Journal of Cancer Research and Clinical Oncology (2025) 151:155
https://doi.org/10.1007/s00432-025-06184-z

REVIEW

PSMA PET/CT for prostate cancer diagnosis: current applications and future directions

Zhengang Shen[1,2] · Zeng Li[1] · Yunlong Li[1] · Xiaodi Tang[2] · Jiayi Lu[3] · Li Chen[1] · Zhu Zhong Cheng[4] · Hong Liao[1] · Shukui Zhou[1]

Received: 7 January 2025 / Accepted: 24 March 2025 / Published online: 4 May 2025

Abstract

Prostate cancer (PCa) requires improved diagnostic strategies beyond conventional imaging. This review aimed to evaluate the role of prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) in diagnosing advanced PCa. The review analyzed the diagnostic performance of PSMA PET/CT in various clinical contexts, including locoregional staging, extracapsular extension (ECE), seminal vesicle invasion (SVI), pelvic lymph node metastases, distant metastases, and biochemical recurrence (BCR). Further, challenges such as PSMA-negative tumors, need for standardized protocols, and potential of emerging imaging targets (neurotensin receptor 1 and fibroblast activation proteins) were reviewed. The role of artificial intelligence (AI) and advancements in tracer development were explored. PSMA PET/CT demonstrated exceptional specificity for locoregional staging, ECE, and SVI while reducing unnecessary biopsies and optimizing biopsy strategies. The diagnostic accuracy for pelvic lymph node metastases was higher with PSMA PET/CT than with traditional methods, although sensitivity for micrometastasis detection remained challenging. For distant metastases, PSMA PET/CT outperformed bone scintigraphy (BS) and conventional imaging, particularly in identifying bone and atypical lesions. In BCR cases, PSMA PET/CT reliably detected recurrent lesions at low prostate-specific antigen levels, significantly influencing treatment strategies. The review findings indicate that PSMA PET/CT is a superior diagnostic tool for PCa due to its high specificity and accuracy. Despite limitations such as PSMA-negative tumors and sensitivity challenges, advancements in AI, novel imaging targets, and affordable tracer development hold promise for broader clinical adoption. This review underscores the transformative potential of PSMA PET/CT in PCa diagnosis and management, advocating for ongoing research and protocol standardization.

Keywords Prostate cancer (PCa) · PSMA PET/CT (Prostate-specific membrane antigen positron emission tomography/Computed tomography) · Locoregional staging · Pelvic lymph node metastasis · Metastatic prostate cancer · Biochemical recurrence

Zhengang Shen and Zeng Li and Yunlong Li contributed equally to this work.

✉ Shukui Zhou
jackten@aliyun.com

✉ Hong Liao
liaohong131@163.com

[1] Department of Urology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of the University of Electronic Science and Technology of China, Chengdu, China

[2] Chengdu Medical College, Chengdu, China

[3] Hong Kong Baptist University, Hong Kong, China

[4] Department of Nuclear Medicine, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of the University of Electronic Science and Technology of China, Chengdu, China

Introduction

Prostate cancer (PCa) remains a significant global wellness challenge—a term encompassing both its impact on individual health management and strain on healthcare systems—with approximately 1.41 million new cases and 375,304 deaths reported annually worldwide (Wang et al. 2022). The American Cancer Society estimated nearly 288,300 new cases and 34,700 deaths in the United States alone in 2023 (Siegel et al. 2023). Conventional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy (BS), and choline positron emission tomography (PET/CT), are essential for PCa diagnosis. However, their limitations in sensitivity and specificity, particularly for early detection and staging, have prompted the development of advanced imaging techniques (Daryanani and Turkbey 2022). One such advancement is prostate-specific membrane antigen (PSMA) positron emission tomography. PSMA is a type II transmembrane glycoprotein containing 750 amino acids (Tino et al. 2000). Due to its high malignant prostate cell expression, the extracellular active domain of folate hydrolase I (PSMA) can be labeled with various radioactive isotopes, including ^{11}C, ^{18}F, ^{89}Zr, ^{64}Cu, ^{86}Y, and ^{68}Ga. Among these, ^{68}Ga and ^{18}F are particularly notable for their excellent PSMA-targeted PET/CT imaging properties, owing to the favorable biological distribution and strong affinity of the PSMA ligand for PCa cells. When a PSMA ligand binds to the active site of the PSMA extracellular segment, it undergoes clathrin-mediated endocytosis, transporting the ligand into PCa cells. The isotope remains within the cell, enabling continuous deposition. This process supports radionuclide imaging and benefits radionuclide therapy (Fig. 1) (Eiber et al. 2017). A practical approach for PCa delineation and reevaluation is PSMA-targeting integration with PET/CT imaging (Hagens et al. 2022). Experts agree that when traditional imaging produces unclear or insufficient results, PSMA PET/CT enhances detection in distant and locoregional lymph nodes, bones, and visceral organs (Huang et al. 2023). Further exploration of the advantages and disadvantages of ^{68}Ga-PSMA PET/CT and ^{18}F-PSMA PET/CT will contribute to a comprehensive understanding of their clinical application value. ^{68}Ga-PSMA PET/CT is renowned for its excellent sensitivity and specificity, particularly in detecting PCa at low prostate-specific antigen (PSA) levels, significantly improving detection rates (Evangelista et al. 2022). In clinical practice, the labeling process for ^{68}Ga-PSMA-11 is relatively simple and can be automated at room temperature. In contrast, ^{18}F-labeled PSMA tracers such as ^{18}F-PSMA-1007 typically require manual labeling and specific temperature conditions (Huang et al. 2023). However, the shorter half-life of ^{68}Ga (68 min) limits its availability, and its primary excretion through the urinary tract may affect lesion imaging near the bladder (De Man et al. 2022). Additionally, non-specific uptake in ganglia, intestines, and other areas may lead to false-positive results with ^{68}Ga-PSMA. In contrast, ^{18}F-PSMA PET/CT benefits from a longer half-life (110 min), facilitating regional production and distribution (Maisto et al. 2022; De Man et al. 2022). Furthermore, the lower positron energy of ^{18}F (635 keV vs. 1.9 MeV) results in higher image resolution, enabling more precise localization of small lesions and local recurrences (Zlatopolskiy et al. 2019). Notably, ^{18}F-PSMA-1007 primarily undergoes hepatobiliary excretion, offering an advantage in detecting lesions near the bladder (Hoberück et al. 2021). However, ^{18}F-PSMA-1007 may exhibit increased uptake in benign bone lesions, potentially compromising diagnostic accuracy (Huang et al. 2023). It is worth noting that some studies have reported comparable sensitivity, specificity, and positive predictive values for both ^{68}Ga-PSMA and ^{18}F-PSMA in initial staging and biochemical recurrence assessment (Dietlein et al. 2017; Kuten et al. 2020). In summary, ^{68}Ga- and ^{18}F-PSMA PET/CT each have distinct advantages and limitations, and the choice between them should be based on specific clinical scenarios and availability. ^{18}F-labeled PSMA tracers demonstrate advantages in production convenience, image resolution, and broader applicability. This review examines recent advancements in PSMA PET/CT for diagnosing primary PCa, pelvic lymph node metastasis, distant metastasis, and biochemical recurrence (BCR) (Fig. 2) It also addresses PSMA PET/CT's limitations in clinical management and highlights future directions for its development.

Diagnosis of locoregional staging of PCa using PSMA PET/CT

Comparison with MRI

Accurate PCa local staging is vital for improving biochemical recurrence-free survival. Key factors in evaluating T staging include lymph node involvement, extracapsular extension (ECE), and seminal vesicle invasion (SVI). Traditionally, MRI has been the primary method for PCa locoregional staging. However, its sensitivity is often limited, particularly in the early phases of ECE and SVI. Studies have shown that for tumors with a volume of <0.5 cc and a Gleason score of <6, the detection rates of MRI are considerably lower (Le et al. 2015; Bonekamp et al. 2019). In recent years, the performance of PSMA PET/CT has markedly surpassed that of traditional imaging methods. PSMA PET/CT demonstrates markedly higher sensitivity than mpMRI for detecting PCa invasion along the posterior

