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Overview of the Impact of PSMA PET on the Management of Prostate Cancer Patients

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Abstract

Prostate cancer (PCa) is the second most common type of cancer among men worldwide and one of the leading causes of cancer-related deaths. According to data from the World Health Organization (WHO), this cancer causes hundreds of thousands of new cases and tens of thousands of male deaths globally each year. The incidence of PCa varies across different regions and populations, generally being higher in developed countries. This disparity may be attributed to lifestyle factors and the widespread availability of screening and diagnostic technologies. Prostate-specific membrane antigen (PSMA) is a membrane-bound enzyme predominantly expressed in prostate tissue and PCa cells, with lower expression in normal tissues. This high expression makes PSMA a critical target for the diagnosis and treatment of PCa, particularly in the field of molecular imaging and radiopharmaceutical therapy. Recently, various studies have emerged on radiopharmaceuticals developed based on PSMA ligands, which can be used to specifically identify and locate PCa cells. Research on the radiomics of these novel drugs has also been updated. This article will discuss the role and limitations of PSMA PET in the diagnosis and management of PCa treatment.

Keywords

PSMA PET, Prostate Cancer, Molecular Imaging, Radioligand Therapy

1. Introduction

In 2018, it was estimated that there were approximately 1,276,000 new cases of prostate cancer (PCa) globally, along with 359,000 deaths attributed to PCa [1]. Data from that year show that PCa was the most frequently diagnosed cancer among men in 106 countries, particularly in Central America, South America, Western Europe, Northern Europe, and sub-Saharan Africa. The incidence of PCa is comparatively higher in these regions. Notably, in 46 countries across sub-Saharan Africa and Latin America, PCa was almost invariably the leading cause of cancer-related deaths [1]. However, PCa often does not exhibit any symptoms in its early stages, which complicates the diagnosis and treatment process.

Prostate-specific membrane antigen (PSMA) is a membrane-bound enzyme that is highly expressed in prostate tissue and PCa cells, with lower expression in normal tissues [2]. This antigen is present in all grades of PCa, particularly reaching its highest levels of expression in more advanced cases. The expression of PSMA increases progressively from benign epithelium to high-grade prostatic intraepithelial neoplasia (PIN) or adenocarcinoma, while the expression of prostate-specific antigen (PSA) gradually decreases, especially during the transition from benign to more severe lesions [3]. Additionally, PSMA also shows immunoreactivity in subsets of neuroendocrine cells in the duodenal mucosa, some proximal renal tubules, and colonic crypts [4]. As a folate hydrolase enzyme, PSMA in PCa cells can utilize methotrexate polyglutamate (MTXGlu3) and pteroylpentaglutamate (PteGlu5) as substrates, demonstrating its folate hydrolase activity [5]. Due to its high expression in most cases of PCa, PSMA has become a crucial target for molecular imaging techniques and radiopharmaceuticals in the diagnosis and treatment of prostate cancer.

Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy have certain limitations, particularly in cases where PSA levels are low and recurrent lesions may be small [6] [7]. Although MRI offers high soft tissue contrast, its sensitivity and specificity post-radical prostatectomy (RPE) are limited. This is because post-surgical changes can mimic recurrent disease (e.g., seminal vesicle remnants), or post-radiation changes may complicate the differentiation between benign and malignant tissues in the prostate area after radiation therapy [8] [9]. CT and MRI struggle to detect non-localized and small-volume diseases, with a sensitivity of only 57% for detecting lymph node metastases that are 5 - 6 millimeters in size [10]-[13].

Due to the fact that most primary prostate tumors grow slowly, are well-differentiated, multifocal, and relatively small, the uptake level of tumors in FDG PET-CT can overlap with the uptake level in normal tissues and benign prostatic hyperplasia, which limits its utility in detecting and localizing primary PCa and in initial staging of the disease [14]. In contrast, PSMA PET-CT is a more advanced imaging technique that specifically visualizes PSMA to detect and evaluate PCa. This technique utilizes radiolabeled PSMA ligands to identify and locate PCa cells. Researchers have explored several targets based on the PSMA target, with the most common including ^{18}F-fluciclovine, which targets amino acid trapping by PCa [15], and PSMA ligands that target the extracellular domain of PSMA membrane-bound in PCa cells [16]. Globally, the more established PSMA radioligands include ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{68}Ga-PSMA-I&T, ^{18}F-rhPSMA-7, and ^{68}Ga-RM2 [17]-[23]. It is noteworthy that with the increasing development and progress of PSMA-based radioligands, selecting the optimal radioligand with differing diagnostic performance for initial diagnosis, staging, and monitoring of recurrent PCa has become a critical issue that needs to be addressed. These advancements have the potential to significantly improve the precision and effectiveness of PCa management, offering more tailored and effective treatment options based on individual patient profiles and disease characteristics.

