trial design and self-reporting of molecular imaging in PCa[15]. In 2023, the second version, PROMISE-V2, was published with two standardized hierarchy levels by whole-body molecular imaging TNM staging (miTNM) and PSMA expression for primary staging (PRIMARY score) or recurrence (PSMA expression score) in patients with PCa[16]. The reproducibility and clinical application of the PRIMARY score in patients with primary staging of PCa have not been sufficiently evaluated. In addition, the relationship between the SULmax and zone involvement and the pattern of PSMA expression proposed in the PRIMARY score has not been defined. This study determined the relationship between SULmax on [^{18}F]PSMA-1007 PET/CT and the PROMISE-V2 PRIMARY score in patients with untreated PCa undergoing primary staging.

MATERIAL AND METHODS

A cross-sectional study was conducted from June 1, 2019, to May 31, 2023, in the Radiology and Imaging Service of the Hospital Angeles Pedregal in Mexico City, Mexico. Patients with histopathologically confirmed PCa for primary staging were referred by oncology, urology, and radiation oncology specialists for PET/CT examination with [^{18}F]PSMA-1007. Patients without information on prostate-specific antigen (PSA), a Gleason score, or previously treated PCa were excluded. Informed consent was not requested due to the observational and retrospective design of the study. The Institutional Research Ethics and the Research Committees approved the protocol.

Study development and variables

The information was obtained from the clinical records. The variables included were age, the [^{18}F]PSMA-1007 dose administered to perform PET/CT, the PSA value, and the Gleason score. The SULmax value of the intraprostatic lesion from the [^{18}F]PSMA PET/CT examination and the presence or absence of lymph node spread (pelvic or extrapelvic) and metastases (bone, lung, brain) were recorded.

Definitions

Primary staging: patients with a recent and confirmed diagnosis of PCa without treatment before the [^{18}F]PSMA PET/CT.

Tumor staging: organ-confined tumor (unifocal or multifocal); non-organ-confined tumor (extracapsular extension and/or tumor invading the seminal vesicle[s]); tumor invading adjacent structures such as the external sphincter, rectum, bladder, levator muscles, and/or pelvic wall[15,16].

Pelvic lymph nodes: internal iliac, external iliac, obturator, presacral, and other pelvic lymph nodes[15,16].

Metastasis: extrapelvic lymph nodes (common iliac, retroperitoneal, supradiaphragmatic, inguinal, other extrapelvic); bone uptake patterns (unifocal, oligometastatic, disseminated, diffuse bone marrow involvement); other involved organs (lung and brain)[15,16].

PRIMARY score: a staging system for intraprostatic lesions in men diagnosed with previously untreated PCa[8,9,16]:

Score 1: no dominant intraprostatic pattern; low-grade activity.
Score 2: diffuse activity in the transition zone (TZ) or symmetric activity in the central zone (CZ) that does not extend to the prostate margin on CT.
Score 3: focal TZ activity that is visually twice as high as background activity.
Score 4: focal activity in the peripheral zone (PZ) (no minimum intensity).
Score 5: PSMA SUVmax >12. In this study, SULmax was used to replace SUVmax with comparable values.

SULmax: maximum standardized uptake value normalized to the lean body mass concentration of the radiotracer [^{18}F]PSMA-1007, measured in g/mL[5,17].

Gleason score: low-risk PCa (Gleason score 6 = 3 + 3), intermediate-risk PCa (Gleason score 7 = 3 + 4/4 + 3, and 8), and high-risk PCa (Gleason score > 8)[18]. Intermediate and high-risk Gleason scores were considered together in the study analysis.

miTNM system: the staging system proposed by PROMISE-V2 allows standardized reporting of [^{18}F]PSMA by tumor stage, nodal stage, and distant metastases[16].

Imaging protocol and analysis

PET/CT acquisition was performed with the hybrid PET/CT Philips Vereos Digital (Philips Medical Systems Technologies Ltd, Haifa, Israel) with the patient supine after intravenous administration of [^{18}F]PSMA-1007 with a biodistribution time of 60 minutes. CT acquisition in 64-slice, multidetector, helical equipment was performed with axial slices from the convexity of the skull to the medial third of the thighs in single phase and/or after administration of oral and intravenous water-soluble contrast agent, as needed, for attenuation correction and anatomical localization. PET images were reconstructed using the iterative method and analyzed with and without CT image fusion on a medical-grade workstation (Philips, Shanghai, China).

The SULmax value was determined using software (IntelliSpace Portal IX/XL version 7.2, Philips, Amsterdam, The Netherlands) in the region of interest (ROI) with the features described below. The SULmax value was quantified in the intraprostatic lesion (≥10 mm) to ensure adequate spatial resolution with a ROI of 1 cm diameter over the voxel with maximum uptake in the axial plane.

According to the PRIMARY score, the pattern of tumor involvement in the prostatic zones (TZ, CZ, PZ) was recorded and based on the combination of the intraprostatic pattern and the uptake intensity of the radiotracer [^{18}F]PSMA-1007 (Figure 1**)**. The local morphological extent of the tumor was also determined by CT: tumor confined to the prostate, involvement of the capsule/seminal vesicles, or infiltration of adjacent structures (external sphincter, rectum, urinary bladder, pelvic wall, or levator muscles). The findings were reported by an experienced nuclear medicine physician (JASM) with 20 years of experience in PET/CT.

Statistical analysis

The mean, standard deviation, minimum, median, and maximum SULmax value of intraprostatic tumor and its relation with the PROMISE-V2 PRIMARY score and extent of PCa and the mean, standard deviation, minimum, median and maximum SULmax value of the prostate tumor and PSA levels were determined according to the location and extent of PCa. The p-value for normality was calculated using the Kolmogorov-Smirnov or the Shapiro-Wilk test. The OR was calculated for the expression patterns [^{18}F]PSMA (PRIMARY score) and

