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Review Article

PSMA PET/CT improves precision diagnosis, treatment, and clinical decision-making in prostate cancer

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Abstract: Prostate cancer is one of the most prevalent malignancies in males worldwide. Its diagnosis and treatment have long faced challenges, including inaccurate disease staging, difficulty in localizing recurrence sites, and a lack of evidence for individualized decision-making. Recently, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) technology has emerged as a major breakthrough in addressing these limitations. This review systematically summarizes the technical principles and clinical applications of PSMA PET/CT, and evaluates its impact on diagnostic and therapeutic paradigms of prostate cancer, including its role in precision staging for high-risk patients at initial diagnosis, early localization of biochemical recurrence sites, target delineation for radical therapy, screening of oligometastatic patients for targeted metastatic treatment, as well as its central function in integrated diagnosis and treatment. In addition, this review discusses current limitations of the technology, including inconsistent interpretation standards and controversies over health economics. Future perspectives are also outlined, focusing on the development of novel tracers, the integration of artificial intelligence, and multidisciplinary collaboration. Through the integration of a large amount of clinical research data, this review aims to demonstrate the transformative value of PSMA PET/CT in the diagnosis and treatment of prostate cancer, and to provide evidence-based support for clinical practice and future guideline updates.

Keywords: Prostate cancer, prostate-specific membrane antigen, diagnosis and treatment, clinical decision-making

Introduction

Prostate cancer is a prevalent malignancy in men worldwide and imposes a significant disease burden. According to epidemiological data, prostate cancer is one of the leading causes of cancer-related deaths among men in the United States, with an age-adjusted mortality rate of 52.92 per 100,000 individuals [1]. In China, the number of new cases increased from 13,800 to 81,400 (a 490.27% increase) between 1990 and 2013, and the number of deaths rose from 5,800 to 17,800 (a 206.86% increase) [2]. In Mexico, the incidence and mortality of prostate cancer are 279.6 and 99.1 per 100,000 individuals, respectively [3].

Despite advances in diagnostic and therapeutic technologies, several key challenges remain in prostate cancer management. Overtreatment of low-risk patients and undertreatment of high-risk patients coexist, increasing healthcare burdens and adversely affecting overall prognosis [4]. Treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC) remain limited, and the optimal timing and combination strategies for novel therapies are still unclear [5]. In addition, the sensitivity of traditional imaging approaches, such as computed tomography (CT) and bone scans, is insufficient for detecting early recurrence, which may result in missed opportunities for timely salvage therapy [6]. Tumor heterogeneity further complicates clinical decision-making. For example, prostate cancer in indigenous West African men exhibits unique biological characteristics, with 83% of patients lacking the transmembrane Serine Protease 2 (TMPRSS2)- ETS transcription factor (ERG) fusion, and 29% presenting a double-negative phenotype (ERG-negative/Phosphatase and tensin homolog (PTEN)-deficient), which

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may influence their response to conventional therapies [7]. At the therapeutic level, zoledronic acid has been shown to significantly reduce bone turnover markers, including Procollagen type I N-terminal propeptide (P1NP) and C-terminal telopeptide of type I collagen (CTX), in patients with bone metastases; however, its impact on overall survival remains limited [8, 9]. Immunotherapies show survival benefits in patients, whereas its efficacy is reduced in those with a high tumor burden [10]. Therefore, it is urgent to develop novel strategies for the precise diagnosis and treatment of prostate cancer.