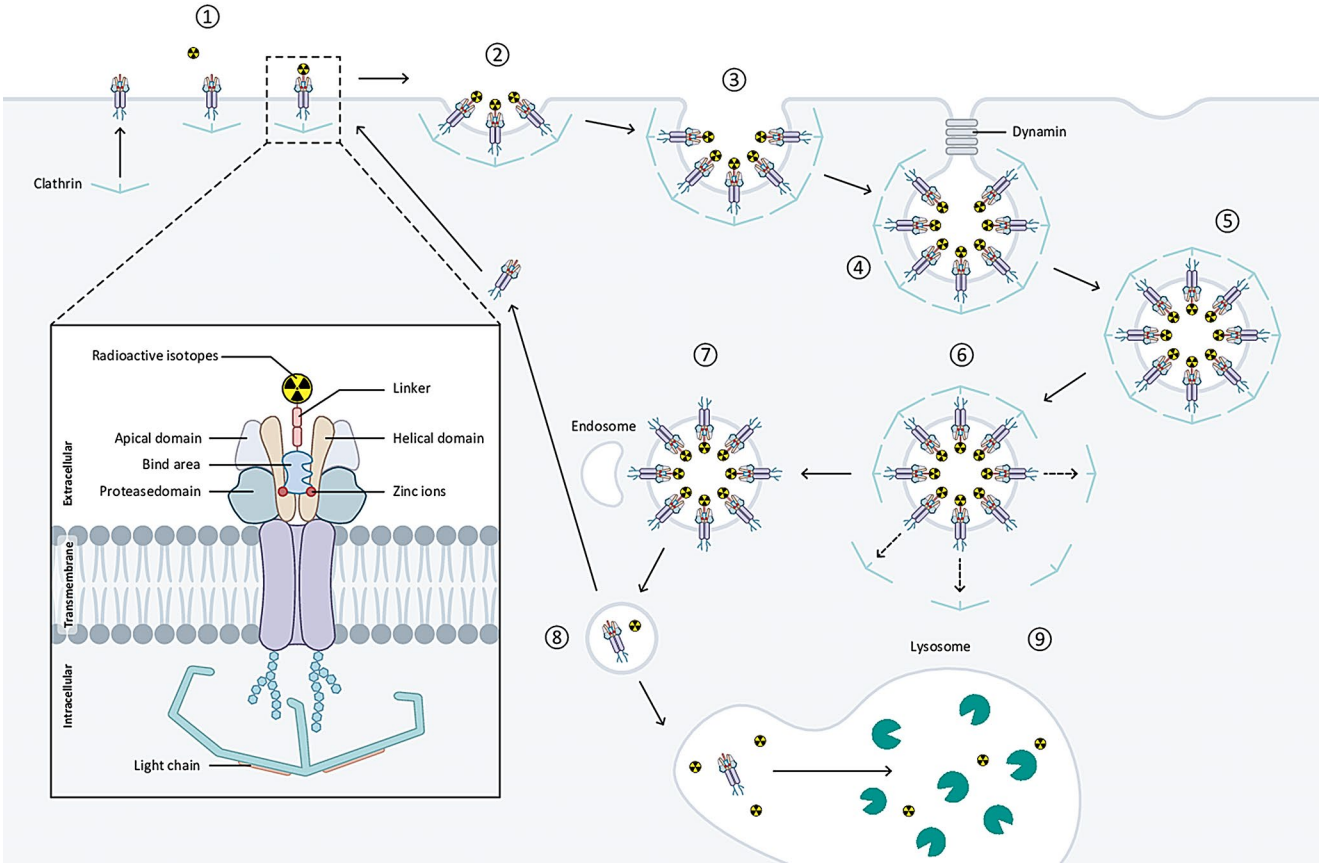

Fig. 1 PSMA-targeted radiolabeling and internalization for PET/CT imaging and therapy. PSMA ligands are divided into extracellular, transmembrane, and intracellular. The radionuclide mainly binds to the binding area of the extracellular part through a linker. After binding to PSMA, the PSMA-ligand-isotope complex is internalized into PCa cells through clathrin-mediated endocytosis. ⑤Inside the cell, the endocytic vesicles persist, leading to continuous accumulation of the radioisotope within the PCa cells. ⑥-⑨Upon detachment from the clathrin coat, endocytic vesicles carrying radioactive isotopes and the PSMA–radionuclide ligand complex undergo sorting in the endosome. The radionuclides subsequently enter lysosomes for degradation, whereas some PSMA is recycled back to the cell surface for repeated ligand binding. Another fraction of the PSMA–ligand complexes is transported to late endosomes and lysosomes, where they are ultimately broken down. This mechanism facilitates effective radionuclide imaging, enabling the visualization of PCa cells in PET/CT scans. Furthermore, the prolonged intracellular retention of radioisotopes may offer therapeutic benefits in radionuclide therapy, potentially leading to improved treatment outcomes. Abbreviations: PSMA, prostate-specific membrane antigen; PET/CT, positron emission tomography/CT; PSA, prostate-specific antigen

neurovascular bundles (86% vs. 57%) (Bahler et al. 2024) and exhibits superior sensitivity compared to MRI in detecting small-volume tumors (Witkowska-Patena et al. 2020). A comparative study of PSMA PET/CT and MRI indicates that ^{18}F-PSMA PET/CT is more effective than MRI in identifying the dominant nodule (94% of 126 cases vs. 83% of 112 cases), tumor lateralization (64% of 86 cases vs. 44% of 60 cases), and ECE (75% of 100 cases vs. 63% of 84 cases), while both techniques showed similar efficacy for SVI (Mookerji et al. 2024). However, a later multicenter prospective study (Soeterik et al. 2024) demonstrated that in patient-based ECE detection, PSMA PET/CT exhibited higher specificity (83% vs. 77%) but lower sensitivity (41% vs. 60%) compared to MRI, with combined modalities achieving 73% sensitivity, whereas in SVI detection, MRI and PSMA PET/CT showed sensitivities of 36% and 44%, respectively, both maintaining 96% specificity. This study indicated that PSMA PET/CT has lower sensitivity in detecting ECE. However, adding PSMA PET information to MRI can improve the sensitivity of ECE and SVI detection. Therefore, combining these two imaging modalities is recommended to guide treatment decisions.

PSMA PET/CT for image-guided biopsy and precision local staging

Precise local staging is critical for determining the optimal treatment strategy. PSMA PET/CT demonstrates a marked

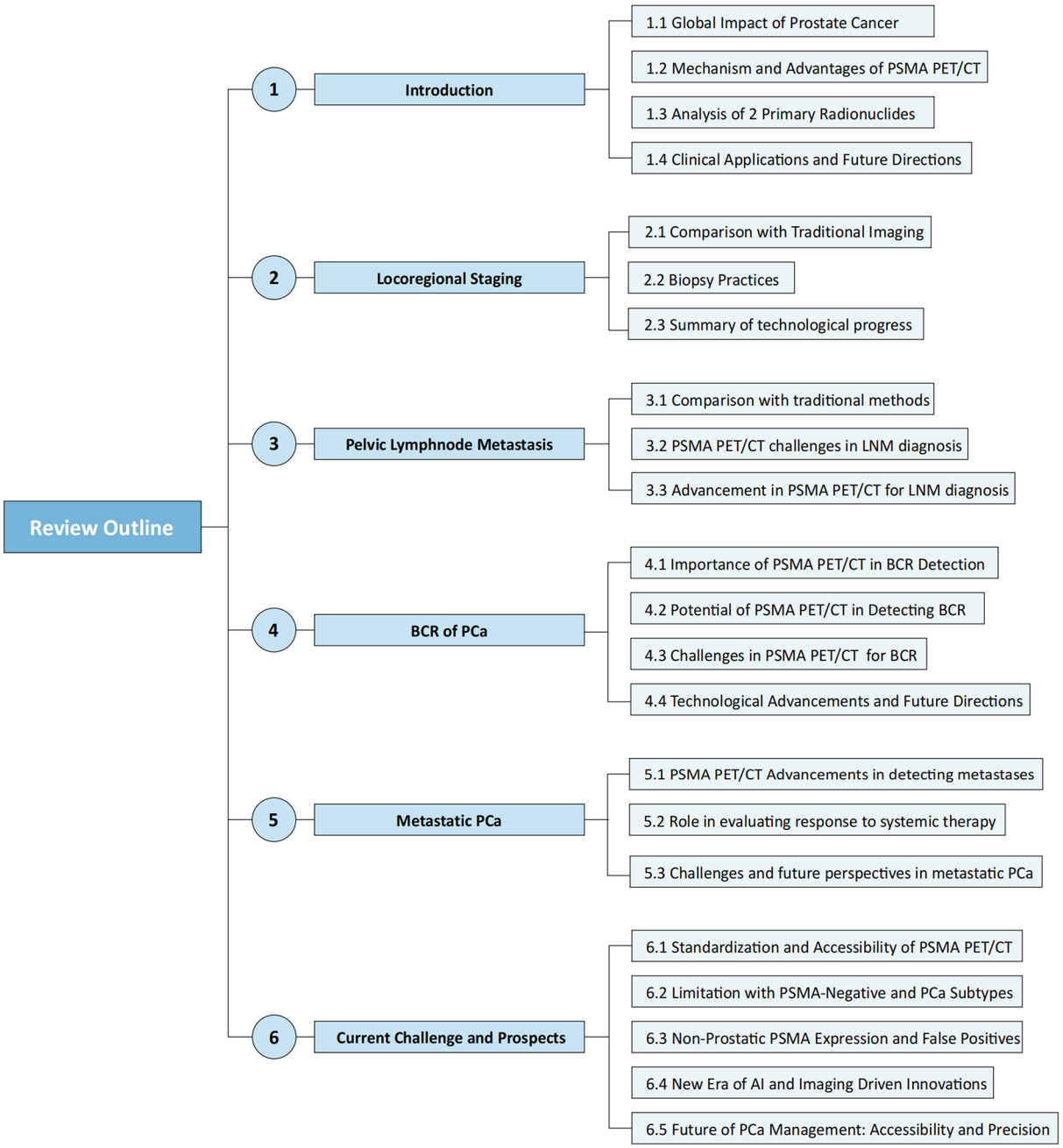

Fig. 2 Analysis workflow of this review. Abbreviations: PSMA, prostate-specific membrane antigen; PET/CT, positron emission tomography/CT; BCR, Biochemical Recurrence; LNM, lymph node metastasis; PSA, prostate-specific antigen

advantage in detecting local recurrence. For patients with previously negative PSA levels, ^{68}Ga-PSMA PET/CT-guided biopsy can substantially enhance the detection rate of clinically significant PCa (csPCa). One study reported 100% sensitivity and negative predictive values (NPV), confirming the direct correlation between the csPCa detection rate and the standardized uptake value (SUV) (Liu et al. 2020). Subsequent studies emphasized the superiority of ^{68}Ga-PSMA PET/CT biopsy (PSMA-TB) over transrectal ultrasound-guided biopsy (TRUS-GB) in detecting csPCa, particularly in males with blood PSA levels between 4.0 and 20.0 ng/mL, where TRUS-GB proved less effective. A previous study showed that ^{68}Ga-PSMA PET/CT could be a more effective and less invasive method for prostate biopsy (Zhang et al. 2021). Another study suggested that PSMA PET/CT alone is a viable imaging method for guiding biopsies in high-risk men without prior biopsy. PSMA-TB identified PCa in 86.7% of men and csPCa in 100% of men with metastases (Bodar et al. 2023). In addition, the integration of PSMA-PET with mpMRI increases sensitivity

in assessing extra-prostatic extension and SVI compared to mpMRI alone (Muehlematter et al. 2019; Chow et al. 2023; Sharma et al. 2023). These results indicate that PSMA PET/CT accuracy not only enables more precise delineation of primary lesions and adjacent high-risk anatomical regions but also facilitates the identification of candidates who may safely forego invasive biopsy procedures. This capability consequently reduces perioperative risks while alleviating patients' financial and psychological burdens associated with overtreatment.

Brief summary of technological progress

The performance improvement of PSMA PET/CT benefits from technological advancements. For example, the "Time-of-Flight Block Sequential Regularized Expectation Maximization (TOF BSREM)" algorithm considerably enhances the accuracy of quantitative assessment with its remarkable advantages in noise control and edge preservation (Seo et al. 2020; Sadeghi et al. 2023). Furthermore, the combined application of PSMA PET/CT and mpMRI further optimizes local staging accuracy, especially in complex clinical scenarios where mpMRI or initial biopsy results are negative (Cereser et al. 2023).