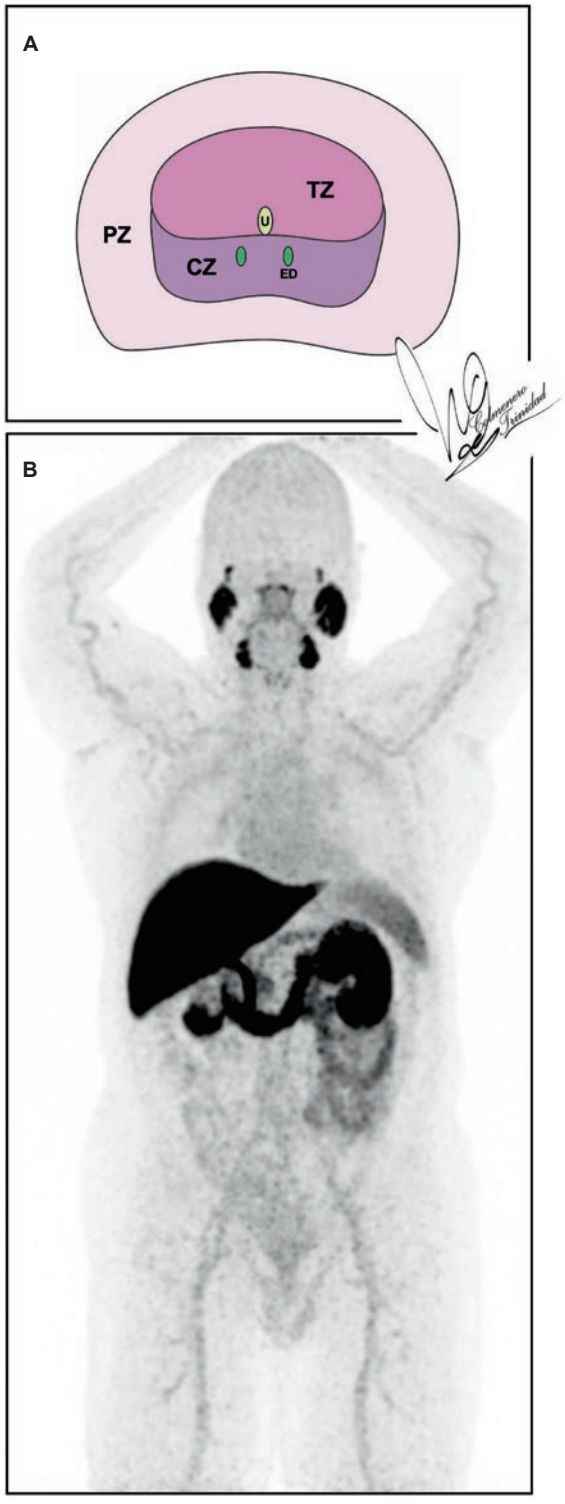

Figure 1. A: diagram of the anatomical zones of the prostate defined in the PSMA PET/CT expression patterns in the PRIMARY score. **B:** normal biodistribution of PSMA-PET on a maximum intensity projection (MIP) in lacrimal glands, parotid glands, liver, spleen, stellate ganglia, renal parenchyma, and bladder, mainly biliary excretion.

CZ: central zone; ED: ejaculatory ducts; PET/CT: positron emission tomography/computed tomography; PSMA: prostate-specific membrane antigen; PZ: peripheral zone; TZ: transition zone; U: urethra.

Table 1. Relationship between the intraprostatic tumor SULmax value and the PRIMARY score and the extent of PCa in primary staging

Description[a]	Total (n = 55)	Intraprostatic tumor SULmax, g/mL	p
PRIMARY score 2, n (%)	3 (5.0)	5.15 ± 0.54 (4.7, 4.9, 5.7)	ns
PRIMARY score 3, n (%)	1 (2.0)	7.11	-
PRIMARY score 4, n (%)	35 (64.0)	8.31 ± 1.92 (5.3, 8.5, 11.6)	ns
PRIMARY score 5, n (%)	16 (29.0)	22.64 ± 7.77 (13.3, 19.1, 35.9)	< 0.001
PCa local tumor and extent	Total (n = 55)	Intraprostatic tumor SULmax, g/mL	p
Intraprostatic tumor only, n (%)	24 (43.6)	11.49 ± 6.69 (4.7, 9.6, 31.2)	< 0.001
Intraprostatic tumor and pelvic lymph nodes, n (%)	9 (16.4)	15.17 ± 9.72 (5.9, 11.6, 32.4)	ns
Intraprostatic tumor and metastases (extrapelvic lymph nodes, bone, brain, and/or lung), n (%)	22 (40.0)	12.43 ± 8.73 (5.3, 9.0, 35.9)	< 0.001

All values are means ± SD (minimum, median, maximum). [a]Primary score 1 no patients.

[^{18}F]: radionuclide fluor-18; PSMA: prostate-specific membrane antigen; 1007: ligand; ns: not significant; PCa: prostate cancer; PET/CT: positron emission tomography/computed tomography; SULmax: standardized uptake value maximum normalized to the lean body mass of PSMA.

disease spread with the Gleason score risk. Significance was defined as a p-value < 0.05. The analysis was performed with SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Sixty-three PCa patients were eligible to participate. Eight men were excluded because a radiopharmaceutical other than [^{18}F]PSMA-1007 was used. Fifty-five patients were included in the primary staging of PCa. The mean age was 65.1 ± 10.0 years. A mean of 9.50 millicuries (mCi) of [^{18}F]PSMA was administered.

Relationship between the SULmax value and the PRIMARY score and the extent of PCa in primary staging

The mean intraprostatic tumor SULmax value for score 2 was 5.15 ± 0.54 g/mL; for score 3, it was 7.11 g/mL; for score 4, the value was 8.31 ± 1.92 g/mL; and for score 5, it was 22.64 ± 7.77 g/mL (p < 0.001) (Table 1). The SULmax value of [^{18}F]PSMA increased in direct association with the increase in the PRIMARY score (Figure 2). The SULmax value was 11.49 ± 6.69 g/mL in 24 (43.6%) patients with intraprostatic tumor (p < 0.001), while it was 15.17 ± 9.72 g/ml in 9 (16.4%) patients with intraprostatic tumor + pelvic lymph nodes. In contrast, in 23 (40.0%) patients with intraprostatic tumor + metastases (extrapelvic lymph nodes, bone, brain, and/or lung), the SULmax value decreased to 12.43 ± 8.73 g/mL (p < 0.001).

Regarding the morphological local extension of the tumor, the distribution was 30 patients had miT2, tumor confined to the intraprostatic gland (focal or multifocal pattern); 20 patients had miT3, tumor involving the prostatic capsule and/or seminal vesicles. Only 5 patients had infiltration of adjacent structures such as the external anal sphincter, rectum, bladder, pelvic wall, or levator muscles (miT4) (Figure 3).

PSA value and its relationship with the PRIMARY score and extent of PCa in primary staging

The PSA, in relation to the PRIMARY score, showed increased values for scores 2, 4, and 5 (Table 2). The PSA value for score 2 was 7.82 ± 0.87 ng/mL; scores 4 and 5 were 20.11 ± 27.22 ng/mL and 42.15 ± 48.15 ng/mL, respectively (p < 0.001). In one case with score 3, the PSA was 131.9 ng/mL. PSA values gradually increased depending on the extent of PCa and were 15.75 ± 26.35 ng/mL in patients with intraprostatic tumors (p < 0.001). The PSA increased to 20.93 ± 20.15 ng/mL in patients with pelvic lymph nodes. In the presence of metastases (extrapelvic lymph nodes, bone, brain, and/or lung), the PSA value was higher, with a mean of 43.97 ± 48.05 ng/mL (Figures 4, 5, and 6).