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is highly expressed in prostate cancer cells, and its expression levels are positively correlated with tumor aggressiveness, castration resistance, and metastatic potential [11]. PSMA is not only an ideal diagnostic target, but also a component of a theranostic strategy integrating diagnosis and treatment when its ligand is conjugated with a radionuclide [12, 13]. The imaging principle of PSMA positron emission tomography (PET)/computed tomography (CT) is based on the specific binding of radiolabeled PSMA ligands (e.g., ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007) to PSMA on the cell surface, followed by internalization. Positron-emitting radionuclides enable high-sensitivity detection of PSMA-expressing lesions via PET, while CT provides anatomical localization. This molecular imaging technique can detect micrometastatic disease (e.g., lymph node micrometastases) missed by traditional imaging methods. In patients with biochemical recurrence (BCR), PSMA PET/CT demonstrates a significantly higher detection rate than traditional methods, and can even identify recurrence even at prostate-specific antigen (PSA) levels are below 0.5 ng/mL [7, 14].

In addition to prostate cancer, PSMA is also expressed in the neovascularization of various solid tumors, including renal cell carcinoma, bladder cancer, lung cancer, and glioblastoma [15]. Therefore, PSMA PET/CT also holds potential for imaging and targeted therapy in these malignancies; however, its clinical application remains in the research stage.

Although existing research has confirmed the significant value of PSMA PET/CT in the diagnosis and treatment of prostate cancer, most reviews have not systematically integrated its role across the entire clinical workflow, from initial staging to treatment decision-making. In addition, few have incorporated the latest evidence from the past three years. Furthermore, critical analysis of technological limitations and future directions is also insufficient. Therefore, this review systematically summarizes the principles and clinical applications of PSMA PET/CT, with a focus on its role in precise staging, BCR localization, target delineation, selection of patients for metastasis-directed therapy in oligometastatic lesions, and integrated diagnosis and treatment. It incorporates the latest research evidence, discusses current technical limitations, and highlights future development directions, including artificial intelligence-assisted interpretation and the development of novel radiotracers. This review aims to provide evidence-based guidance for optimizing individualized treatment strategies and to serve as a reference for future guideline development.

Principles and technological advancements of PSMA PET/CT

Biological characteristics of PSMA and the basis of targeted diagnosis and treatment

Due to the unique biological characteristics of PSMA, including high expression on the surface of prostate cancer cells and efficient internalization upon ligand binding, it is considered as an ideal target [16, 17]. Its extracellular domain shows glutamic acid carboxypeptidase activity, enabling the hydrolysis of N-acetyl-L-aspartic acid-L-glutamic acid (NAAG), which provides a biochemical basis for the design of high-affinity ligands [18]. Upon binding to PSMA, ligand-receptor complexes undergo endocytosis, facilitating radionuclide accumulation within tumors for imaging or treatment [17].

Tumor microenvironment affects PSMA expression, with inflammatory responses and angiogenesis elevating its expression, offering potential targets for combination therapies [7]. The clinical value of PSMA-based targeting has been well established: PSMA PET/CT demonstrates notably higher detection rates and staging accuracy than conventional imaging in patients with BCR and newly diagnosed high-risk prostate cancer [19, 20]. In addition,

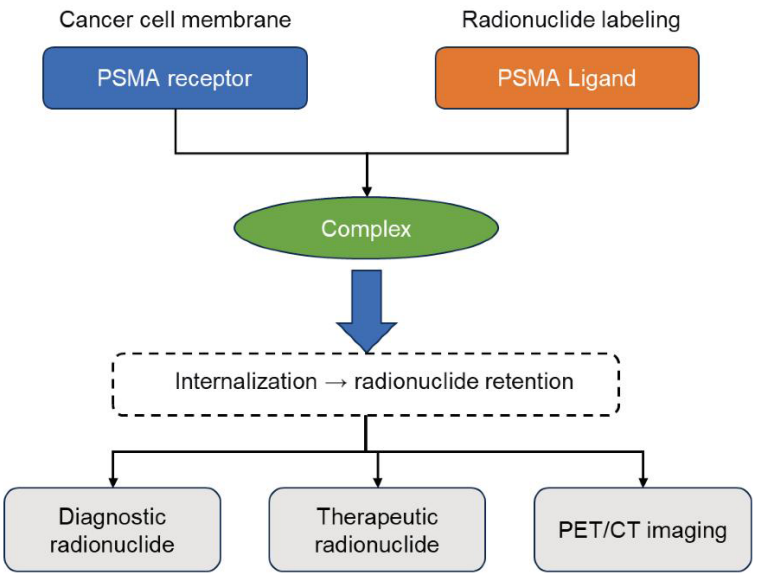

Figure 1. Simplified mechanism of Prostate-specific membrane antigen (PSMA)-targeted theranostics. Notes: PSMA, Prostate-specific membrane antigen; PET/CT, positron emission tomography (PET)/computed tomography (CT).