In conclusion, PSMA-PET/CT represents a significant advancement in the local staging of PCa, improving the accuracy of detecting critical conditions such as ECE and SVI. Furthermore, combining PSMA PET/CT with mpMRI-guided biopsy shows promise in detecting csPCa, particularly in individuals with negative prior findings and elevated PSA levels.

Diagnosis of pelvic lymph node metastasis using PSMA PET/CT

Comparison with traditional methods

The primary site of PCa dissemination is the pelvic lymph nodes, and lymph node metastasis (LNM) affects tumor staging and prognosis (Fig. 3). Early diagnosis of LNM is crucial, as it forms the basis for clinical decision-making. Patients with PCa are typically diagnosed with pelvic LNM using CT and MRI. In a study by Malaspina et al., 79 patients with newly diagnosed moderate-to-high-risk PCa were included; among these patients, 17 (22%) were classified as intermediate-risk and 62 (78%) as high-risk. Patients underwent whole-body MRI (wbMRI), ^{18}F-PSMA PET/CT, and thoracoabdominal CT. The precision rates of ^{18}F-PSMA PET/CT, wbMRI, and CT in detecting pelvic LNs in 31 (39%) patients diagnosed with pelvic LNM were 87%, 45%, and 26%, respectively, whereas the sensitivity, specificity, and precision of PSMA PET/CT in diagnosing LNM were 87%, 96%, and 92%, respectively, as determined by double reading. The diagnostic efficacy of PSMA PET/CT surpassed that of traditional imaging (Malaspina et al. 2021), which is consistent with the findings of our center's study (sensitivity of 95.1%, positive predictive value (PPV) of 100.0%, and accuracy of 95.1% for ^{18}F-PSMA vs. sensitivity of 82.9%, PPV of 100.0%, and accuracy of 82.9% for MRI) (Ye et al. 2024).

PSMA PET/CT challenges in LNM diagnosis

Although traditional methods for identifying LNM have lower accuracy than PSMA PET/CT, some issues remain. PSMA PET/CT often shows superior specificity but limited sensitivity. A meta-analysis found that the sensitivity of ^{18}F-PSMA PET/CT in lymph node staging was 57% (95% confidence interval [CI]: 49–64%) (Jeet et al. 2023). Another study reported that the sensitivity of ^{68}Ga-PSMA PET in detecting lymph node metastases at initial staging was 65.9% (Maurer et al. 2016). Another significant limitation is that PSMA PET/CT has a limited capacity to identify smaller lymph node metastases. A previous study reported that the median diameter of lymph node metastases detected by PSMA PET/CT was 5.5 mm, whereas the median diameter of undetected metastases was only 4.3 mm (Budäus et al. 2016).While the diagnostic performance of PSMA PET/CT for pelvic LNM remains inadequate, recent advances are promising (Ingvar et al. 2022).

Advancement in PSMA PET/CT for LNM diagnosis

One notable advancement to enhance the sensitivity of PSMA PET/CT for lymph node assessment involves its integration with biopsy and examination of the sentinel lymph nodes, as discussed by Hinsenveld et al. This method demonstrates a 100% detection rate for PN1 patients (100% sensitivity; 95% CI, 86–100%), and the diagnostic accuracy is reported at 94% (95% CI, 84–99%) (Hinsenveld et al. 2020).

Another progress is the effectiveness of dual time-point ^{68}Ga-PSMA-PET/CT hybrid imaging in identifying LNMs as small as 3 mm, a marked improvement over traditional diagnostic techniques, as highlighted in recent research on PCa staging and restaging (Hoffmann et al. 2020). Artificial intelligence (AI) is another advancement for PSMA PET/CT in pelvic LNM detection for PCa. Research using ^{18}F-PSMA-1007 PET/CT shows that AI improves pelvic LNM identification accuracy (Trägårdh et al. 2022a). This AI-based method achieved a sensitivity of 82%, comparable to nuclear medicine (78%) (Trägårdh et al. 2022b), providing improved repeatability and shorter reading times

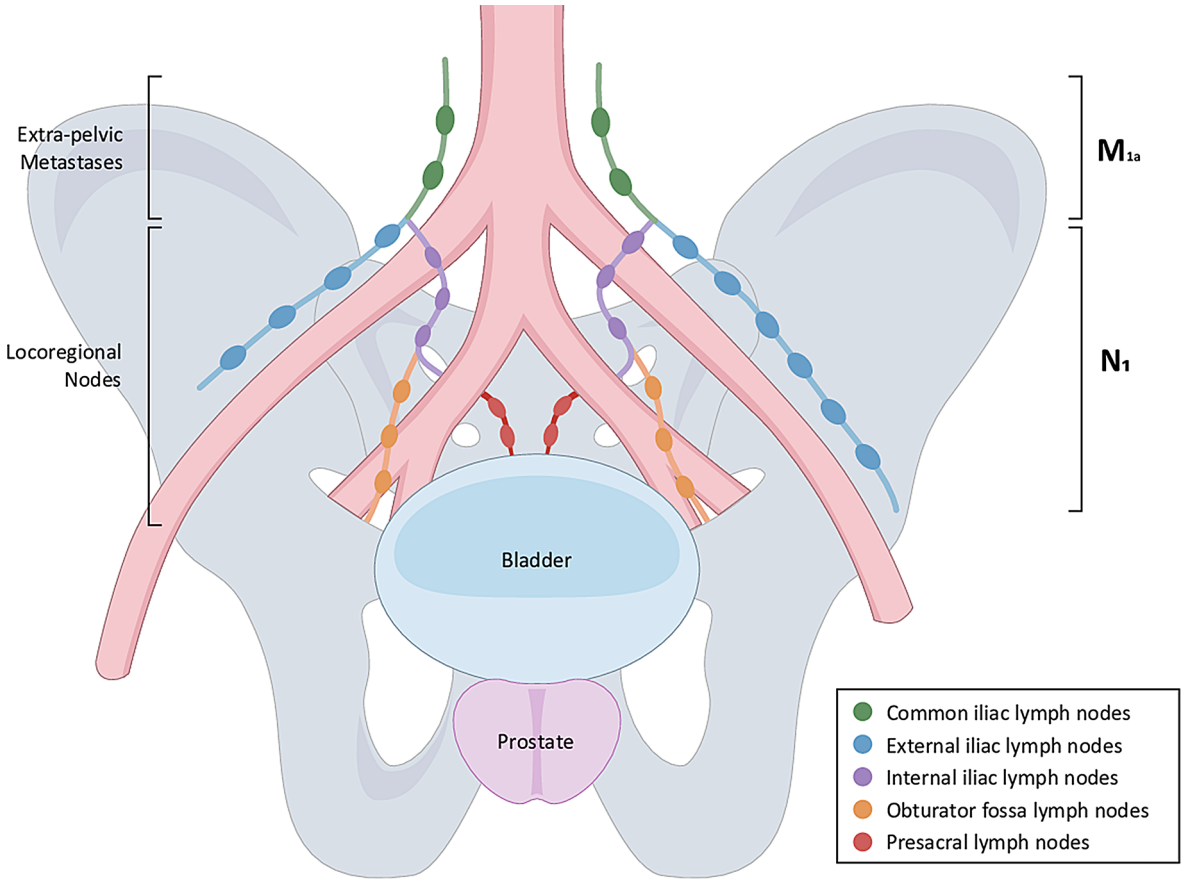

Fig. 3 Pelvic lymph node staging in prostate cancer. This illustration depicts the pelvic lymph node staging relevant to prostate cancer. The locoregional lymph nodes below the common iliac bifurcation are categorized as stage N1. These nodes consist of three leading chains: the iliac chain (including the internal and external iliac lymph nodes), the sacral chain (presacral lymph nodes), and the obturator chain (obturator fossa lymph nodes). Each chain is color-coded for clear identification. Lymph nodes above the bifurcation of the common iliac vessels are considered non-regional and are thus staged as M1a in the TNM system

for PET/CT analysis. In summary, PSMA PET/CT is the preferred method for detecting pelvic LNM in patients with PCa. Although extended lymph node dissection (eLPND) remains the gold standard for lymph node diagnosis, PSMA PET/CT can help avoid unnecessary lymph node scanning prior to surgery (Ditonno et al. 2024). However, the sensitivity challenges associated with micrometastases underscore the need for further technological enhancements and research into the detection of small metastatic deposits.

PCa BCR diagnosis using PSMA PET/CT

Biochemical relapse

After local treatments such as radical prostatectomy (RP) or radiotherapy, PCa BCR affects approximately one-third of patients (Simon et al. 2022). The 2023 European Association of Urology (EAU) guidelines emphasize the importance of distinguishing between detectable and csPSA relapse. The criteria for this distinction are >0.4 ng/mL post-prostatectomy and >NADIR+2 ng/mL post-IMRT/VMAT with IGRT (±ADT) (Gelardi et al. 2023). The 5-year recurrence-free survival rates for BCR decrease remarkably with each additional risk factor: 92.9% (no risk factors) to 28.8% (three risk factors), emphasizing the influence of risk factors on prognosis (Murata et al. 2018). Therefore, diagnosing recurrent PCa and identifying its risk factors is critical for effective management and appropriate salvage therapy. In this scenario, PSMA PET/CT shows great potential.

PSMA PET/CT potential in diagnosing PCa BCR

In a comparison study, wbMRI only detected 23.2% (13 lesions) of the 56 PCa lesions in 11 individuals following RP, while ^{68}Ga-PSMA PET/CT identified all 56 lesions in 20 of 28 patients (Sawicki et al. 2019). Compared to CT, PSMA PET/CT demonstrates better detection efficacy for early metastatic lesions in individuals experiencing BCR after RP (Morawitz et al. 2021). Its greatest advantage lies

in its ability to minutely spread lesions in the pelvic LNs or bones (Bagguley et al. 2021). When locating recurring lesions in patients with BCR, ^{18}F-PSMA-1007 PET/CT outperforms ^{68}Ga-PSMA PET/CT, indicating a greater positive detection rate for recurrent PCa lesions, particularly when PSA levels are <0.5 ng/mL (Giesel et al. 2018; Treglia et al. 2019). The studies above demonstrate PSMA PET/CT's effectiveness in identifying microrecurrences at very low PSA levels and underscoring PSMA PET/CT's benefit in PCa BCR detection.