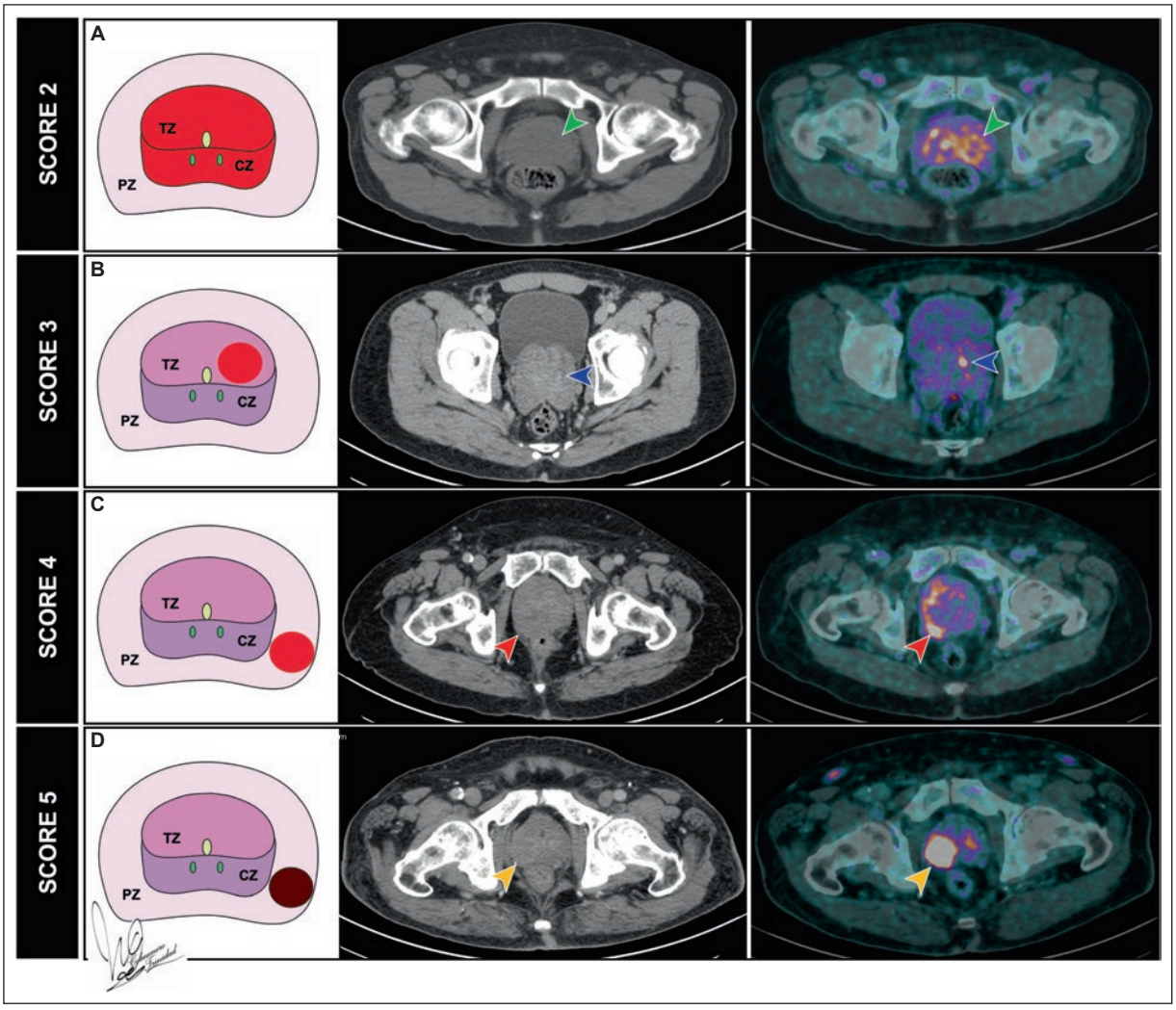

Figure 2. PSMA expression patterns of the PRIMARY score are shown in the diagram, CT, and PET/CT, axial projection. **A:** score 2, diffuse TZ activity or symmetric CZ activity that does not extend to the prostate margin on CT (green arrowheads). **B:** score 3, focal TZ activity that is visually twice as high as the background TZ activity (blue arrowheads). **C:** score 4, focal PZ activity, no minimum intensity (red arrowheads). **D:** score 5, PSMA SUVmax >12 (yellow arrowheads). In this study, SULmax was used to replace SUVmax with comparable values.

CT: computed tomography; CZ: central zone; PET/CT: positron emission tomography/computed tomography; PSMA: prostate-specific membrane antigen; PZ: peripheral zone; SULmax: standardized uptake value maximum normalized to the lean body mass concentration of the radiotracer [^{18}F]PSMA-1007; SUVmax value: standardized uptake value maximum; TZ: transition zone.

Figure 7 shows the boxplot of PSA values in relation to the PRIMARY score and extent of PCa. PSA values were higher for PZ (score 4), and PZ /SULmax was > 12 (score 5) ($p = 0.019$), and according to disease progression, the more advanced the disease, the higher the PSA values ($p < 0.001$). PSA outlier values (127 ng/mL, 128 ng/mL, 131.9 ng/mL, and 174 ng/mL) are not shown in the figure.

A high number of scores of 4 and 5 was found in the PZ location of intraprostatic tumor with a focal pattern and/or SULmax > 12 g/mL, followed by intraprostatic tumor + extrapelvic lymph nodes and metastases (bone, brain, and/or lung). Scores 2 and 3, located in CZ and TZ, had a symmetric and/or focal diffuse pattern with disease often confined to the prostate (Figure 8).

Association of PRIMARY score with Gleason score risk in patients with PCa in primary staging

An [^{18}F]PSMA expression pattern in PZ and/or SULmax > 12 g/mL and a low-risk Gleason score was found in 5 (71.4%) of 7 patients, while 46 (96.0%) of 48 patients had an intermediate- or high-risk Gleason

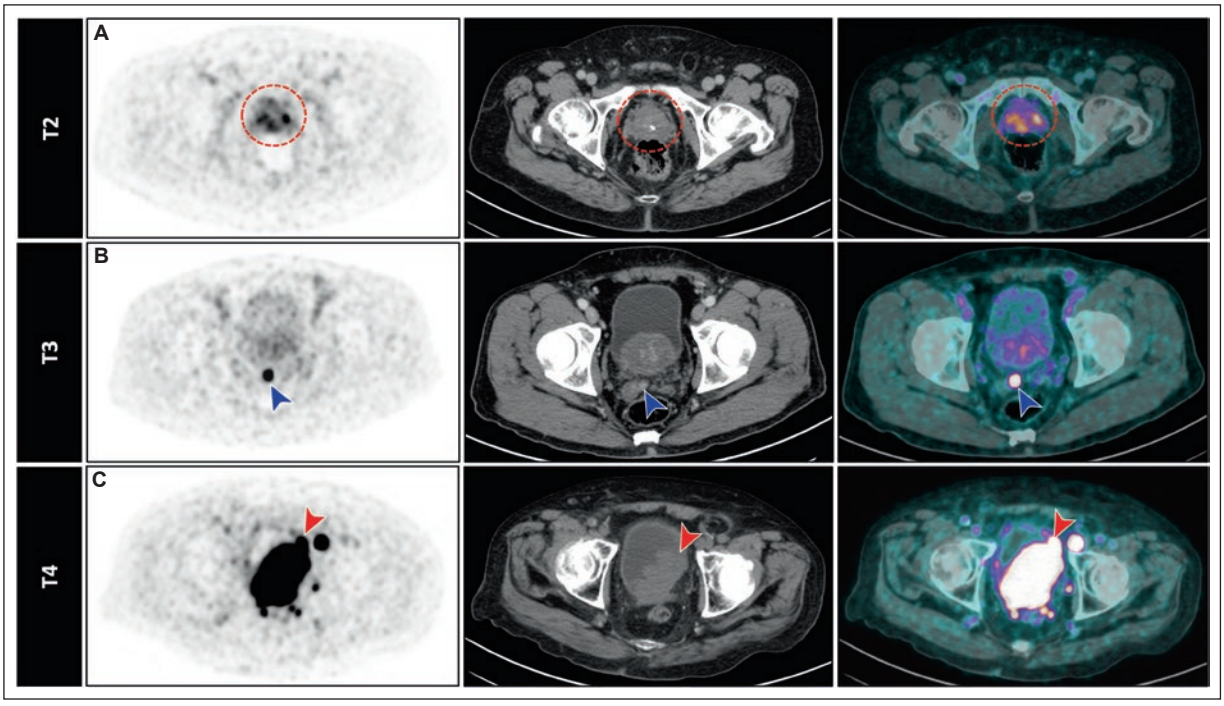

Figure 3. Intraprostatic tumor (miT) characteristics: maximum intensity images, CT and PET/ CT, axial projection. **A:** miT2, the tumor is confined to the prostate (dotted red circle). **B:** miT3, the tumor is not confined to the prostate but extends to the seminal vesicles (blue arrowheads). **C:** miT4, the tumor invades adjacent structures beyond the seminal vesicles (red arrowheads).

CT: computed tomography; miT: molecular tumor imaging; PET/CT: positron emission tomography/computed tomography.