Given the crucial role of PSMA expression in the progression and evolution of PCa, and the increasing evidence indicating its significance in evaluating and predicting PCa prognosis, this article will review and analyze the latest research developments regarding the use of PSMA PET/CT in the prognostic assessment of PCa.While this review comprehensively covers the applications of PSMA PET imaging, it particularly seeks to address the following research question: How does the application of PSMA PET in guiding salvage therapy decisions impact outcomes for prostate cancer patients across different clinical stages? This analysis aims to provide targeted insights into the clinical and prognostic benefits of PSMA PET in this critical treatment context.

2. PSMA PET for Initial Diagnosis and Staging of PCa

For patients suspected of PCa due to clinical symptoms, clinical findings, and elevated serum PSA levels, prostate biopsy is recommended [24]. The 2024 EAU-EANM-ESTRO-ESUR-ISUP-SIOG PCa guidelines suggest using a risk-adapted strategy to identify men at risk for PCa, starting typically at age 50 and based on individualized life expectancy. Multiparametric MRI (mpMRI) is recommended to avoid unnecessary biopsies, and when a biopsy is considered, both targeted and systematic biopsies should be performed [25]. Due to the lower sensitivity and specificity of transrectal ultrasound (TRUS)-guided biopsies [26], these have been replaced by MRI-guided biopsies. MpMRI is an advanced imaging technique that combines multiple imaging sequences, such as T1-weighted, T2-weighted, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. By integrating anatomical, functional, and metabolic information, mpMRI enables comprehensive disease evaluation. While mpMRI has proven to optimize PCa biopsies, comparison studies indicate that PSMA PET/CT achieves a cancer detection rate of 85% compared to 83% for mpMRI [27]. Therefore, further research on the diagnostic efficacy and patient benefits of PSMA PET/CT-guided biopsies is warranted.

PCa varies in aggressiveness, with tumor aggressiveness graded according to the Gleason score or the latest International Society of Urological Pathology (ISUP) grading system. ISUP grade 1 PCa is typically indolent and managed with active surveillance, whereas clinically significant PCa (ISUP grades 2 to 5, Gleason score ≥ 7) is more aggressive with a poorer overall prognosis [25]. Therefore, the goal of image-guided prostate biopsy is not only to accurately detect PCa lesions but also to prevent unnecessary biopsies and overdiagnosis of ISUP grade 1 lesions while improving detection of clinically significant PCa (csPCa) defined by ISUP grades. Currently, the Prostate Imaging Reporting and Data System (PI-RADS) is commonly used to grade PCa lesions assessed by multiparametric MRI. A study involving 75 participants found 102 lesions, 80 of which were PI-RADS 3 or higher, leading to targeted biopsies [28]. Sensitivities for detecting csPCa were 95% for mpMRI and 91% for ^{18}F-PSMA-1007 PET CT, with specificities of 45% and 62%, respectively. ^{18}F-PSMA-1007 PET CT accurately identified 17 of 26 PI-RADS 3 lesions (65%), with negative and positive predictive values for excluding or detecting csPCa of 93% and 27%. Additionally, ^{18}F-PSMA-1007 PET CT detected significant and insignificant PCa lesions (PI-RADS 1 or 2) that otherwise went undetected. However, two participants with ISUP grade 2 tumors showed no PSMA uptake and were not detected by PET CT. Thus, PSMA PET CT may help reduce unnecessary biopsies, but further research is needed to confirm these findings.

With increasing comparative studies on the diagnostic efficacy of traditional imaging versus PSMA PET imaging for PCa, research indicates that PSMA PET may be as clinically valuable or even superior to traditional imaging for local staging of PCa. Specifically, PSMA PET MRI is more sensitive than mpMRI for detecting extraprostatic extension (EPE) and seminal vesicle invasion (SVI), though PSMA PET CT is less sensitive than mpMRI for SVI detection [29]. Sonni's study showed that the area under the curve (AUC) for PSMA PET CT was 0.70 (sensitivity 0.84; specificity 0.55), while mpMRI had an AUC of 0.73 (sensitivity 0.86; specificity 0.59), with no significant statistical difference ($P = 0.093$) [30]. However, the AUC change when combining PSMA PET CT with mpMRI was statistically significant ($P < 0.001$). Doan's research revealed that simultaneous reading of mpMRI/PSMA PET improved sensitivity (93% vs 80% vs 88%) without enhancing specificity (63% vs 58% vs 78%) compared to using either modality alone [31]. When mpMRI/PSMA PET results were concordant and positive, 95% of patients had clinically significant PCa. Compared to single PSMA PET, simultaneous PSMA PET MRI reading increased reader confidence by 20%. Eiber's study found that for PCa localization, simultaneous PSMA PET MRI was statistically superior to mpMRI (AUC: 0.88 vs 0.73; $p < 0.001$) and PSMA PET CT (AUC: 0.88 vs 0.83; $p = 0.002$) [32]. PET imaging was more accurate than mpMRI (AUC: 0.83 vs 0.73; $p = 0.003$). However, due to the high cost and lower availability of PET MRI devices, researchers are more inclined to improve PSMA PET CT diagnostic performance by modifying PSMA ligand drugs or diagnostic criteria.