PSMA PET/CT challenges in diagnosing BCR

Nevertheless, albeit helpful, PSMA PET/CT's application has some challenges. A key challenge in PCa management is determining the optimal cutoff points for PSA levels and other clinicopathological variables to enhance detection rates. A previous study revealed a considerable relationship between pre-PET PSA levels and PCa recurrence detection rates, with the identification rate being 28% at a level below 0.5 ng/mL (Treglia et al. 2019). In contrast, at PSA levels of 5 ng/mL or higher, the detection rate considerably rose to 97%, indicating that both elevated PSA levels and higher Gleason scores contribute to increased detection rates (Christensen et al. 2022). Recent advances in PSMA PET/CT for PCa BCR have markedly improved, particularly in refining PSA cutoff levels and enhancing the detection of systemic metastases, which are pivotal for tailoring treatment decisions. Research on the Indonesian population has provided insights into regional variations in PSA cutoff points for PCa detection. An ideal PSA cutoff of 6.95 ng/mL was determined in a study conducted in this cohort, with a high sensitivity of 97.8% but a low specificity of 19.6%. A PSA density cutoff of 0.7072 was identified, demonstrating a sensitivity of 62.2% and specificity of 78.7% (Shahab et al. 2013). A different study demonstrated the effectiveness of 68Ga-labeled PSMA PET/CT in detecting metastases and guiding treatment plans in patients with rapid bladder cancer recurrence after prostatectomy, showing a detection rate of 80% for localized and systemic recurrence 2019 (Janice et al. 2019). Another study in a region with a lower incidence of PCa suggested that increasing the PSA cutoff to 8 ng/mL considerably improved cancer detection, achieving 100% sensitivity and 85.8% specificity (Cahill et al. 2020). These regional studies highlight the importance of considering demographic and epidemiological factors when determining PSA thresholds for cancer detection. Further advancements in imaging methods and radiotracers for PSMA PET/CT are expected to enhance diagnostic precision and reduce false-positive findings (Luining et al. 2021; Hagens et al. 2022). Incorporating advanced analytical methods such as AI for image interpretation may also contribute. Research in this field will likely focus on enhancing specificity, particularly in differentiating between benign and malignant tumors (Menon et al. 2023). However, the updated 2023 EAU guidelines recommend a cautious approach. Given the current data, modifying therapy based on the PSMA PET/CT findings is not advised, highlighting the need for a balanced assessment (Gelardi et al. 2023).

Thus, with its exceptional sensitivity, we determined that adopting PSMA PET/CT considerably enhances PCa BCR identification and treatment, especially with advanced radiotracers such as ^{18}F-PSMA-1007. However, challenges remain in determining the optimal PSA cutoff levels, highlighting the need for individualized approaches considering demographic and epidemiological variables.

Diagnosis of metastatic PCa using PSMA/PET-CT

Advantages in detecting distant metastases

Accurately identifying and assessing distant metastatic sites are pivotal for tailoring treatment strategies and predicting PCa progression. The skeletal system is a primary site for PCa metastases. However, the uptake of Tc-labeled bisphosphonates is influenced by osteoblast activity, limiting the specificity of BS (Zirakchian Zadeh 2024). If the metastatic cells are restricted to the bone marrow and osteoblasts exhibit minimal response, early bone metastases can go unnoticed. Traditionally, identifying and accurately staging bone metastases have been challenging due to the low specificity of BS. With the advent of PSMA PET/CT, a new era in detecting PCa bone metastases has emerged. PSMA PET can effectively detect pathological lymph nodes and low-volume bone marrow lesions that are often challenging to identify with traditional imaging techniques (Ravi Kumar et al. 2020).

Compared to conventional imaging methods, PSMA PET exhibits higher sensitivity and specificity, enabling the detection of a greater number of metastatic lesions. A recent study indicates that PSMA PET/CT considerably improves the detection rates of lymph nodes (n) and/or distant metastases (m1), showing a detection rate of 56.7% compared to 13.3% for CT. Additionally, in cases of unknown bone metastasis, PSMA PET/CT identified such lesions in 15% (9/60) of patients without any false negatives. The TNM staging was ultimately enhanced in 45.0% (27/60) of cases, leading to a change in treatment plans for 28.8% (17/59) of patients (Rovera et al. 2024). Similarly, a previous study conducted at our center revealed that PSMA PET/CT demonstrates superior diagnostic performance and earlier detection of metastatic

lesions compared with traditional imaging approaches (Zhou et al. 2022). PSMA PET/CT demonstrates remarkable superiority over PET/CT. A study found that ^{18}F-PSMA-1007 and ^{68}Ga-PSMA PET/CT outperformed ^{18}F-FDG PET/CT in identifying distant metastases, influencing treatment decisions in 28% of cases (Hofman et al. 2020). Traditional imaging techniques have limitations in terms of detecting PCa metastases in nonconventional locations, including the liver, pancreas, genital and urinary tracts, peritoneum, abdominal wall, and areas of perineural spread (Patra et al. 2022; Rekha et al. 2022). Atypical metastatic lesions were observed in 6.4% of the 764 PCa analyzed with ^{68}Ga-PSMA PET/CT in a study by Vaz et al. These studies highlight the ability of PSMA PET/CT to detect PCa metastases in uncommon locations such as the thyroid, liver, and cervical and mediastinal lymph nodes (Carrilho Vaz et al. 2020). Currently, the definition of disease volume based on traditional imaging primarily follows the CHAARTED standards: high-volume disease (HVD) is characterized by the presence of internal organ involvement or at least four bone metastases, with at least one located in the spine or pelvis; low-volume disease (LVD) refers to cases that do not meet these criteria (Unterrainer et al. 2025). Analyzing the metabolic volume parameters in PSMA PET imaging, specifically PSMA tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA), provides valuable metabolic information throughout the body, extending beyond mere anatomical structure data. This metabolic information offers a more comprehensive reflection of the disease's burden and distribution, aiding in a more accurate definition of disease volume. Studies conducted by Aksu et al. have demonstrated significant differences in PSMA-TV and TL-PSMA values between metastatic and non-metastatic patients, with P values of 0.008 and <0.001, respectively (Aksu et al. 2021). Furthermore, patients exhibiting a metabolic tumor volume of the whole body (MTVWB) and total lesion PSMA (TLPWB) show considerably higher values compared to those with a short biochemical recurrence time (0–6 months) (Yildirim et al. 2021). Additionally, the metabolic volume parameters derived from PSMA PET (PSMA-TVPrimary and PSMA-TVWHOLE BODY) can more directly reflect the metabolic activity and disease burden of tumors, suggesting their potential as new standards in clinical practice. The aforementioned literature indicates that PSMA PET/CT, as a novel and superior imaging modality, has the potential to transform the diagnostic criteria for defining tumor burden that are currently based on traditional tools. This is particularly evident through its derived parameters, including tumor segmentation volume (Table 1).

Role in evaluating response to systemic therapy

For patients with high-risk, recurrent, and metastatic PCa, single-modality therapies often yield suboptimal outcomes, necessitating systemic treatment. PSMA PET/CT has demonstrated remarkable potential in systemic therapy decision-making, as its high sensitivity and specificity for detecting oligometastatic lesions enable efficient identification of patients requiring systemic interventions (Gawish et al. 2023). In systemic therapy management, PSMA PET/CT facilitates longitudinal monitoring to promptly identify treatment responses. A study evaluating post-systemic therapy in patients with metastatic castration-resistant PCa (mCRPCa) revealed that PSMA PET/CT could detect individual treatment-responsive lesions even in cases of overall disease progression (Probst et al. 2022). Regarding comprehensive assessment of systemic therapy efficacy, PSMA PET/CT exhibits robust capabilities. In a previous study, the derived parameter PSMA total tumor volume (PSMA-TV) achieved 94.6% concordance (35/37 patients) with biochemical responses (PSA changes) in patients with metastatic PCa (Shagera et al. 2022). Furthermore, PSMA PET/CT surpasses PSA in prognostic stratification post-systemic therapy. A study identified that 31% of patients with $>50\%$ PSA decline showed disease progression on PSMA PET/CT, correlating with elevated mortality risk (Kleiburg et al. 2024). While multiple imaging-based tools exist for systemic therapy evaluation, PSMA PET-specific criteria demonstrate superior clinical potential. Gafita et al. (2022) performed a multicenter comparison of assessment frameworks—including RECIST 1.1, adapted PCWG3 (aPCWG3), adapted PERCIST (aPERCIST), PSMA PET progression (PPP), and RECIP 1.0—and revealed that RECIP 1.0 more accurately reflects true treatment responses compared to other criteria prone to overestimating progression (A et al. 2022) (Table 2).

Challenges and future perspectives in metastatic PCa

Although PSMA PET/CT has demonstrated significant advantages in the diagnosis and treatment of metastatic PCa, its applications still encounter several challenges. For instance, research at our center has shown that ^{18}F-PSMA-1007 PET/CT exhibits a higher distant false-positive rate compared to ^{18}F-FDG PET/CT in the differentiation of benign lesions. This finding suggests the need for further optimization of imaging technology and diagnostic standards for PET/CT in order to reduce the misdiagnosis rate of distant metastatic lesions (Zhou et al. 2019). Integrating a computer-aided diagnosis (CAD) system into PET/CT imaging represents an important developmental direction.