Table 2. PSA value and its relationship with the PRIMARY score and extent of PCa in primary staging

Description[a]	Total (n = 55)	PSA, ng/mL	p
PRIMARY score 2, n (%)	3 (5.4)	7.82 ± 0.87 (6.9, 7.8, 8.6)	ns
PRIMARY score 3, n (%)	1 (1.8)	131.9	-
PRIMARY score 4, n (%)	35 (63.7)	20.11 ± 27.22 (3.9, 12.0, 128.0)	< 0.001
PRIMARY score 5, n (%)	16 (29.1)	42.15 ± 48.15 (3.3, 22.8, 174.0)	< 0.001
PCa local tumor and extent	**Total (n = 55)**	**PSA, ng/mL**	**p**
Intraprostatic tumor only, n (%)	24 (43.6)	15.75 ± 26.35 (3.3, 7.8, 131.9)	< 0.001
Intraprostatic tumor and pelvic lymph nodes, n (%)	9 (16.4)	20.93 ± 20.15 (4.9, 15.1, 69.0)	ns
Intraprostatic tumor and metastases (extrapelvic lymph nodes, bone, brain, and/or lung), n (%)	22 (40.0)	43.97 ± 48.05 (6.9, 20.2, 174.0)	ns

[a]Primary score 1 no patient. All values are means ± SD (minimum, median, maximum).

ns: not significant; PCa: prostate cancer; PSA: prostate-specific antigen.

score (Table 3). There were 2 (28.6%) of 7 patients with a [^{18}F]PSMA expression pattern in CZ or TZ (score 2 and 3) with a low Gleason risk, while an intermediate or high Gleason score risk was found in two (4.0%) of 48 patients. A significant risk association of focal [^{18}F] PSMA expression in the ZP or SULmax >12 g/mL had an intermediate or high-risk Gleason score (OR: 9.20, 95% CI 1.05 - 80.28).

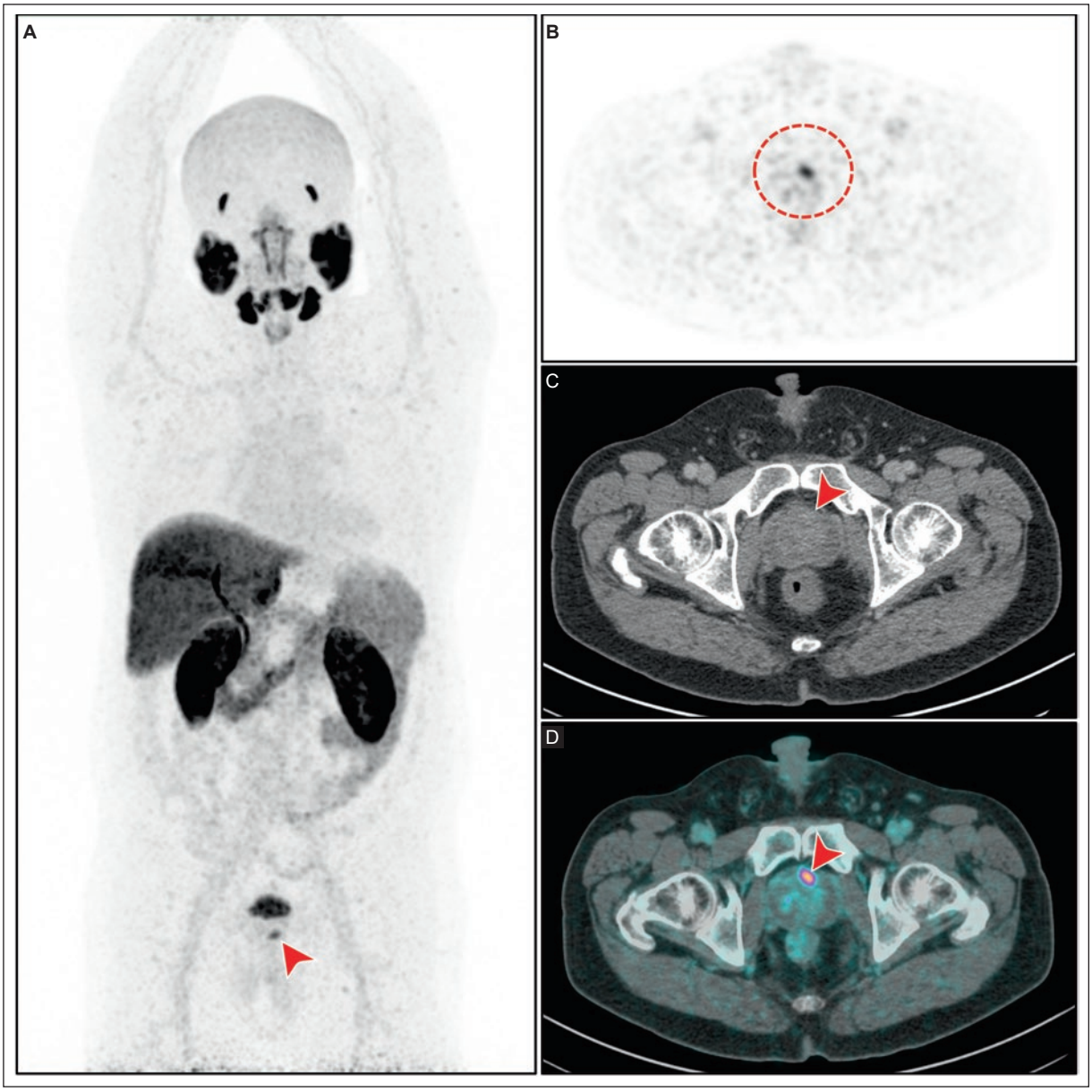

Figure 4. A 60-year-old man in primary staging of PCa. PSA 12.15 ng/mL. Gleason score 7 (3 + 4). **A:** a maximum intensity projection shows the physiologic distribution of the radiotracer with abnormal uptake of PSMA in the prostate (red arrowhead). No spread to pelvic lymph nodes or metastases was detected. **B:** PET, abnormal uptake of the intraprostatic PSMA tumor (dotted red circle). **C:** CT scan; PZ of the prostate shows a lobulated lesion with a partially defined border, homogeneous with enhancement, 15 x 9 mm (red arrowhead). **D:** [^{18}F]PSMA PET/CT fusion, intraprostatic lesion in the PZ with focal PSMA uptake, SULmax value 8.68 g/mL (red arrowhead).

[^{18}F]: radionuclide fluor-18; CT: computed tomography; PCa: prostate cancer; PET/CT: positron emission tomography/computed tomography; PSA: prostate-specific antigen (ng/mL); PSMA: prostate-specific membrane antigen; PZ: peripheral zone; SULmax: standardized uptake value maximum normalized to the lean body mass concentration of the radiotracer [^{18}F]PSMA-1007.

Risk association of local intraprostatic tumor and extent with the Gleason score in primary staging of PCa

We found 6 (86.0%) of 7 patients with an intraprostatic tumor, with or without pelvic lymph nodes and a low-risk Gleason score, and 27 (57.2%) of 48 patients with an intermediate- or high-risk Gleason score (Table 4). There was only one (14.0%) patient with an intraprostatic tumor and metastases (extrapelvic lymph nodes, bone, brain, and/or lung) and a low-risk Gleason score; in contrast, there were 21 (43.4%) patients with an intermediate- or high-risk Gleason score (OR 4.66, 95% CI, 0.52-41.80).