PSMA imaging offers significant advantages over traditional imaging in assessing metastases, particularly in N/M staging. Research indicates that preoperative ^{68}Ga-PSMA PET CT has positive and negative predictive values of 66.7% and 84.3%, respectively, for detecting lymph node metastases (LNM), compared to 59.1% and 78.7% for mpMRI, suggesting that ^{68}Ga-PSMA PET CT is more sensitive than 3-T mpMRI in identifying histological pelvic lymph node metastases [33]. A systematic review and meta-analysis involving 1,597 patients showed that the pooled sensitivity and specificity for ^{68}Ga-PSMA PET in detecting LNM were 0.65 (95% CI: 0.49 - 0.79) and 0.94 (95% CI: 0.88 - 0.97), respectively, while MRI had values of 0.41 (95% CI: 0.26 - 0.57) and 0.92 (95% CI: 0.86 - 0.95) [34]. The

AUC for the symmetric receiver operating characteristic (SROC) curves was 0.92 for ^{68}Ga-PSMA PET and 0.83 for MRI, indicating higher sensitivity and slightly different specificity for PSMA PET in detecting lymph node metastases. Additionally, a systematic review and meta-analysis comparing PET MRI and PET CT for LNM prediction found that ^{68}Ga-PSMA PET MRI had a lnDOR value of 4.73 (95% CI: 2.93 - 6.52) versus 2.42 (95% CI: 2.07 - 2.78) for ^{68}Ga-PSMA PET CT, suggesting that ^{68}Ga-PSMA PET MRI may be more effective for detecting LNM compared to ^{68}Ga-PSMA PET CT [35].

Radical prostatectomy combined with extended pelvic lymph node dissection (ePLND) offers effective long-term disease control for PCa, with ePLND and subsequent lymph node biopsy serving as the gold standard for staging. However, due to the associated morbidity with extensive tissue dissection in ePLND, current guidelines recommend ePLND only for patients with a predicted lymph node metastasis risk greater than 7%, as determined by new predictive nomograms [25] [36]. Predictive models for pelvic lymph node metastasis in PCa patients vary, and with the increasing use of PSMA PET imaging in preoperative staging, these nomograms need further refinement to enhance their ability to avoid unnecessary ePLND and improve lymph node staging. Incorporating positive PSMA PET information into existing predictive nomograms has been reported to enhance the predictive capability of these tools for lymph node invasion, thereby improving the selection of optimal candidates for preoperative ePLND [37] [38].

Interestingly, different PSMA tracers may vary in diagnostic performance and exhibit distinct characteristics in non-specific uptake by benign lesions. Studies suggest that in cases of biochemical recurrence or ambiguous lesions near the ureter or bladder, ^{18}F-PSMA-1007 PET might outperform ^{68}Ga-PSMA-11 PET. This advantage arises from the urinary excretion profile of 18F-PSMA-1007, which facilitates better differentiation between ureter or bladder activity and local recurrence or regional lymph node metastases. Additionally, an exploratory paired study involving 102 prostate cancer patients revealed that ^{18}F-PSMA-1007 PET detected PSMA-ligand-positive findings of benign origin (primarily ganglia, non-specific lymph nodes, and bone lesions) nearly five times more frequently than ^{68}Ga-PSMA-11 PET (245 findings vs. 52) [39]. The study also highlighted that the most common pitfalls in ^{18}F-PSMA-1007 PET are non-specific physiological uptake of the radiotracer in cervical, abdominal, or sacral ganglia. Additionally, cases of non-specific bone PSMA-ligand uptake are significantly more frequent with ^{18}F-PSMA-1007 PET compared to ^{68}Ga-PSMA-11 PET. In terms of diagnostic performance, the detection rate of recurrent PCa in post-RP patients is comparable between ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 PET. Similarly, ^{18}F-rhPSMA-7 PET may also present PSMA-ligand-positive findings of benign origin. One study comparing ^{18}F-rhPSMA-7 PET and ^{68}Ga-PSMA-11 PET in a head-to-head analysis identified 566 and 289 PSMA-ligand-positive lesions, respectively. Of these, 379 (67.0%) and 100 (34.6%) were deemed benign, with a similar distribution across ganglia, bones, and non-specific lymph nodes. Despite these differences, both tracers demonstrated the same detection rate for recurrent PCa (70%) [40]. In a prospective study comparing the diagnostic performance of ^{68}Ga-RM26 PET/CT and ^{68}Ga-PSMA-617 PET/CT in the initial evaluation of 207 participants, ^{68}Ga-RM26 PET/CT demonstrated higher uptake in benign prostatic hyperplasia, resulting in a higher false-positive rate. On the other hand, ^{68}Ga-PSMA-617 PET/CT showed superior performance in detecting clinically significant prostate cancer. However, ^{68}Ga-RM26 PET/CT exhibited greater accuracy in imaging low-risk prostate cancer, suggesting that it may serve as a complementary tool to ^{68}Ga-PSMA-617 PET/CT in initial imaging [41]. A meta-analysis also evaluated the diagnostic performance of ^{18}F-DCFPyL PET/CT and ^{68}Ga-PSMA PET/CT. The study reported pooled sensitivity, specificity, and AUC values of 0.92, 0.59, and 0.92 for ^{18}F-DCFPyL PET/CT, and 0.96, 0.71, and 0.92 for ^{68}Ga-PSMA PET/CT, respectively. These findings suggest that both ^{18}F-DCFPyL PET/CT and ^{68}Ga-PSMA PET/CT could serve as potential rule-out tests for patients suspected of having PCa based on clinical or biochemical evidence. Such tests could help reduce unnecessary biopsies, warranting further investigation in related studies [42].