Table 1 "Comparison of PSMA-targeted radiopharmaceutical characteristics" summarizes the radionuclide labeling, clinical applications, and performance features of commonly used PSMA-targeted compounds in prostate cancer management, covering both diagnostic (e.g., $^{68}Ga/^{18}F$-labeled PET imaging) and therapeutic (e.g., $^{177}Lu/^{225}Ac$-labeled targeted radiotherapy) domains

Compound Name	Labeling Isotope	Imaging Purpose	Advantages	Disadvantages
PSMA-11	^{68}Ga	Imaging	Most widely used in literature; EMA and FDA approval	68Ga-related disadvantages; high accumulation in urinary tract
PSMA-617	^{68}Ga	Imaging and therapy	Reduced kidney uptake compared with PSMA-11	68Ga-related disadvantages; slightly slower tracer kinetics than PSMA-11; high accumulation in urinary tract; complex production process and higher costs
PSMA-I&T	^{68}Ga	Imaging and therapy	Reduced hepatic uptake compared with PSMA-11	68Ga-related disadvantages; lower lesion binding and higher background than PSMA-11
DCFPyL	^{18}F	Imaging	Low hepatic uptake	High accumulation in urinary tract
PSMA-1007	^{18}F	Imaging	Low accumulation in urinary tract; moderate half-life (~109 min), suitable for clinical use	High hepatic uptake; higher number of PSMA-positive lesions attributed to benign origin
rhPSMA-7	^{18}F, ^{68}Ga	Imaging and therapy	Radiohybrid concept; low accumulation in urinary tract with 18 F	Higher number of PSMA-positive lesions attributed to benign origin; unspecified 68Ga-related disadvantages
DOTA-DIPSM	^{68}Ga	Imaging	Clearer visualization of small lesions near the bladder; lower background uptake	Small sample size; limited clinical validation; unclear urinary tract accumulation
JKPSMA-7	^{18}F	Imaging	High affinity for PSMA; reduced uptake in normal tissues	Limited clinical data; certain uptake in non-tumor tissues
AlF-PSMA-1	^{18}F	Imaging	High affinity for PSMA; reduced hepatic uptake compared to 68Ga-PSMA-11	Poor stability; affects detection of small bone metastases; limited clinical data
PSMA-617	^{177}Lu	Imaging and therapy	High uptake in prostate cancer lesions; α and βparticles from decay aid therapy	Longer half-life (~6.6 days) increases radiation exposure risk; high liver/kidney uptake raises toxicity concerns
PSMA-617	^{99m}Tc	Imaging	High radiochemical purity; good in vitro stability; selective uptake in prostate cancer cells	Potential non-specific uptake; lower resolution compared to PET
PSMA-I&T	^{225}Ac	Therapy and diagnosis	High-efficiency α-particle therapy; significant tumor cell killing	Complex implementation requiring dose escalation; treatment interruption risks; delayed tumor response
PSMA1	^{211}At	Diagnosis and therapy	Suitable for precise radiotherapy; short half-life (~8 h) reduces systemic exposure	High toxicity to normal tissues; low labeling efficiency requiring optimization
PSMA-617	^{64}Cu	Imaging and diagnosis	High targeting specificity; good tumor contrast	High liver uptake may affect image quality; requires optimization for stability
DOTA-Acp-PSMA	^{44}Sc	Imaging	High targeting specificity; good tumor contrast	Low labeling efficiency requiring optimization
PSMA-I&T	^{111}In	SPECT imaging and diagnosis	Long half-life (~110 h) for extended imaging; high targeting specificity	Low γ-ray energy reduces sensitivity
PSMA-617	^{152}Tb	Diagnosis	High targeting specificity; good tumor contrast	Low labeling efficiency; β+ emission may affect image quality

The CAD system can automatically process quantitative indicators in PET/CT and single-photon emission computed tomography, thereby facilitating a rapid assessment of the overall burden of bone tumors. This automation not only enhances efficiency but also alleviates the cumbersome process of manual calculations (Chen et al. 2022). Looking ahead, the incorporation of advanced imaging technologies such as PSMA PET/CT into clinical practice is anticipated to aid in the early detection of PCA metastases and provide patients with personalized treatment plans (Barletta et al. 2023). However, further research and clinical trials are essential to evaluate the impact of these new technologies on patient prognosis and to establish a standardized clinical application guide. PSMA PET/CT has surpassed traditional BS, CT, and MRI in detecting and staging distant metastases, considerably improving treatment planning. AI introduction has further refined the diagnostic process and enhanced the quality of patient care.

Table 2 "Advantages and limitations of imaging modalities for assessing prostate cancer therapy" compares the characteristics of mainstream imaging tools (CT, ultrasound, MRI, and PSMA-PET) in evaluating therapeutic responses, highlighting their strengths (e.g., CT for bone visualization, MRI for soft-tissue resolution, PSMA-PET for lymph node metastasis detection) and limitations (radiation exposure, operator dependence, cost)

Diagnostic Modality	Advantages	Disadvantages
CT	Rapid image acquisition; High spatial resolution & penetration depth; Excellent bone visualization; High sensitivity/specificity for anatomical characterization; Short examination time; Widely available	Ionizing radiation exposure; Requires contrast administration for vascular studies; Limited soft tissue contrast resolution; Motion/beam-hardening artifacts; Requires heart rate control for cardiac imaging; Nephrotoxic contrast risks
US	Radiation-free; Real-time imaging capability; Low cost & non-invasive; High resolution with endoscopic US (EUS); Enables guided tissue sampling; Portable for bedside use	Operator-dependent; Limited field of view; Reduced efficacy in obese patients/intestinal gas interference; Poor penetration depth for deep structures; Endoscopic US invasiveness; Inability to evaluate deep arterial systems
MRI	Superior soft tissue contrast resolution; Non-ionizing radiation; Multiplanar imaging capability; High sensitivity for vascular wall inflammation; Detects early vascular changes; Contrast administration optional for many protocols	Prolonged scan duration; High operational costs; Limited availability in resource-constrained settings; Susceptibility to motion/metallic artifacts; Claustrophobia induction; Poor calcium detection sensitivity; Requires patient proximity to receive coils
PSMA-PET	Superior sensitivity/specificity for nodal & oligometastatic disease; Provides functional tumor characterization; Outperforms conventional imaging in N-staging; Detects extrapelvic metastases effectively	Limited spatial resolution; Elevated radiation dose (combined PET/CT); High operational costs; Requires large anatomical coverage; Diagnostic accuracy influenced by PSA levels & Gleason score; Suboptimal performance in T-staging; Limited availability of radiotracers

Current challenge and prospects

Technological advancements and a deeper understanding of PCa drive the rapid progress of PSMA PET/CT applications for its detection. However, challenges remain in standardization and accessibility. The prospects are promising, signaling a shift toward more accurate, personalized, and safer diagnostic methods. While PSMA PET/CT shows potential for improving PCa diagnosis, several obstacles remain.

First, optimizing PSMA PET/CT protocols, including tracer selection and imaging parameters, is ongoing (Piron et al. 2020). Although guidelines have enhanced the clinical utility of PSMA PET/CT and tracers such as ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 are promising, the clinical acceptance of PSMA PET/CT is still under study, especially with respect to its impact on treatment plan modification (McKone et al. 2024). More comprehensive data and high-level evidence from prospective, large-sample, randomized, multicenter clinical trials are required to establish efficacy.

Second, some PCa subtypes, such as neuroendocrine PCa, may have low or no PSMA expression, affecting their detection and treatment. Patients with these tumors may not be suitable candidates for PSMA PET/CT scans (Ferraro et al. 2020), as they often have poorer prognosis and higher metastatic potential (Adebahr et al. 2024). One study indicated that 20–25% of patients in an unselected population may be excluded from PSMA PET/CT screening (Hotta et al. 2022). Combining PSMA with other imaging techniques, such as mpMRI, could improve tumor detection in these individuals (Vetrone et al. 2023). Alternative pathways have been identified for PSMA-negative tumors, which often exhibit a strong positive response to specific receptors, such as neurotensin receptor 1, fibroblast activation protein, and gastrin-releasing peptide receptor (Verena et al. 2023; Schollhammer et al. 2023). These receptors could be targeted for more accurate imaging and therapy in these PSMA-negative cases.

Third, PSMA expression is not limited to PCa tissue (Eapen et al. 2019); various non-prostate solid tumors, including renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer, have also been found to exhibit elevated PSMA expression. This extra-prostatic expression can lead to diagnostic inaccuracies, particularly when differentiating between metastatic and benign tissues. For example, increased PSMA uptake in sympathetic ganglia, such as the supraclavicular and retroperitoneal regions, is often misinterpreted as LNM (Uijen et al. 2021). Additionally, the excretion of ^{68}Ga-PSMA, primarily through the urinary system, can lead to focal accumulations that may be mistaken for suspicious lymph nodes or overlooked as local recurrences near the bladder (Morawitz et al. 2022). Although alternative tracers, including ^{18}F-labeled molecules, bypass renal excretion, they may cause false positives in bone lesions, particularly benign abnormalities such as fibrous dysplasia or fractures (Arnfield et al. 2021). Adopting the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria helps mitigate these pitfalls by refining the interpretation of imaging results (Eiber et al. 2018).

Fourth, the accessibility of PSMA PET/CT for PCa in resource-limited settings, particularly in developing nations, remains a significant challenge due to the high cost

of producing PSMA radiotracers and operating PET/CT scanners. Thus, applying PSMA PET/CT in resource-poor locations may improve by introducing affordable tracers. Duncan et al. conducted a comparative analysis in Australia using the more cost-effective ^{99}mTc-PSMA in different groups of patients with PCa. Compared to ^{68}Ga-PSMA and mpMRI, ^{99}mTc-PSMA demonstrated favorable sensitivity, specificity, NPV, and PPV (Duncan et al. 2023). In conclusion, further research and development are needed to make PSMA PET/CT more accessible and affordable in resource-limited settings.