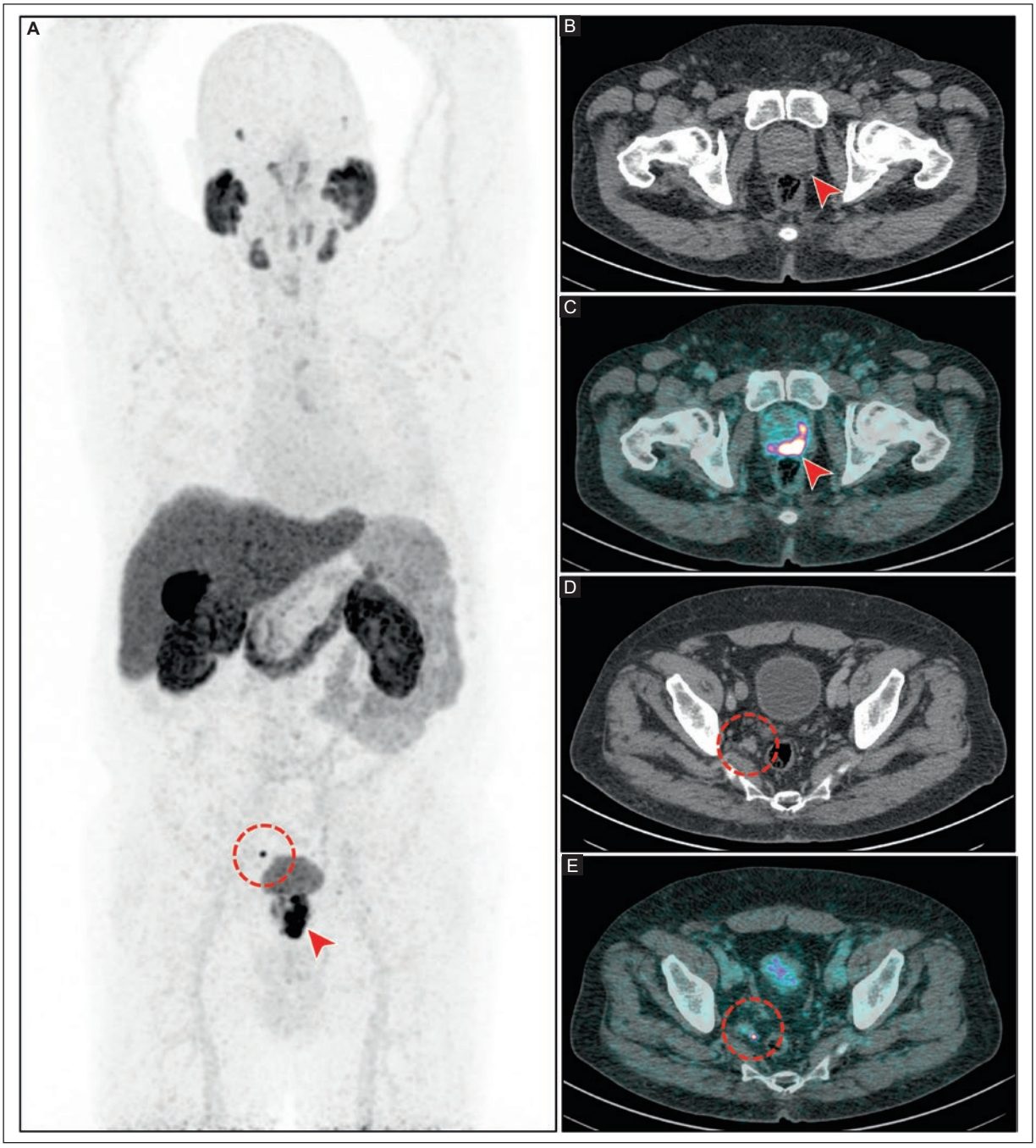

Figure 5. An 80-year-old man in primary staging of PCa. PSA 31 ng/mL. Gleason score of 7 (4 + 3). **A:** maximum intensity projection showing a physiologic distribution of the radiotracer with abnormal PSMA uptake in the prostate (red arrowhead) and pelvic lymph nodes (dotted red circle). No spread to extrapelvic lymph nodes or metastases (bone, brain, or lung) was detected. **B:** CT scan; a multilobular lesion in the PZ of the prostate with a poorly defined margin, homogeneous with enhancement, 12 x 8 mm (red arrowhead). **C:** [^{18}F]PSMA PET/CT fusion**,** intraprostatic tumor in the PZ with abnormal focal uptake and a SULmax value of 28.76 g/mL (red arrowhead). **D:** CT, oval, 7 mm pelvic lymph node of the right internal iliac chain (dotted red circle). **E)** [^{18}F]PSMA PET/CT fusion**;** abnormal PSMA uptake in the right inner iliac chain (dotted red circle).

[^{18}F]: radionuclide fluor-18; CT: computed tomography; PCa: prostate cancer; PET/CT: positron emission tomography/computed tomography; PSA: prostate-specific antigen (ng/mL); PSMA: prostate-specific membrane antigen; PZ: peripheral zone; SULmax: standardized uptake value maximum normalized to lean body mass of PSMA.