In the M staging of PCa, the European Association of Urology's 2024 guidelines introduce the molecular imaging TNM (miTNM) classification based on PSMA PET CT results. The miT, miN, and miM sub-stages may provide better prognostic information compared to their conventional T, N, and M counterparts because PSMA PET CT is more sensitive than traditional bone scans and abdominal-pelvic CTs. The extent and implications of this prognostic shift are yet to be fully assessed [25] [43]. Second Version of The Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation (PRIOMISE v2) offers a standardized approach for molecular imaging evaluation based on PSMA PET. This framework allows for both horizontal assessment of image features at a single time point and longitudinal comparison of images over time for the same patient [44]. PRIOMISE v2 provides a unified miTNM classification, improved local disease assessment, and slightly revised PSMA expression scoring. It also introduces a reporting template for response evaluation in clinical trials, defining qualitative and quantitative imaging parameters to serve as a foundation for current and future response assessment frameworks.

Preliminary validation studies using the PROMISE v2 framework have compared pathological staging with molecular imaging staging by evaluating miT staging against pT staging according to ISUP protocols [45]. These studies assessed sensitivity, specificity, and diagnostic accuracy, finding that PSMA PET CT had high intra-observer consistency for ≥T3 staging (k = 0.70) and ≥T3b staging (k = 0.75), while inter-observer consistency was moderate for ≥T3 staging (k = 0.47) and ≥T3b staging (k = 0.41). Additionally, studies have evaluated different tracers within the PROMISE v2 framework, including gastrin-releasing peptide receptor (GRPR) targeted PET. GRPR PET, assessed using the PROMISE v2 framework, showed moderate inter-rater reliability for GRPR expression (0.59;

95% CI: 0.40 - 0.78), high reliability for T staging (0.78; 95% CI: 0.63 - 0.94), and near-perfect reliability for N staging (0.97; 95% CI: 0.92 - 1.00) and final assessment (0.92; 95% CI: 0.82 - 1.00) [46]. The use of the PROMISE v2 standard for interpreting GRPR-targeted PET indicates strong reliability with high or near-perfect inter-rater consistency across all major categories. A validation trial was also conducted to assess the performance of ^{18}F-DCFPyL in prostate tumor analysis using the automated prostate cancer molecular imaging standardized evaluation (aPROMISE) software. The study found a high degree of consistency between the aPROMISE software and an internal semi-automated manual-guided segmentation program for detecting primary and index tumors ($\kappa = 0.733$, $p < 0.001$ and $\kappa = 0.812$, $p < 0.001$, respectively). Although the agreement with histopathology was moderate ($p < 0.001$), the results suggest that diagnostic software based on the PROMISE framework could potentially assist clinicians in image interpretation. Further research in this area should be pursued [47].

Recently, Karpinski and colleagues aimed to develop a nomogram or comprehensive model for accurately predicting OS by integrating reproducible PSMA PET indicators. They collected imaging, clinical, and follow-up data from a large cohort of 667 patients to compare PSMA PET with established clinical risk scores. PSMA PET scans were conducted according to international consensus guidelines and analyzed using the PROMISE criteria to determine molecular imaging tumor-node-metastasis status, total tumor lesion count, total tumor volume, and total tumor expression (SUVmean). In the combined development and internal validation cohorts, the quantitative PSMA PET nomogram outperformed traditional scores like STARCAP or EAU in accurately stratifying high-risk and low-risk groups for OS in both early and late-stage PCa. Therefore, the integration of clinical and imaging findings may provide better prognostic value in the future [48].