Despite these challenges, the prospects for PSMA PET/CT in PCa detection are promising. The recent surge in AI advancements, led by OPEN AI, has introduced breakthroughs in the traditional field of machine learning, particularly with the introduction of the attention mechanism, first introduced by Google (Vaswani et al. 2023). Research in PSMA PET/CT continues to advance, exploring new applications and improvements. A meta-analysis incorporating 14 studies demonstrated that in differentiating high-grade PCa (ISUP GG≥3), AI is capable of automatically detecting small metastatic lesions in PSMA PET scans, particularly in complex anatomical regions, thereby reducing the likelihood of missed diagnoses caused by human factors and achieving a high accuracy rate (98%) in identifying lymph node and distant metastases of PCa (Liu et al. 2024). Furthermore, AI can predict patients' treatment response and prognosis by analyzing features in PSMA PET images. The latest research indicates that combining deep learning with preoperative PSMA PET/CT images of patients can yield higher benefits than traditional nomograms, with an AI value of 0.89 (95% CI: 0.81–0.97) compared to 0.79 (95% CI: 0.61–0.97) for the MSKCC nomogram and 0.69 (95% CI: 0.50–0.88) for the Briganti −2017 nomogram (Ma et al. 2025). Additionally, AI can automate the processing of PSMA PET images, reducing the time and subjectivity associated with manual image reading while also enhancing image quality and lesion detection rate (Kersting et al. 2025). It also aids radiotherapists in better planning radiotherapy regimens by performing automated segmentation and measurement of tumor volume (Liu et al. 2025). Advanced PET scanner technologies have enhanced PSMA PET/CT's role in PCa diagnosis and management. Clinically used PSMA PET/CT scanners typically have a relatively small axial field of view (aFOV), usually ranging from tens of centimeters to around 100 cm, and cannot cover the entire body in a single scan. In contrast, whole-body PET/CT scanners have an aFOV that can reach up to 194 cm, enabling a single continuous scan from head to toe without the need for multi-bed acquisitions (Spencer et al. 2021). Due to their large FOV, they can complete a whole-body scan with quality similar to that of a conventional PET/CT scan, which typically takes 20–30 min, in just 2–4 min (Drzezga et al. 2012; Tan et al. 2021).Whole-body PET scanners possess extremely high sensitivity. For example, the sensitivity of the uEXPLORER PET/CT system can reach 174 kcps/MBq, which is about 40 times higher than that of traditional PET scanners, and can provide high-quality images with a spatial resolution of within 3.0 millimeters (FWHM) (Spencer et al. 2021). Moreover, high sensitivity indicates that a lower dose of radioactive tracer can be used, thereby reducing the radiation dose received by patients (Katal et al. 2022).

In summary, PSMA PET/CT is confronted with several challenges. However, the future prospects are bright, particularly with the integration of AI and the automation of image processing. Ongoing research is committed to addressing these challenges and enhancing the accessibility and effectiveness of PSMA PET/CT.

Conclusion

PSMA PET/CT is a significant advancement in PCa imaging, offering high specificity, especially in high-risk cases. Its applications include diagnosis, biopsy guidance, and prognostication. However, sensitivity and accessibility issues persist, highlighting the need for further study and innovation. Future PSMA PET/CT developments are expected to enhance imaging techniques and radiotracers, improving diagnostic accuracy and reducing false positives. AI advancements are also expected to refine diagnostic precision. As our understanding of PCa biology evolves, PSMA PET/CT will be crucial in personalized and effective management.

Acknowledgements We acknowledge the support of the Health Commission of Sichuan Province Medical Science and Technology Program (grant number 23LCYJ004) for funding our research, titled "Clinical Value of Early Adjuvant Stereotactic Radiotherapy for Oligorecurrent Metastases in High-Risk Prostate Cancer Patients After Radical Prostatectomy Guided by Precision Evaluation Using 18F-PSMA-1007 PET/CT." This funding was instrumental in enabling the successful completion of our study.

Author contributions Zhengang Shen wrote the original draft and conceptualized the study. Zeng Li funded this project. Xiaodi Tang and Jiayi Lu managed the project. Yunlong Li was responsible for visualization. Li Chen collected the literature. Zhuzhong Cheng Critical reviewed the manuscript. Hong Liao and Shukui Zhou contributed to supervision and guidance. All authors read and approved the final manuscript.

Funding This research was supported by the Health Commission of Sichuan Province Medical Science and Technology Program (grant number 23LCYJ004): Clinical Value of Early Adjuvant Stereotactic Radiotherapy for Oligorecurrent Metastases in High-Risk Prostate Cancer Patients After Radical Prostatectomy Guided by Precision Evaluation Using ^{18}F-PSMA-1007 PET/CT.

Data availability No datasets were generated or analysed during the current study.

Declarations

Informed consent Not applicable.

Research involving human participants and/or animals Not applicable.

Competing interests The authors declare no competing interests.

References

Adebahr S, Althaus A, Scharl S et al (2024) The prognostic significance of a negative PSMA-PET scan prior to salvage radiotherapy following radical prostatectomy. Eur J Nucl Med Mol Imaging 51:558–567. https://doi.org/10.1007/s00259-023-06438-3

Aksu A, Karahan Şen NP, Tuna EB, Aslan G, Çapa Kaya G (2021) Evaluation of 68ga-PSMA PET/CT with volumetric parameters for staging of prostate cancer patients. Nucl Med Commun 42:503–509. https://doi.org/10.1097/MNM.0000000000001370

Arnfield EG, Thomas PA, Roberts MJ et al (2021) Clinical insignificance of [18F]PSMA-1007 avid non-specific bone lesions: a retrospective evaluation. Eur J Nucl Med Mol Imaging 48:4495–4507. https://doi.org/10.1007/s00259-021-05456-3

Bagguley D, Ong S, Buteau JP et al (2021) Role of PSMA PET/CT imaging in the diagnosis, staging and restaging of prostate cancer. Future Oncol 17:2225–2241. https://doi.org/10.2217/fon-2020-1293

Bahler CD, Tachibana I, Tann M et al (2024) Comparing magnetic resonance imaging and prostate-specific membrane antigen-positron emission tomography for prediction of extraprostatic extension of prostate cancer and surgical guidance: a prospective nonrandomized clinical trial. J Urol 212:290–298. https://doi.org/10.1097/JU.0000000000004032

Barletta F, Ceci F, van den Bergh RCN et al (2023) The role of nuclear medicine tracers for prostate cancer surgery: from preoperative to intraoperative setting. Curr Opin Urol 33:502–509. https://doi.org/10.1097/MOU.0000000000001118

Bodar YJL, Boevé LMS, van Leeuwen PJ et al (2023) Using prostate-specific membrane antigen positron-emission tomography to guide prostate biopsies and stage men at high risk of prostate cancer. BJU Int 132:705–712. https://doi.org/10.1111/bju.16167

Bonekamp D, Schelb P, Wiesenfarth M et al (2019) Histopathological to multiparametric MRI Spatial mapping of extended systematic sextant and MR/TRUS-fusion-targeted biopsy of the prostate. Eur Radiol 29:1820–1830. https://doi.org/10.1007/s00330-018-5751-1

Budäus L, Leyh-Bannurah S-R, Salomon G et al (2016) Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol 69:393–396. https://doi.org/10.1016/j.eururo.2015.06.010

Cahill LC, Wu Y, Yoshitake T et al (2020) Nonlinear microscopy for detection of prostate cancer: analysis of sensitivity and specificity in radical prostatectomies. Mod Pathol 33:916–923. https://doi.org/10.1038/s41379-019-0408-4

Carrilho Vaz S, Silva Â, Oliveira C et al (2020) Impact of PSMA PET/CT in prostate cancer patient's clinical management: a pictorial essay of interesting cases with histologic confirmation. Clin Transl Imaging 8:207–226. https://doi.org/10.1007/s40336-020-00372-2

Cereser L, Evangelista L, Giannarini G, Girometti R (2023) Prostate MRI and PSMA-PET in the primary diagnosis of prostate cancer. Diagnostics (Basel) 13:2697. https://doi.org/10.3390/diagnostics13162697

Chen Z, Chen X, Wang R (2022) Application of SPECT and PET / CT with computer-aided diagnosis in bone metastasis of prostate cancer: a review. Cancer Imaging 22:18. https://doi.org/10.1186/s40644-022-00456-4

Chow KM, So WZ, Lee HJ et al (2023) Head-to-head comparison of the diagnostic accuracy of prostate-specific membrane antigen positron emission tomography and conventional imaging modalities for initial staging of intermediate- to high-risk prostate cancer: A systematic review and meta-analysis. Eur Urol 84:36–48. https://doi.org/10.1016/j.eururo.2023.03.001

Christensen MT, Jochumsen MR, Klingenberg S et al (2022) Evaluation of predictors of biochemical recurrence in prostate cancer patients, as detected by 68ga-PSMA PET/CT. Diagnostics (Basel) 12:195. https://doi.org/10.3390/diagnostics12010195

Daryanani A, Turkbey B (2022) Recent advancements in CT and MR imaging of prostate cancer. Semin Nucl Med 52:365–373. https://doi.org/10.1053/j.semnuclmed.2021.11.013

De Man K, Van Laeken N, Schelfhout V et al (2022) 18F-PSMA-11 versus 68Ga-PSMA-11 positron emission tomography/computed tomography for staging and biochemical recurrence of prostate cancer: a prospective double-blind randomised cross-over trial. Eur Urol 82:501–509. https://doi.org/10.1016/j.eururo.2022.05.010

Dietlein F, Kobe C, Neubauer S et al (2017) PSA-stratified performance of 18F- and 68Ga-PSMA PET in patients with biochemical recurrence of prostate cancer. J Nucl Med 58:947–952. https://doi.org/10.2967/jnumed.116.185538

Ditonno F, Franco A, Manfredi C et al (2024) Novel non-MRI imaging techniques for primary diagnosis of prostate cancer: micro-ultrasound, contrast-enhanced ultrasound, elastography, multiparametric ultrasound, and PSMA PET/CT. Prostate Cancer Prostatic Dis 27:29–36. https://doi.org/10.1038/s41391-023-00708-9

Drzezga A, Souvatzoglou M, Eiber M et al (2012) First clinical experience with integrated whole-body PET/MR: comparison to PET/CT in patients with oncologic diagnoses. J Nucl Med 53:845–855. https://doi.org/10.2967/jnumed.111.098608

Duncan I, Ingold N, Martinez-Marroquin E, Paterson C (2023) An Australian experience using Tc-PSMA SPECT/CT in the primary diagnosis of prostate cancer and for staging at biochemical recurrence after local therapy. Prostate 83:970–979. https://doi.org/10.1002/pros.24538

Eapen RS, Nzenza TC, Murphy DG et al (2019) PSMA PET applications in the prostate cancer journey: from diagnosis to theranostics. World J Urol 37:1255–1261. https://doi.org/10.1007/s00345-018-2524-z

Eiber M, Fendler WP, Rowe SP et al (2017) Prostate-specific membrane antigen ligands for imaging and therapy. J Nucl Med 58(Supplement 2):67S–76S. https://doi.org/10.2967/jnumed.116.186767

Eiber M, Herrmann K, Calais J et al (2018) Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed MiTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med 59:469–478. https://doi.org/10.2967/jnumed.117.198119