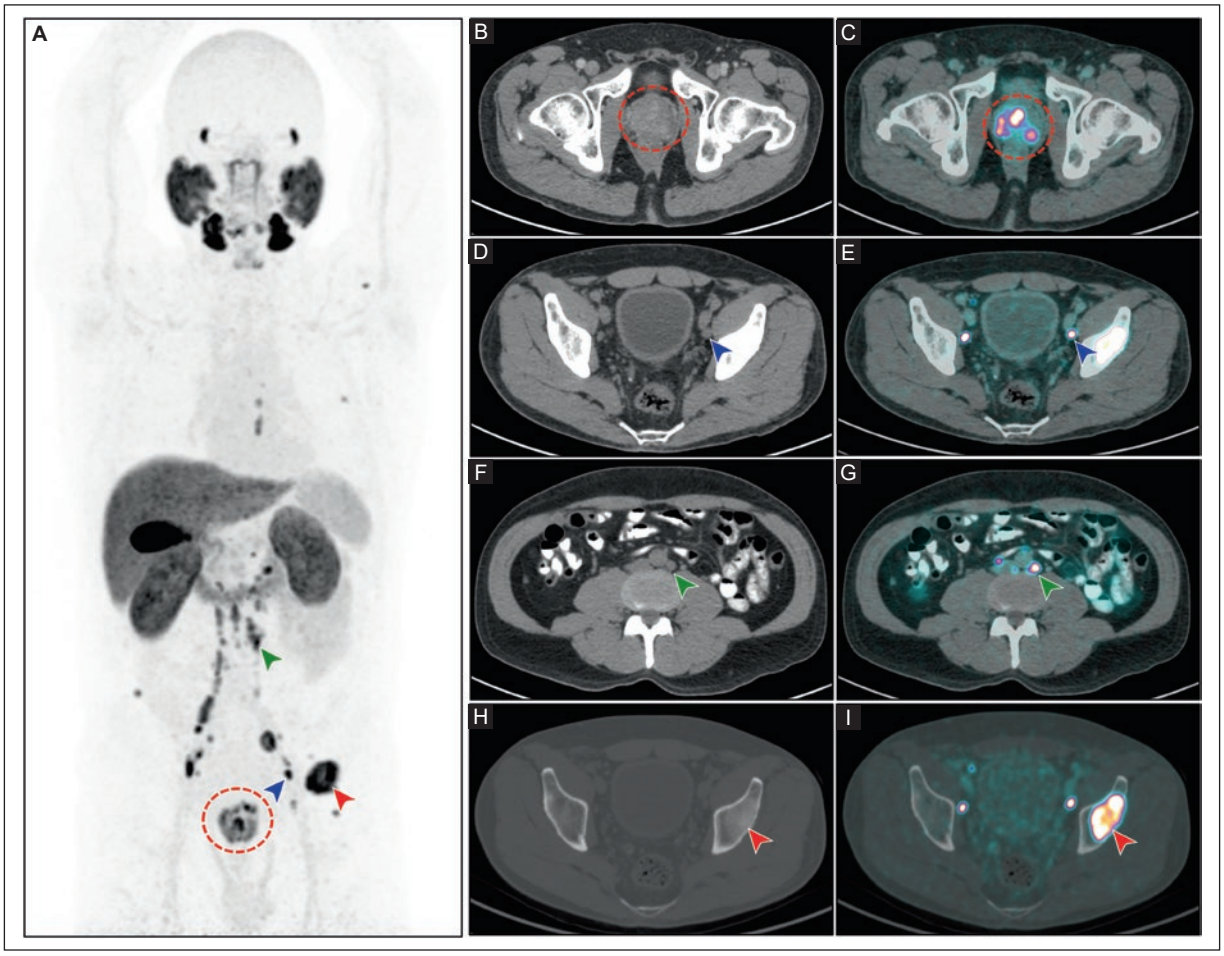

Figure 6. A 61-year-old man with PCa in primary staging. PSA 74 ng/mL with a Gleason score of 9 (5 + 4). **A:** maximum intensity projection with physiologic distribution of radiotracer showing abnormal PSMA uptake in the prostate (dotted red circle), multiple pelvic lymph nodes (blue arrowhead), multiple extrapelvic lymph nodes (green arrowhead), and bone metastases with disseminated pattern (red arrowhead). **B:** CT: multiple hyperdense lesions are observed in the prostate apex (PZ) with a defined border and homogeneous content, with the largest measuring 16 mm (dotted red circle). **C:** [^{18}F]PSMA PET/CT fusion, intraprostatic tumor in the apex (PZ) with abnormal multifocal uptake, SULmax 18.91 g/mL (dotted red circle). **D:** CT, multiple (> 2) pelvic lymph nodes of the inner and outer iliac chains, round margin, 9 mm in size (blue arrowhead). **E:** [^{18}F]PSMA PET/CT fusion, abnormal PSMA uptake in multiple (> 2) pelvic lymph nodes at the inner and outer iliac chains (blue arrowhead). **F:** CT, lymph nodes in the retroperitoneum (paraaortic and paracaval), measuring 7 mm (green arrowhead). **G:** [^{18}F]PSMA PET/CT fusion, abnormal focal uptake in the retroperitoneum, paraaortic and paracaval (green arrowhead). **H:** CT, left acetabulum with osteoblastic lesion, cortical bone preserved (red arrowhead). **I:** [^{18}F]PSMA PET/CT fusion, abnormal focal uptake of an osteoblastic lesion in the left acetabulum (red arrowhead). [^{18}F]: radionuclide fluor-18; CT: computed tomography; PCa: prostate cancer; PET/CT: positron emission tomography/computed tomography; PSA: prostate-specific antigen (ng/mL); PSMA: prostate-specific membrane antigen; PZ: peripheral zone; SULmax: standardized uptake value maximum normalized to the lean body mass of PSMA (g/mL).

DISCUSSION

In this study, the SULmax was associated with the expression patterns of [^{18}F]PSMA-1007 PET/CT according to the PROMISE-V2 PRIMARY score in PCa patients in primary staging. The highest SULmax was associated with PRIMARY scores 4 and 5, increased intensity of [^{18}F]PSM-1007 PET/CT expression, and involvement of the PZ. This study is the first that demonstrates the association between the highest SULmax of [^{18}F]PSMA PET/CT and PCa confined to the pelvic cavity; however, the SULmax decreased in patients with distant lymph nodes and metastases at other sites.

A post-hoc analysis showed that the increase in SUVmax was associated with an increased probability of malignancy only in focal patterns of the PRIMARY score predicting clinically significant (cs) PCa[9]. Our SULmax values were comparable to the SUVmax previously reported by other authors identifying intraprostatic neoplastic processes. However, the value obtained

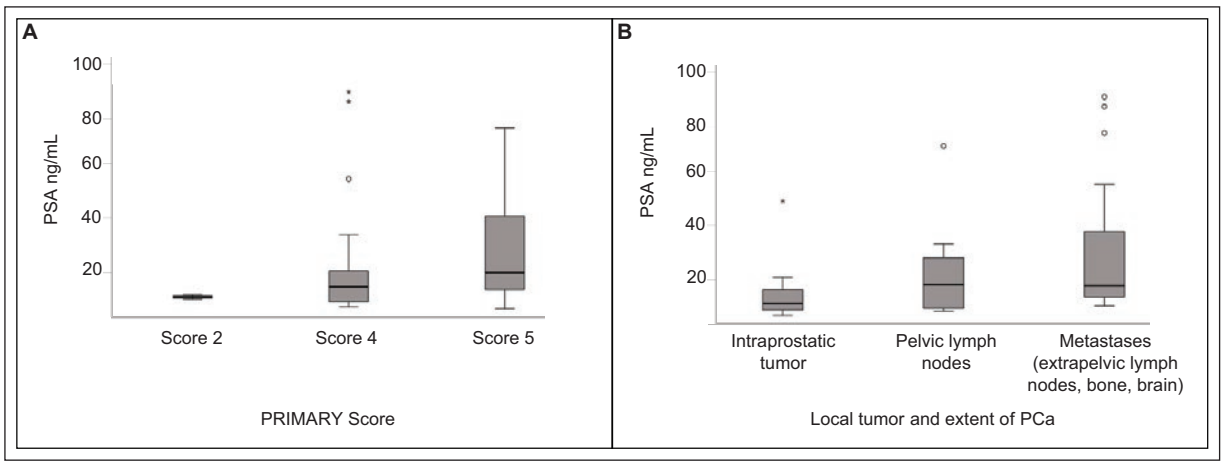

Figure 7. Boxplot of PSA values in relation to PRIMARY score and local tumor and extent of PCa. **A:** scores 4 and 5 were associated with a high PSA value ($p < 0.001$). **B:** the greater the local tumor involvement and extent of PCa, the higher the PSA values. Intraprostatic tumor showed statistical significance ($p \leq 0.001$).

PCa: prostate cancer; PSA: prostate-specific antigen (ng/mL).

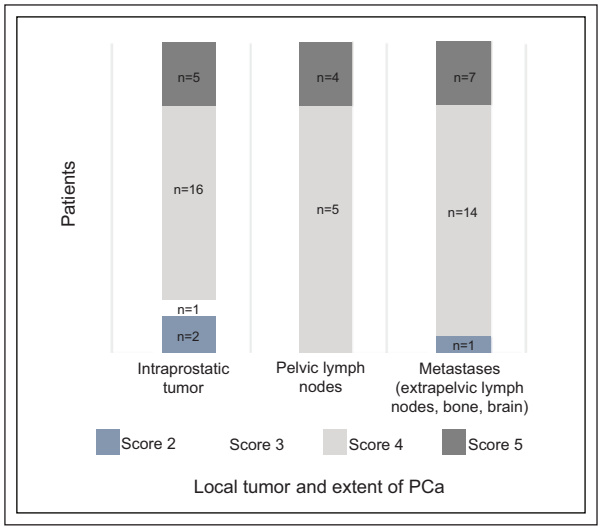

Figure 8. The overall distribution between PRIMARY score and local tumor involvement and extent of PCa. Numbers within bars are the patients per PRIMARY score category. PRIMARY scores 2 and 3 mostly showed disease confined to the prostate with a low frequency of CZ and TZ involvement. The highest prevalence was found for PRIMARY scores 4 and 5 with intraprostatic tumor, followed by metastases (extrapelvic lymph nodes, bone, brain and/or lung).