3. PSMA PET in the Detection of Recurrence

After initial radical local treatment for PCa, a significant portion of patients eventually experience disease recurrence, often indicated by rising PSA levels during long-term follow-up. The most predictive threshold for further metastasis is a PSA level increase of >0.4 ng/ml [49]-[52]. The goal of treating PCa patients with biochemical recurrence (BCR) is to quickly and accurately identify the site of recurrence, followed by salvage therapy [53]. In one study, the detection rate of ^{68}Ga-PSMA-11 PET/CT was 34.4% in those series of patients with PSA levels <0.5 ng/ml. In intention-to-treat analysis, 30.2% of patients had their planned treatment regimen altered. This result supports the hypothesis that ^{68}Ga-PSMA-11 PET/CT is a valuable method for detecting early recurrence in PCa patients after Radical Prostatectomy (RP) and should be implemented in routine clinical practice [54]. A multicenter, international, prospective study also validated the ability of PSMA PET/CT to detect local and metastatic recurrence in most PCa patients with BCR [55]. Therefore, PSMA PET imaging is the recommended imaging modality for restaging PCa before salvage therapy [35] [56] [57].

BCR is most likely to occur within the first five years after primary treatment [58]. While PSA is crucial for indicating disease recurrence, imaging is necessary to determine the location of the recurrence. Understanding the location and extent of the disease allows for better treatment selection and strategies, such as curative salvage radiotherapy for local recurrence or systemic treatments like ADT, chemotherapy, or radioligand therapy (RLT) in the presence of distant metastases. The overall detection rate of PSMA varies with different PSA levels, with rates of 33.7%, 50.0%, 62.8%, 73.1%, and 91.7% in subgroups with PSA concentrations of <0.2 ng/ml, 0.2 - 0.49 ng/ml, 0.50 - 0.99 ng/ml, 1.0 - 1.99 ng/ml, and ≥2.0 ng/ml, respectively, showing no differences between different tracers [59]. Large studies have confirmed the capability of PSMA PET/CT in assessing BCR in patients after RPE [60]. One study demonstrated that 222 patients (89.5%) had pathological findings on ^{68}Ga-PSMA ligand PET/CT. The detection rates were 96.8%, 93.0%, 72.7%, and 57.9% for PSA levels of ≥2, 1 to <2, 0.5 to <1, and 0.2 to <0.5 ng/ml, respectively. In 61 patients (24.6%), PET identified additional affected areas, compared to 17 patients (6.9%) identified by CT. Regarding the histological differentiation of primary PCa, ^{68}Ga-PSMA ligand PET/CT had a detection efficiency of 86.7% (111/128) in patients with a Gleason score ≤ 7 and 96.8% (90/93) in those with a Gleason score ≥ 8 ($p = 0.0190$).

PSMA PET can localize recurrence to the prostate bed, pelvic lymph nodes, or distant metastatic sites. The likelihood of PSMA PET-positive recurrence localization increases with rising serum PSA levels. One study analyzed 164 men with rising PSA after RP and found that PSMA PET could independently predict the response to SRT, categorizing men into two groups: those with a high response to SRT (negative or intraprostatic PSMA) and those with a poor response (lymph node or distant PSMA-positive disease). Notably, a negative PSMA PET result was predictive of a high response to salvage intraprostatic radiotherapy [61]. Similarly, another study found that for men receiving sRT for BCR after RP, PSMA PET results were highly predictive of freedom from progression (FFP) at 3 years [62]. Specifically, men with negative PSMA PET results or disease confined to the prostate bed exhibited higher 3-year FFP rates, despite receiving a smaller radiotherapy field and lower rates of additional androgen deprivation therapy, compared to those with extraprostatic disease. Therefore, different PSMA PET patterns have prognostic significance for bPFS and the time to metastatic progression following salvage therapy.

For men with lymph node recurrence of PCa, salvage lymph node dissection (sLND) is a treatment option. Effective eradication of the disease through sLND requires the preoperative localization of recurrent lymph nodes using sensitive imaging probes. A study introduced PSMA-targeted radioguided surgery (RGS) and explored its prognostic significance. The study included 121 consecutive patients with recurrent PCa, and nearly all patients (120/121, 99%) had their metastatic tissue successfully removed. A complete biochemical response (cBR; PSA < 0.2 ng/ml) without additional treatment was achieved in 77 patients (66%).