Evangelista L, Maurer T, van der Poel H et al (2022) [68Ga]Ga-PSMA versus [18F]PSMA positron emission tomography/computed tomography in the staging of primary and recurrent prostate cancer. A systematic review of the literature. Eur Urol Oncol 5:273–282. https://doi.org/10.1016/j.euo.2022.03.004

Ferraro DA, Rüschoff JH, Muehlematter UJ et al (2020) Immunohistochemical PSMA expression patterns of primary prostate cancer tissue are associated with the detection rate of biochemical recurrence with 68Ga-PSMA-11-PET. Theranostics 10:6082–6094. https://doi.org/10.7150/thno.44584

Gafita A, Rauscher I, Fendler WP et al (2022) Measuring response in metastatic castration-resistant prostate cancer using PSMA PET/CT: comparison of RECIST 1.1, aPCWG3, aPERCIST, PPP, and RECIP 1.0 criteria. Eur J Nucl Med Mol Imaging 49:4271–4281. https://doi.org/10.1007/s00259-022-05882-x

Gawish A, Abdullayev N, El-Arayedh S et al (2023) Metabolic response after 68Ga-PSMA-PET/CT-directed IGRT/SBRT for oligometastases prostate cancer. Clin Transl Oncol 25:987–994. https://doi.org/10.1007/s12094-022-03002-7

Gelardi F, Briganti A, Pini C et al (2023) European guidelines update on PSMA PET/CT for prostate cancer staging-snap back to reality. Eur J Nucl Med Mol Imaging 50:2572–2575. https://doi.org/10.1007/s00259-023-06287-0

Giesel FL, Will L, Kesch C et al (2018) Biochemical recurrence of prostate cancer: initial results with [18F]PSMA-1007 PET/CT. J Nucl Med 59:632–635. https://doi.org/10.2967/jnumed.117.196329

Hagens MJ, Oprea-Lager DE, Vis AN et al (2022) Reproducibility of PSMA PET/CT imaging for primary staging of treatment-naïve prostate cancer patients depends on the applied radiotracer: A retrospective study. J Nucl Med 63:1531–1536. https://doi.org/10.2967/jnumed.121.263139

Hinsenveld FJ, Wit EMK, van Leeuwen PJ et al (2020) Prostate-specific membrane antigen PET/CT combined with Sentinel node biopsy for primary lymph node staging in prostate cancer. J Nucl Med 61:540–545. https://doi.org/10.2967/jnumed.119.232199

Hoberück S, Löck S, Borkowetz A et al (2021) Intraindividual comparison of [68 ga]-Ga-PSMA-11 and [18F]-F-PSMA-1007 in prostate cancer patients: a retrospective single-center analysis. EJNMMI Res 11:109. https://doi.org/10.1186/s13550-021-00845-z

Hoffmann MA, Buchholz H-G, Wieler HJ et al (2020) Dual-Time point [68Ga]Ga-PSMA-11 PET/CT hybrid imaging for staging and restaging of prostate cancer. Cancers 12:2788. https://doi.org/10.3390/cancers12102788

Hofman MS, Lawrentschuk N, Francis RJ et al (2020) Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 395:1208–1216. https://doi.org/10.1016/S0140-6736(20)30314-7

Hotta M, Gafita A, Czernin J, Calais J (2022) Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: A multicenter retrospective analysis. J Nucl Med 63:1484–1488. https://doi.org/10.2967/jnumed.121.263441

Huang S, Ong S, McKenzie D et al (2023) Comparison of 18F-based PSMA radiotracers with [68Ga]Ga-PSMA-11 in PET/CT imaging of prostate cancer—a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 1–11. https://doi.org/10.1038/s41391-023-00755-2

Ingvar J, Hvittfeldt E, Trägårdh E, Simoulis A, Bjartell A (2022) Assessing the accuracy of [18F]PSMA-1007 PET/CT for primary staging of lymph node metastases in intermediate- and high-risk prostate cancer patients. EJNMMI Res 12:48. https://doi.org/10.1186/s13550-022-00918-7

Jeet V, Parkinson B, Song R, Sharma R, Hoyle M (2023) Histopathologically validated diagnostic accuracy of PSMA-PET/CT in the primary and secondary staging of prostate cancer and the impact of PSMA-PET/CT on clinical management: a systematic review and meta-analysis. Semin Nucl Med 53:706–718. https://doi.org/10.1053/j.semnuclmed.2023.02.006

Katal S, Eibschutz LS, Saboury B, Gholamrezanezhad A, Alavi A (2022) Advantages and applications of total-body PET scanning. Diagn (Basel Switz) 12:426. https://doi.org/10.3390/diagnostics12020426

Kersting D, Borys K, Küper A et al (2025) Staging of prostate cancer with ultra-fast PSMA-PET scans enhanced by AI. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-024-07060-7

Kleiburg F, de Geus-Oei LF, Luelmo SAC et al (2024) PSMA PET/CT for treatment response evaluation at predefined time points is superior to PSA response for predicting survival in metastatic castration-resistant prostate cancer patients. Eur J Radiol 181:111774. https://doi.org/10.1016/j.ejrad.2024.111774

Kuten J, Fahoum I, Savin Z et al (2020) Head-to-head comparison of 68ga-PSMA-11 with 18F-PSMA-1007 PET/CT in staging prostate cancer using histopathology and immunohistochemical analysis as a reference standard. J Nucl Med 61:527–532. https://doi.org/10.2967/jnumed.119.234187

Le JD, Tan N, Shkolyar E et al (2015) Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol 67:569–576. https://doi.org/10.1016/j.eururo.2014.08.079

Liu C, Liu T, Zhang Z et al (2020) 68ga-PSMA PET/CT combined with PET/ultrasound-guided prostate biopsy can diagnose clinically significant prostate cancer in men with previous negative biopsy results. J Nucl Med 61:1314–1319. https://doi.org/10.2967/jnumed.119.235333

Liu J, Cundy TP, Woon DTS, Lawrentschuk N (2024) A systematic review on artificial intelligence evaluating metastatic prostatic cancer and lymph nodes on PSMA PET scans. Cancers 16:486. https://doi.org/10.3390/cancers16030486

Liu J, Sandhu K, Woon DTS, Perera M, Lawrentschuk N (2025) The value of artificial intelligence in prostate-specific membrane antigen positron emission tomography: an update. Semin Nucl Med:S. https://doi.org/10.1053/j.semnuclmed.2024.12.001.0001-2998(24)00120-X

Luining WI, Meijer D, Dahele MR, Vis AN, Oprea-Lager DE (2021) Nuclear imaging for bone metastases in prostate cancer: the emergence of modern techniques using novel radiotracers. Diagnostics (Basel) 11:117. https://doi.org/10.3390/diagnostics11010117

Maisto C, Aurilio M, Morisco A et al (2022) Analysis of pros and cons in using [68Ga]Ga-PSMA-11 and [18F]PSMA-1007: production, costs, and PET/CT applications in patients with prostate cancer. Molecules 27:3862. https://doi.org/10.3390/molecules27123862

Malaspina S, Anttinen M, Taimen P et al (2021) Prospective comparison of 18F-PSMA-1007 PET/CT, whole-body MRI and CT in primary nodal staging of unfavourable intermediate- and high-risk prostate cancer. Eur J Nucl Med Mol Imaging 48:2951–2959. https://doi.org/10.1007/s00259-021-05296-1

Ma Q, Chen B, Seifert R et al (2025) PSMA PET/CT based multimodal deep learning model for accurate prediction of pelvic

lymph-node metastases in prostate cancer patients identified as candidates for extended pelvic lymph node dissection by preoperative nomograms. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-024-07065-2

Maurer T, Gschwend JE, Rauscher I et al (2016) Diagnostic efficacy of (68)gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 195:1436–1443. https://doi.org/10.1016/j.juro.2015.12.025

McKone EL, Sutton EA, Johnson GB, Phillips RM (2024) Application of advanced imaging to prostate cancer diagnosis and management: A narrative review of current practice and unanswered questions. J Clin Med 13:446. https://doi.org/10.3390/jcm13020446

Menon N, Guidozzi N, Chidambaram S, Markar SR (2023) Performance of radiomics-based artificial intelligence systems in the diagnosis and prediction of treatment response and survival in esophageal cancer: a systematic review and meta-analysis of diagnostic accuracy. Dis Esophagus 36:doad034. https://doi.org/10.1093/dote/doad034

Mookerji N, Pfanner T, Hui A et al (2024) Fluorine-18 prostate-specific membrane antigen-1007 PET/CT vs multiparametric MRI for locoregional staging of prostate cancer. JAMA Oncol 10:1097–1103. https://doi.org/10.1001/jamaoncol.2024.3196

Morawitz J, Kirchner J, Hertelendy J et al (2022) Is there a diagnostic benefit of late-phase abdomino-pelvic PET/CT after urination as part of whole-body 68 ga-PSMA-11 PET/CT for restaging patients with biochemical recurrence of prostate cancer after radical prostatectomy? EJNMMI Res 12:12. https://doi.org/10.1186/s13550-022-00885-z

Morawitz J, Kirchner J, Lakes J et al (2021) PSMA PET/CT vs. CT alone in newly diagnosed biochemical recurrence of prostate cancer after radical prostatectomy: comparison of detection rates and therapeutic implications. Eur J Radiol 136:109556. https://doi.org/10.1016/j.ejrad.2021.109556

Muehlematter UJ, Burger IA, Becker AS et al (2019) Diagnostic accuracy of multiparametric MRI versus 68ga-PSMA-11 PET/MRI for extracapsular extension and seminal vesicle invasion in patients with prostate cancer. Radiology 293:350–358. https://doi.org/10.1148/radiol.2019190687

Murata Y, Tatsugami K, Yoshikawa M et al (2018) Predictive factors of biochemical recurrence after radical prostatectomy for high-risk prostate cancer. Int J Urol 25:284–289. https://doi.org/10.1111/iju.13514

Patra A, Khasawneh H, Suman G et al (2022) Cal metastases in the abdomen and pelvis from biochemically recurrent prostate cancer. AJR Am J Roentgenol Atypi 218:141–150. https://doi.org/10.2214/AJR.21.26426.:11 C-Choline PET/CT With Multimodality Correlation