CZ: central zone; PCa: prostate cancer; TZ: transition zone.

of the SULmax suggests a better approximation of the cutoff parameter according to the prostatic involvement zone, which is the first reference site where PCa appears; the CZ and TZ showed lower SULmax values. In addition, the PRIMARY score integrates qualitative and quantitative assessment based on the anatomic zone (PZ, CZ, or TZ), pattern (diffuse or focal), and the SUVmax. Emmett et al.[8] compared MRI and [^{18}F]PSMA PET/CT, individually and in combination, for the detection of csPCa with histologic confirmation in a prospective, multicenter study. The combination of MRI + PSMA uptake increased sensitivity and positive predictive value compared to MRI alone. An SUVmax of 12 g/mL showed 100% specificity and negative predictive value NPV for csPCa, independent of MRI findings. Guo et al.[19] validated the diagnostic performance of the PRIMARY score in combination with MRI in detecting csPCa in a retrospective cohort study of 431 men who underwent [^{68}Ga]PSMA PET/CT and MRI. PRIMARY score + MRI increased sensitivity (96.0% vs. 87.9%, $p < 0.001$) and NPV (91.5% vs. 79.1%, $p < 0.001$). The performance of the PRIMARY score was superior to MRI in detecting csPCa. In our study, The PRIMARY score showed that the expression of PSMA uptake in the local tumor was highest in the pattern of focal involvement in the peripheral zone (PZ) as long as the disease was confined to the pelvis.

PSMA is a transmembrane glycoprotein on the cell surface expressed in >90% of PCa cases. Higher-grade PCa variants, metastatic disease, and castration-resistant PCa are associated with increased expression of the PSMA receptor, leading to an increase in SULmax value[8,20]. Our study found a higher SULmax value was found in PCa confined to the pelvic cavity (intraprostatic tumor with or without local lymph node spread). Once extrapelvic spread (metastasis) occurred, the SULmax value at the intraprostatic level showed decreasing values. In a retrospective study, Koerber et al.[13] examined

Table 3. Risk association of PRIMARY score with Gleason score risk in patients with PCa in primary staging

Pattern	Low-risk Gleason score (≤ 6) Total (n = 7)	Intermediate/high-risk Gleason score (≥ 7) Total (n = 48)	OR (95% CI)
PZ/SULmax >12 g/mL (PRIMARY score 4 and 5)[a], n (%)	5 (71.4)	46 (96.0)	9.20 (1.05-80.28)
CZ/TZ (PRIMARY score 2 and 3)[b], n (%)	2 (28.6)	2 (4.0)	

[a]High-risk group with PZ and/or intense maximal PSMA uptake (SULmax > 12) (Score 4 and 5); [b]Low-risk group, with uptake in the CZ and/or TZ with diffuse or focal distribution (score 2 and 3); p = 0.04.

CI: confidence interval; CZ: central zone; OR: odds ratio; PCa: prostate cancer; PZ: peripheral zone; SULmax: standardized uptake value maximum normalized to lean body mass of PSMA; TZ: transition zone.

Table 4. Risk association of local intraprostatic tumor and extent with Gleason score in primary staging of PCa

PCa local tumor and extent	Low-risk Gleason score (≤ 6) Total (n = 7)	Intermediate/high-risk Gleason score (≥ 7) Total (n = 48)	OR (95% CI)
Intraprostatic tumor with or without pelvic lymph nodes, n (%)	6 (86.0)	27 (56.2)	4.66 (0.52-41.80)
Intraprostatic tumor and metastases (extrapelvic lymph nodes, bone, brain, and/or lung), n (%)	1 (14.0)	21 (43.8)	

p = 0.16. PCa: prostate cancer; OR: odds ratio; CI: confidence interval.

335 men with biopsy-proven PCa and PSMA-PET/CT for primary staging. They analyzed and correlated the SUVmax value of the intraprostatic malignant lesion with the number and location of metastases. They found a statistically significantly higher SUVmax value in men with metastatic disease than in the cohort without distant metastases (mean 16.1 g/mL vs. 11.2 g/mL, $p < 0.001$) with a cutoff value of 11.9 g/mL for SUVmax and a sensitivity and specificity of 76.0% and 58.4%, respectively. These findings may be related to the increased tumor volume of the disease, with the tumor burden being expressed to a greater extent in some of the metastatic lesions and acting as a sequestering lesion for [^{18}F]PSMA uptake. The SULmax is probably higher and progressive according to the uptake measured at the metastatic lesion (extrapelvic lymph nodes, bone, brain, lung), as expression may act through the sequestration phenomenon of the radiopharmaceutical (PSMA) so that the SULmax value of the intraprostatic tumor is non-specific once extrapelvic dissemination is detected. The results reported by other authors are comparable to ours. Our study determined a mean SULmax value of 12.43 g/ml in patients with intraprostatic tumors and metastases. The intraprostatic SULmax value seems to be a promising parameter for predicting distant metastatic disease.

Several parameters can predict the severity of PCa, such as the PSA value and the Gleason score. In intraprostatic lesions, the intensity of PSMA ligand uptake in PET has been shown to correlate with tumor aggressiveness. Bostwick et al.[21] showed that the greater the extent and intensity of PSMA expression, the higher the Gleason score. Topuz et al.[11], in a retrospective study of 139 patients between different PCa risk groups concerning metastases and [^{68}Ga]PSMA uptake patterns in primary staging of PCa, reported that SUVmax values correlated significantly with the Gleason score risk group and pre-treatment PSA values. Bilobar involvement of PSMA in the prostate, a Gleason score of 8 or more, and a PSA value of 20 ng/mL or more were independent predictors of metastasis. In a retrospective study of 147 patients, the ability of [^{68}Ga]PSMA PET/CT to differentiate between intermediate- and high-risk PCa was assessed. The authors reported that PSMA uptake measured by SUVmax was closely related to the Gleason score[20]. Our mean value of SULmax was directly related to the PSA value and the Gleason score risk group. PCa with an intermediate and high Gleason score had a higher risk of intraprostatic tumor affecting PZ and a higher risk of extrapelvic spread of disease. The PRIMARY score showed a significant association with the PSA level and an association with the Gleason score. The relationship between the highest SULmax values and intermediate- and high-risk Gleason score was comparable to previous SUVmax reports[8,12,14,20-26].

The strengths of our study relate to the fact that all included patients had a histopathologically confirmed diagnosis of PCa with a low, intermediate, or high-risk Gleason score. We calculated the SULmax using a workstation and automated software. On the other hand,

the radionuclide in our study is based on [^{18}F]PSMA with a longer half-life (~2 hours) and high-quality images. The limitations of our study were related to the retrospective design, small sample size, and single institution. In the present study, the analysis to characterize the affected anatomical areas was based on the expression pattern of PSMA and CT images. However, the gold standard for identifying prostate areas is MRI, which could be in line with the preamble of PET/MRI and a useful reference for patients who cannot undergo MRI and/or in locations that cannot compare the diagnostic approach with MRI. On the other hand, the SULmax of the metastases was not calculated for comparison with the SULmax of the intraprostatic tumor.

CONCLUSION

In our study, the SULmax value was associated with the PROMISE-V2 PRIMARY score in patients with PCa in primary staging according to the affected anatomic zone (PZ, CZ, or TZ), expression patterns, and SULmax > 12 g/mL. Expression of PSMA uptake in the local tumor was highest for the pattern of focal involvement in the ZP as long as the disease was confined to the pelvic cavity (intraprostatic tumor with or without pelvic lymph nodes). We also showed the risk association according to PSA levels and the Gleason score for the PRIMARY score and PCa extent, respectively.

Acknowledgments

The authors thank Professor Ana M. Contreras-Navarro for her guidance in preparing and writing this scientific paper. This original research in the Radiology Specialty field was an awarded thesis at the Segunda Convocatoria Nacional 2023-2024, *"Las Mejores Tesis para Publicar en el JMeXFRI."*

Funding

This research received no external funding.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of individuals. This study complied with the Declaration of Helsinki (1964) and subsequent amendments.

Confidentiality of data. The authors declare they followed their center's protocol for sharing patient data.

Right to privacy and informed consent. Informed consent was not required for this observational study of information collected during routine clinical care.

Use of artificial intelligence. The authors did not use generative artificial intelligence to prepare this manuscript and/or create tables, figures, or figure legends.