Patients with lower preoperative PSA levels (p = 0.004, hazard ratio 1.48, 95% confidence interval 1.13 - 1.93) and those with a single lesion on preoperative PSMA ligand PET (14.0 vs. 2.5 months, p = 0.002) had significantly longer median bRFS. This indicates that PSMA-targeted RGS can lead to a significantly prolonged bRFS interval in some patients. The highest frequency of cBR and the longest duration of bRFS were observed in patients with lower preoperative PSA levels and a single lesion on PSMA ligand PET [63]. Therefore, PSMA PET has valuable roles in both localization and prediction in the context of sLND treatment.

4. The Application of PSMA PET in Restaging

Notably, a study indicated that in restaging BCR patients, those with no disease or low-volume disease detected by BS and CT showed a higher overall prevalence of PSMA PET/CT-positive disease. More than half of these patients were oligometastatic, with nearly two-thirds having disease confined to the pelvis. This finding confirms that PSMA PET/CT has significantly higher sensitivity than standard restaging imaging and may help identify patients for subsequent targeted therapies. In this study, across the entire cohort, 183 patients (77%) had PSMA-HBED-positive lesions (682 lesions) suggestive of PCa, with 132 patients (55%) exhibiting oligometastatic disease. Among the oligometastatic group, 65% had PSMA-positive lesions confined to the pelvis, involving the prostate or lymph nodes (AJCC stage N1). The study also found that PSMA-HBED positivity correlated positively with PSA levels, and ^{68}Ga-PSMA-11 PET/CT was shown to be an important predictor of PSMA positivity and the presence of multiple metastatic diseases [64].

Castration-resistant prostate cancer (CRPC) is defined as having serum testosterone levels < 50 ng/dL or 1.7 nmol/L, along with one of the following: 1) biochemical progression, indicated by three consecutive increases in PSA levels leading to a 50% rise from the lowest point, with PSA > 2 ng/mL; 2) radiographic progression, defined by the appearance of two or more new bone lesions on bone scan, or soft tissue lesions as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) [65]. Non-metastatic CRPC (nmCRPC) is characterized by biochemical disease progression despite adequate androgen deprivation therapy (ADT), with no evidence of metastasis on cross-sectional imaging (CT/MRI) or bone scans, while metastatic CRPC (mCRPC) is identified as macroscopic disease on conventional imaging. A retrospective study suggested that PSMA PET has potential for detecting lesions in nmCRPC [66]. This study found that out of 200 patients undergoing PSMA PET, 196 had positive results, with a detection rate of nearly 98%. Another study aimed at assessing the impact of gallium-68 labeled PSMA ligand (PSMA-11) PET CT on restaging castration-resistant non-metastatic PCa patients, reported a 100% positivity rate in patients with PSA > 2 ng/mL (20/20), and a 70% positivity rate in patients with PSA < 2 ng/mL (7/10). Among 17 patients with established truth standards, the overall sensitivity and specificity of PSMA-11 PET CT for detecting residual disease in castration-resistant PCa were 87% and 100%, respectively [67]. Therefore, we can infer that PSMA PET CT may provide significant value in evaluating lesions in nmCRPC patients.

5. The Application of PSMA PET in Radioligand Therapy

Once metastatic prostate cancer (mPC) develops resistance to hormone therapy, treatment options become limited, and the prognosis is not optimistic. For patients with mCRPC) PSMA PET can be used to verify eligibility for targeted radionuclide therapy (TRT) and assess treatment response. Theranostics describes the technique of imaging and treating specific cancers using the same targeting agent, differing only in the radioactive isotopes used for diagnosis and therapy. For imaging, short-lived radioactive isotopes such as ^{68}Ga or ^{18}F are used, while for therapy, isotopes with high linear energy transfer and longer half-lives, such as ^{177}Lu and ^{225}Ac, are preferred to induce single or double-strand DNA breaks. The beta particles emitted by the radiolabeled ligand 177Lu primarily target PSMA-positive cells and the surrounding tissues [68]. Due to the narrow range of alpha particles in human tissue—less than 0.1 millimeters, which is only a few cell diameters—the ligands labeled with ^{225}Ac, which emit alpha particles, may be more effective in treating cancer than those labeled with ^{177}Lu. Based on the results of the VISION trial, the FDA approved ^{177}Lu-PSMA-617 for the treatment of mCRPC patients [69]. Similarly, the 2024 European Urology Guidelines also list ^{177}Lu-RLT as a second-line treatment option. A systematic review and recent meta-analysis evaluated overall survival (OS) and the proportion of patients with a decline in PSA or a decline of >50% in PSA. This review included 69 articles with a total of 4157 patients. The results showed that patients receiving ^{177}Lu-PSMA-617 treatment had a significantly enhanced response compared to the control group (PSA decline ≥ 50%) (OR = 5.33, 95% CI: 1.24 - 22.90, $p < 0.05$). The meta-analysis indicated that OS improved after treatment with ^{177}Lu-PSMA-617, with a pooled HR for PSA decline of 0.26 (95% CI 0.18 - 0.37, $p < 0.00001$) and a pooled HR for PSA decline ≥50% of 0.52 (95% CI 0.40 - 0.67; $p < 0.00001$) [70].