Piron S, De Man K, Schelfhout V et al (2020) Optimization of PET protocol and interrater reliability of 18F-PSMA-11 imaging of prostate cancer. EJNMMI Res 10:14. https://doi.org/10.1186/s13550-020-0593-7

Probst S, Bjartell A, Anand A, Skamene T, Ferrario C (2022) Interval changes in PSMA PET/CT during radium-223 therapy for metastatic bone disease from castration-resistant prostate cancer. Nucl Med Mol Imaging 56:188–195. https://doi.org/10.1007/s13139-022-00754-6

Ravi Kumar AS, Lawrentschuk N, Hofman MS (2020) Prostate-specific membrane antigen PET/computed tomography for staging prostate cancer. Curr Opin Urol 30:628–634. https://doi.org/10.1097/MOU.0000000000000799

Rekha KP, Ray DS, Jubaida R, Sharif MM, Hussain M (2022) MDCT detection of omental metastases with peritoneal carcinomatosis and Ascites in prostate cancer: an unusual metastatic site. KYAMC J 13:124–126. https://doi.org/10.3329/kyamcj.v13i2.61344

Rovera G, Grimaldi S, Oderda M et al (2024) Comparative performance of 68ga-PSMA-11 PET/CT and conventional imaging in the primary staging of high-risk prostate cancer patients who are candidates for radical prostatectomy. Diagnostics (Basel) 141964. https://doi.org/10.3390/diagnostics14171964

Sadeghi F, Sheikhzadeh P, Farzanehfar S et al (2023) The effects of various penalty parameter values in Q.Clear algorithm for rectal cancer detection on 18F-FDG images using a BGO-based PET/CT scanner: a Phantom and clinical study. EJNMMI Phys 10:63. https://doi.org/10.1186/s40658-023-00587-y

Sawicki LM, Kirchner J, Buddensieck C et al (2019) Prospective comparison of whole-body MRI and 68ga-PSMA PET/CT for the detection of biochemical recurrence of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 46:1542–1550. https://doi.org/10.1007/s00259-019-04308-5

Schollhammer R, Quintyn Ranty M-L, de Clermont Gallerande H et al (2023) Theranostics of primary prostate cancer: beyond PSMA and GRP-R. Cancers (Basel) 15:2345. https://doi.org/10.3390/cancers15082345

Seo Y, Khalighi MM, Wangerin KA et al (2020) Quantitative and qualitative improvement of low-count [68ga]citrate and [90Y] microspheres PET image reconstructions using block sequential regularized expectation maximization algorithm. Mol Imaging Biol 22:208–216. https://doi.org/10.1007/s11307-019-01347-0

Shagera QA, Artigas C, Karfis I et al (2022) 68ga-PSMA PET/CT for response assessment and outcome prediction in metastatic prostate cancer patients treated with taxane-based chemotherapy. J Nucl Med 63:1191–1198. https://doi.org/10.2967/jnumed.121.263006

Shahab AA, Soebadi DM, Djatisoesanto W et al (2013) Prostate-specific antigen and prostate-specific antigen density cutoff points among Indonesian population suspected for prostate cancer. Prostate Int 1:23–30. https://doi.org/10.12954/PI.12003

Sharma AP, Kumar R, Chauhan R et al (2023) Accuracy of combined multi-parametric MRI and PSMA PET-CT in diagnosing localized prostate cancer: newer horizons for a biopsy-free pathway. Eur J Hybrid Imaging 7:24. https://doi.org/10.1186/s41824-023-00182-5

Siegel RL, Miller KD, Wagle NS, Jemal A (2023) Cancer statistics, 2023. CA Cancer J Clin 73:17–48. https://doi.org/10.3322/caac.21763

Simon NI, Parker C, Hope TA, Paller CJ (2022) Best approaches and updates for prostate cancer biochemical recurrence. Am Soc Clin Oncol Educ Book 42:1–8. https://doi.org/10.1200/EDBK_351033

Soeterik TFW, Heetman JG, Hermsen R et al (2024) The added value of prostate-specific membrane antigen positron emission tomography/computed tomography to magnetic resonance imaging for local staging of prostate cancer in patients undergoing radical prostatectomy. Eur Urol Oncol S 2588–9311. https://doi.org/10.1016/j.euo.2024.11.002. S2588-9311(24)00249-9

Spencer BA, Berg E, Schmall JP et al (2021) Performance evaluation of the uEXPLORER total-body PET/CT scanner based on NEMA NU 2–2018 with additional tests to characterize PET scanners with a long axial field of view. J Nucl Med 62:861–870. https://doi.org/10.2967/jnumed.120.250597

Tan H, Sui X, Yin H et al (2021) Total-body PET/CT using half-dose FDG and compared with conventional PET/CT using full-dose FDG in lung cancer. Eur J Nucl Med Mol Imaging 48:1966–1975. https://doi.org/10.1007/s00259-020-05091-4

Tan JSH, Goh CXY, Koh YS et al (2019) 68 Gallium-labelled PSMA-PET/CT as a diagnostic and clinical decision-making tool in Asian prostate cancer patients following prostatectomy. Cancer

Biol Med 16:157–166. https://doi.org/10.20892/j.issn.2095-3941.2018.0288

Tino WT, Huber MJ, Lake TP et al (2000) Isolation and characterization of monoclonal antibodies specific for protein conformational epitopes present in prostate-specific membrane antigen (PSMA). Hybridoma 19:249–257. https://doi.org/10.1089/027245700501096 48

Treglia G, Annunziata S, Pizzuto DA et al (2019) Detection rate of 18F-labeled PSMA PET/CT in biochemical recurrent prostate cancer: A systematic review and a meta-analysis. Cancers (Basel) 11:710. https://doi.org/10.3390/cancers11050710

Trägårdh E, Enqvist O, Ulén J et al (2022a) Freely available artificial intelligence for pelvic lymph node metastases in PSMA PET-CT that performs on par with nuclear medicine physicians. Eur J Nucl Med Mol Imaging 49:3412–3418. https://doi.org/10.1007/s00259-022-05806-9

Trägårdh E, Enqvist O, Ulén J et al (2022b) Freely available, fully automated AI-based analysis of primary tumour and metastases of prostate cancer in whole-body [18F]-PSMA-1007 PET-CT. Diagnostics (Basel) 12:2101. https://doi.org/10.3390/diagnostics12092101

Uijen MJM, Derks YHW, Merkx RIJ et al (2021) PSMA radioligand therapy for solid tumors other than prostate cancer: background, opportunities, challenges, and first clinical reports. Eur J Nucl Med Mol Imaging 48:4350–4368. https://doi.org/10.1007/s00259-021-05433-w

Unterrainer LM, Hope TA, Fendler WP et al (2025) Low- and high-volume disease in metastatic hormone-sensitive prostate cancer: from CHAARTED to PSMA PET-an international multicenter retrospective study. J Nucl Med 66:54–60. https://doi.org/10.2967/jnumed.124.268441

Vaswani A, Shazeer N, Parmar N et al (2017) Attention is all you need. In: Advances in Neural Information Processing Systems 30 (NeurIPS 2017), pp 5998–6008. https://doi.org/10.48550/arXiv.1706.03762

Verena A, Zhang Z, Kuo H-T et al (2023) Synthesis and preclinical evaluation of three novel 68ga-labeled bispecific PSMA/FAP-targeting tracers for prostate cancer imaging. Molecules 28:1088. https://doi.org/10.3390/molecules28031088

Vetrone L, Cuzzani G, Mei R et al (2023) Case report: PSMA PET/CT addresses the correct diagnosis in a patient with metastatic prostate cancer despite negative core biopsies and MpMRI. A diagnostic challenge. Front Oncol 13:1101221. https://doi.org/10.3389/fonc.2023.1101221

Wang L, Lu B, He M et al (2022) Prostate cancer incidence and mortality: global status and Temporal trends in 89 countries from 2000 to 2019. Front Public Health 10:811044. https://doi.org/10.3389/fpubh.2022.811044

Witkowska-Patena E, Budzyńska A, Giżewska A, Dziuk M, Walęcka-Mazur A (2020) Ordered subset expectation maximisation vs bayesian penalised likelihood reconstruction algorithm in 18F-PSMA-1007 PET/CT. Ann Nucl Med 34:192–199. https://doi.org/10.1007/s12149-019-01433-x

Ye Z, Kou Y, Shen J et al (2024) A comparative study of 18F-PSMA-1007 PET/CT and pelvic MRI in newly diagnosed prostate cancer. BMC Med Imaging 24:192. https://doi.org/10.1186/s12880-024-01376-4

Yildirim ÖA, Gündoğan C, Can C et al (2021) Correlations between whole body volumetric parameters of 68ga-PSMA PET/CT and biochemical-histopathological parameters in castration-naive and resistant prostate cancer patients. Ann Nucl Med 35:540–548. https://doi.org/10.1007/s12149-021-01594-8

Zhang L-L, Li W-C, Xu Z et al (2021) 68ga-PSMA PET/CT targeted biopsy for the diagnosis of clinically significant prostate cancer compared with transrectal ultrasound guided biopsy: a prospective randomized single-centre study. Eur J Nucl Med Mol Imaging 48:483–492. https://doi.org/10.1007/s00259-020-04863-2

Zhou J, Gou Z, Wu R et al (2019) Comparison of PSMA-PET/CT, choline-PET/CT, NaF-PET/CT, MRI, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a systematic review and meta-analysis. Skelet Radiol 48:1915–1924. https://doi.org/10.1007/s00256-019-03230-z

Zhou J, Wu R, Wang W, Zhao Y, Liu X (2022) 68ga-PSMA PET/CT for the evaluation of metastasis in patients with prostate cancer: A systematic review and meta-analysis. Hell J Nucl Med 25:297–311. https://doi.org/10.1967/s002449912525

Zirakchian Zadeh M (2024) Significance of PET/CT imaging in myeloma assessment: exploring novel applications beyond osteolytic lesion detection and treatment response. Onco 4:15–36. https://doi.org/10.3390/onco4010002

Zlatopolskiy BD, Endepols H, Krapf P et al (2019) Discovery of 18F-JK-PSMA-7, a PET probe for the detection of small PSMA-positive lesions. J Nucl Med 60:817–823. https://doi.org/10.2967/jnumed.118.218495