REFERENCES

1. Farolfi A, Calderoni L, Mattana F, Mei R, Telo S, Fanti S, et al. Current and Emerging Clinical Applications of PSMA PET Diagnostic Imaging for Prostate Cancer. J Nucl Med. 2021;10;62(5):596-604. doi: 10.2967/jnumed.120.257238.
2. Jochumsen MR, Bouchelouche K. PSMA PET/CT for Primary Staging of Prostate Cancer - An Updated Overview. Semin Nucl Med. 2024;54(1):39-45. doi: 10.1053/j.semnuclmed.2023.07.001.
3. Wallitt KL, Khan SR, Dubash S, Tam HH, Khan S, Barwick TD. Clinical PET Imaging in Prostate Cancer. Radiographics. 2017;37(5):1512-1536. doi: 10.1148/rg.2017170035.
4. García FO; Medina SS. Radiotracers Used in Nuclear Medicine for Prostate Cancer Diagnosis and Follow-Up. Gaceta Mex Oncol. 2017;16(1):41-48. doi: 10.24875/j.gamo.17000007.
5. Azmi NHM, Suppiah S, Liong CW, Noor NM, Said SM, Hanafi MH, et al. Reliability of standardized uptake value normalized to lean body mass using the liver as a reference organ, in contrast-enhanced 18F-FDG PET/CT imaging. Radiat Phys Chem. 2018;147:35–39.
6. Aksu A, Çapa Kaya G. Is SUV Corrected for Lean Body Mass Superior to SUV of Body Weight in ^{68}Ga-PSMA PET/CT? Mol Imaging Radionucl Ther. 2021;15;30(3):144-149. doi: 10.4274/mirt.galenos.2021.59254.
7. Gafita A, Calais J, Franz C, Rauscher I, Wang H, Roberstson A, et al. Evaluation of SUV normalized by lean body mass (SUL) in ^{68}Ga-PSMA11 PET/CT: a bicentric analysis. EJNMMI Res. 2019;9(1):103. doi:10.1186/s13550-019-0572-z.
8. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. Eur Urol. 2021;80(6):682-689. doi: 10.1016/j.eururo.2021.08.002.
9. Emmett L, Papa N, Buteau J, Ho B, Liu V, Roberts M, et al. The PRIMARY Score: Using Intraprostatic ^{68}Ga-PSMA PET/CT Patterns to Optimize Prostate Cancer Diagnosis. J Nucl Med. 2022;63(11):1644-1650. doi: 10.2967/jnumed.121.263448.
10. Jiao J, Kang F, Zhang J, Quan Z, Wen W, Zhao X, et al. Establishment and prospective validation of an SUV_{max} cutoff value to discriminate clinically significant prostate cancer from benign prostate diseases in patients with suspected prostate cancer by ^{68}Ga-PSMA PET/CT: a real-world study. Theranostics. 2021;25;11(17):8396-8411. doi: 10.7150/thno.58140.
11. Topuz ÖV, Aksu A, Erinç SR, Tamam MÖ. Correlations of ^{68}Ga-PSMA PET/CT in the initial staging of prostate cancer patients. Hell J Nucl Med. 2021;24(1):60-65. doi: 10.1967/s002449912307.
12. Fendler WP, Schmidt DF, Wenter V, Thierfelder KM, Zach C, Stief C, et al. 68Ga-PSMA PET/CT Detects the Location and Extent of Primary Prostate Cancer. J Nucl Med. 2016;57(11):1720-1725. doi: 10.2967/jnumed.116.172627.
13. Koerber SA, Boesch J, Kratochwil C, Schlampp I, Ristau J, Winter E, et al. Predicting the Risk of Metastases by PSMA-PET/CT-Evaluation of 335 Men with Treatment-Naïve Prostate Carcinoma. Cancers (Basel). 2021;13(7):1508. doi: 10.3390/cancers13071508.
14. Manafi-Farid R, Ranjbar S, Jamshidi Araghi Z, Pilz J, Schweighofer-Zwink G, Pirich C, et al. Molecular Imaging in Primary Staging of Prostate Cancer Patients: Current Aspects and Future Trends. Cancers (Basel). 2021;13(21):5360. doi: 10.3390/cancers13215360.
15. Eiber M, Herrmann K, Calais J, Hadaschik B, Giesel FL, Hartenbach M, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. J Nucl Med. 2018;59(3):469-478. doi: 10.2967/jnumed.117.198119.
16. Seifert R, Emmett L, Rowe SP, Herrmann K, Hadaschik B, Calais J, et al. Second Version of the Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation for Clinical Trials (PROMISE V2). Eur Urol. 2023;83(5):405-412. doi: 10.1016/j.eururo.2023.02.002.

17. Ali H, Rashid-Ul-Amin S, Hai A. Standardised Uptake Value in Organ Confined Prostate Cancer in 68-Ga- Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography Scan and its Correlation with Prostate Specific Antigen Level and Gleason Score. J Cancer Allied Spec. 2023;13;9(2):529. doi: 10.37029/jcas.v9i2.519.
18. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016;40(2):244-252. doi: 10.1097/PAS.0000000000000530.
19. Guo S, Kang F, Ma S, Jiao J, Ren J, Wang J, et al. The PRIMARY Score: Diagnostic Performance and Added Value Compared With MRI in Detecting Clinically Significant Prostate Cancer. Clin Nucl Med. 2024;1;49(1):37-44. doi: 10.1097/RLU.0000000000004951.
20. Yi N, Wang Y, Zang S, Yang L, Liu H, Sun H, et al. Ability of ^{68} Ga-PSMA PET/CT SUVmax to differentiate ISUP GG2 from GG3 in intermediate-risk prostate cancer: A single-center retrospective study of 147 patients. Cancer Med. 2023;12(6):7140-7148. doi: 10.1002/cam4.5516.
21. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82(11):2256-2261. doi: 10.1002/(sici)1097-0142(19980601)82:11<2256::aid-cncr22>3.0.co; 2-s.
22. Demirci E, Kabasakal L, Şahin OE, Akgün E, Gültekin MH, Doğanca T, et al. Can SUVmax values of Ga-68-PSMA PET/CT scan predict the clinically significant prostate cancer? Nucl Med Commun. 2019;40(1):86-91. doi: 10.1097/MNM.0000000000000942.
23. Bagheri H, Mahdavi SR, Geramifar P, Neshasteh-Riz A, Sajadi Rad M, Dadgar H, et al. An Update on the Role of mpMRI and ^{68}Ga-PSMA PET Imaging in Primary and Recurrent Prostate Cancer. Clin Genitourin Cancer. 2024;22(3):102076. doi: 10.1016/j.clgc.2024.102076.
24. Emmett L, Papa N, Counter W, Calais J, Barbato F, Burger I, et al. Reproducibility and Accuracy of the PRIMARY Score on PSMA PET and of PI-RADS on Multiparametric MRI for Prostate Cancer Diagnosis Within a Real-World Database. J Nucl Med. 2024;2;65(1):94-99. doi: 10.2967/jnumed.123.266164.
25. Heetman JG, Paulino Pereira LJ, Kelder JC, Soeterik TFW, Wever L, Lavalaye J, et al. The additional value of 68Ga-PSMA PET/CT SUVmax in predicting ISUP GG≥2 and ISUP GG≥3 prostate cancer in biopsy. Prostate. 2024;84(11):1025-1032. doi: 10.1002/pros.24716.
26. Rahbar K, Weckesser M, Huss S, Semjonow A, Breyholz HJ, Schrader AJ, et al. Correlation of Intraprostatic Tumor Extent with [^{68}Ga]-PSMA Distribution in Patients with Prostate Cancer. J Nucl Med. 2016;57(4):563-567. doi: 10.2967/jnumed.115.169243.