In addition to ^{177}Lu, there are other radionuclide therapies available. A retrospective study investigated the safety and antitumor activity of ^{225}Ac-PSMA RLT in a large cohort of mCRPC patients treated at multiple centers worldwide. These patients received one or more cycles of 8 MBq ^{225}Ac-PSMA RLT via intravenous injection for mCRPC. Previous treatments for mCRPC included taxane chemotherapy, androgen receptor axis inhibitors, ^{177}Lu PSMA RLT, and radium-223 dichloride. A total of 488 men with mCRPC received 1,174 cycles of ^{225}Ac-PSMA RLT (with a median of two cycles, IQR 2 - 4) [71]. The median overall survival for all patients was 15.5 months (95% CI 13.4 - 18.3), and the median progression-free survival was 7.9 months (6.8 - 8.9). Notably, 73% of patients experienced a decline in PSA, with 57% showing a decline of 50% or more. The pooled HR for overall survival based on the number of ^{225}Ac RLT cycles was 0.861 (95% CI 0.801 - 0.927, $p < 0.0001$), and the pooled HR for progression-free survival was 0.887 (95% CI 0.834 - 0.943, $p < 0.0001$). This retrospective study suggests that ^{225}Ac-

PSMA RLT may have significant implications for salvage therapy in mCRPC patients, warranting further prospective clinical research.

Interestingly, the PSMA radioligand labeled with ^{161}Tb appears to have potential in the treatment of mCRPC patients. ^{161}Tb is an emerging candidate radionuclide that has similar chemical properties and physical decay characteristics to the well-established ^{177}Lu. The nuclear medicine team at the King Hussein Cancer Center (KHCC) in Amman, Jordan, recently published the first human SPECT/CT imaging results, showing that patients received well-tolerated doses of ^{161}Tb-PSMA radioligand therapy without any treatment-related adverse events, enhancing the potential of radiotherapy in PCa [72]. At the same time, a prospective study indicated that ^{161}Tb is a promising radionuclide for PSMA-RLT in mCRPC. This study included six patients undergoing head-to-head treatment with ^{161}Tb-PSMA-617 and ^{177}Lu-PSMA-617 [73]. The quantitative results suggested that ^{161}Tb-PSMA-617 delivered significantly higher absorbed doses to tumor lesions compared to ^{177}Lu-PSMA-617. Additionally, the average absorbed dose to risk-related organs was only slightly higher for ^{161}Tb-PSMA-617 than for ^{177}Lu-PSMA-617. These findings support the notion that ^{161}Tb is a promising candidate radionuclide for PSMA-RLT. Further research on larger patient populations is recommended, preferably in a prospective setting, to confirm these observations.

6. The Application of Radiomics in PSMA PET Imaging

Radiomics, when applied to PSMA PET imaging, shows immense potential in advancing personalized medicine for prostate cancer patients. Specific applications include predicting tumor aggressiveness, guiding radiotherapy planning, and assessing treatment response. However, challenges such as standardization of radiomic feature extraction, integration with clinical workflows, and validation across diverse datasets remain. Emerging radionuclides like ^{161}Tb also offer intriguing possibilities. With its higher dose delivery to tumor sites and relatively low off-target toxicity, ^{161}Tb has demonstrated promising results in early studies. These advancements necessitate further investigation into their combined radiomics and theranostic applications, potentially enhancing diagnostic precision and therapeutic efficacy.

Increasing evidence shows that radiomics models applied to PSMA PET images of patients with PCa have potential prognostic value in various settings. Based on the many reviews on MR radiomics in prostate cancer [74]-[76]. This article will only discuss PSMA PET CT related studies. These models are particularly helpful in identifying csPCa in patients suspected of having PCa [77]. One study demonstrated that a radiomics model could serve as a non-invasive tool for predicting csPCa, significantly enhancing the specificity of csPCa detection, reducing unnecessary biopsies, and assisting radiologists in making precise diagnoses [78]. Furthermore, machine learning classifiers using radiomic features from PSMA PET and mpMRI in localized PCa have shown promise in predicting intraprostatic lesions and distinguishing between high and low-grade diseases, which can guide biotargeted radiotherapy plans [79]. While approximately 90% of PCa patients show positive PSMA PET results, about 10% of lesions may go undetected due to insufficient PSMA expression. Studies indicate that visually interpreting PSMA PET images could miss clinically significant but small PCa, which radiomic features derived from PSMA PET can detect, aiding in personalized treatment strategies [80] [81]. Similarly, radiomics models are also effective in detecting small lymph node metastases (less than 4 mm). Research suggests that Ga-PSMA-11 information could enhance lymph node involvement (LNI) predictions in patients with intermediate to high-risk PCa undergoing initial staging, especially when combined with clinical parameters [82]. The problem of detection of intraprostatic lesions was addressed by Zamboglou [80]. The premise of the study is that radiomics may detect intraprostatic lesions that visual inspections might miss. Patient data included 20 cases in the training set and 52 in the external validation set, with histology serving as the gold standard. A total of 154 radiomic features were used. In the training dataset, visual inspections missed lesions in 60% of the patients. Two radiomic features based on local binary pattern (LBP) analysis detected visually unrecognized lesions, achieving an AUC of 0.93. For the validation set, visual inspections missed lesions in 50% of the patients, but the sensitivity values produced by LBP radiomic features exceeded 0.80.

Different PSMA PET tracers have also been studied. Some research has evaluated the use of radiomics with ^{18}F-choline PET images to predict disease outcomes, along with subgroup analysis based on TNM staging [83]. They analyzed ^{18}F-choline image data from 94 high-risk patients for restaging and follow-up data. In the entire dataset, two first-order histogram features were able to predict disease progression with an accuracy of 67.6%. Subgroup analysis based on TNM staging showed that for the T stage, 3 features were used with an accuracy of 87%; for the N stage, 2 features with an accuracy of 82.6%; and for the M stage, 2 features with an accuracy of 72.5%. Additionally, studies have evaluated risk stratification using the PSMA tracer DCFPyL [84]. The radiomics-based machine learning model in the study predicted lymph node involvement (LNI) with an AUC of 0.86 ± 0.15 ($p < 0.01$), lymph node or distant metastasis with an AUC of 0.86 ± 0.14 ($p < 0.01$), Gleason score with an AUC of 0.81 ± 0.16 ($p < 0.01$), and extraprostatic extension (ECE) with an AUC of 0.76 ± 0.12 ($p < 0.01$). This suggests that machine learning-based quantitative analysis of ^{18}F-DCFPyL PET metrics can predict LNI and high-risk pathological tumor characteristics in patients with primary PCa.

7. Cost-Effectiveness and Accessibility

The widespread adoption of PSMA PET imaging faces significant economic and logistical barriers. The high cost of radioligands, limited availability of PET scanners, and the need for specialized training restrict its accessibility, particularly in low-resource settings. Strategies to address these challenges include investing in cost-effective production methods for PSMA tracers, exploring alternative imaging modalities, and expanding training programs for nuclear medicine professionals. Additionally, economic analyses comparing PSMA PET to conventional imaging have consistently demonstrated its cost-effectiveness in reducing unnecessary treatments and improving long-term outcomes. Policymakers must prioritize funding and infrastructure development to ensure broader accessibility to this transformative technology.

8. Conclusions

PSMA PET imaging has revolutionized the management of PCa, with its exceptional sensitivity for lesion detection not only influencing treatment decisions but also increasingly demonstrating a significant impact on patient prognosis across various management settings. In pre-biopsy applications, PSMA PET is highly beneficial in identifying clinically significant prostate cancer (csPCa) among suspected PCa patients, effectively reducing invasive biopsies in patients with low-risk or insignificant lesions through precise risk assessments. Although PSMA PET has sensitivity limitations in preoperative staging of lymph node invasion, it outperforms other imaging techniques in this application and can predict the effectiveness of postoperative treatments. Moreover, most patients who undergo initial surgery or radiation therapy may eventually develop metastatic disease, requiring systemic drug treatment. In such cases, PSMA PET exhibits good prognostic performance, predicting which patients are most likely to respond to treatment. Therefore, PSMA PET plays a crucial role in distinguishing which patients will benefit from systemic therapies and which may not, thus helping to avoid ineffective treatment and its associated complications. However, although PSMA-targeted imaging is highly effective in detecting tumors that express PSMA, it may become ineffective in cases where prostate cancer has neuroendocrine differentiation and does not express PSMA. Additionally, in PSMA PET, determining whether an isolated bone lesion is malignant or benign can be challenging, as this can alter a patient's treatment plan. Misinterpretation leading to false positives could cause unnecessary harm to patients. Therefore, broader and more extensive studies need to be further conducted and discussed.

The studies included in this review were primarily retrospective and heterogeneous in design. Common limitations identified include small sample sizes, potential selection bias, and the lack of standardized protocols across centers. For instance, while studies utilizing 68Ga-PSMA PET have robust detection rates for biochemical recurrence, variability in tracer kinetics and imaging protocols between 18F- and 68Ga-based tracers complicates comparisons. Furthermore, the absence of randomized controlled trials in many areas limits the generalizability of findings. These limitations underscore the need for larger, multicenter trials with standardized methodologies to validate current observations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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