PSMA-targeted radioligand therapies (e.g., ^{177}Lu-PSMA-617) have shown favorable efficacy in patients with mCRPC [21]. Additionally, the combination of PSMA-targeted drugs with immunotherapy has demonstrated synergistic effects in preclinical studies [22]. The relationship between PSMA expression and tumor metabolism also enables the integration of PSMA PET/CT with Fluoro deoxy glucose (FDG) PET/CT for a more comprehensive assessment of tumor biological characteristics [21]. The mechanism underlying PSMA-targeted imaging and therapy is summarized in **Figure 1**.

Principle and development of PSMA PET/CT imaging technology

PSMA PET/CT imaging is based on the specific binding of radiolabeled PSMA ligands to surface PSMA on tumors. Currently, small-molecule inhibitors (e.g., PSMA-11, PSMA-617) are widely used due to their high affinity and favorable pharmacokinetic profiles. For instance, ^{68}Ga-PSMA-11 exhibits nanomolar-level binding affinity, with optimal tumor-to-background contrast peaking at 60 minutes post-injection, making it suitable for imaging [23, 24].

The evolution of PSMA imaging tracers has evolved from antibody-based ligands to small-molecule inhibitors. Small-molecule ligands such as ^{18}F-PSMA-1007 have longer half-lives and higher tracer uptake rates, enabling improved detection of smaller lesions [25]. The application of dynamic imaging techniques (e.g., early-phase imaging within 5 minutes after tracer injection) help distinguish tracer uptake from physiological excretion (e.g., within the bladder), which enhances diagnostic accuracy [26].

Advances in equipment and image processing technologies are also important. Modern PET/CT scanners have higher resolution and sensitivity, enabling the detection of lesions <5 mm in diameter [27]. Artificial intelligence approaches (e.g., deep learning algorithms) can facilitate automated lesion segmentation and standardized uptake values (SUV) quantification, thereby minimizing human errors [27]. Diagnostic capabilities are further enhanced by multimodal imaging (e.g., PSMA PET/MRI) through the integration of functional and anatomical information [28].

Precision diagnosis and restaging of PSMA PET/CT in prostate cancer

PSMA PET/CT for precision staging and metastasis detection in newly diagnosed high-risk patients

For newly diagnosed high-risk patients, accurate staging is the fundamental for treatment decision-making. In a large cohort study involving 691 high-risk patients, PSMA PET/CT detected lymph node and/or distant metastases in 35.3% of patients, including 31.4% lymph node metastases and 16.8% with bone metastases [29]. Its staging accuracy is approximately 27% higher than that of traditional CT and bone scintigraphy [30]. This significant advantage stems primarily from the differences in the mechanisms underlying molecular imaging and conventional imaging. In lymph node assessment, conventional CT primarily relies on size-based criteria (e.g., short-axis

diameter threshold >10 mm), thereby overlooking small metastatic lesions in structurally normal or minimally enlarged lymph nodes. In contrast, PSMA PET/CT overcomes these anatomical limitations by targeting PSMA overexpression, enabling detection and characterization of metastatic involvement even in small lymph nodes measuring approximately 4-5 mm [31]. A similar limitation is observed with conventional bone scintigraphy using technetium-99m-labeled diphosphonates. Because tracer uptake primarily reflects osteoblastic activity and reactive bone remodeling rather than tumor cells themselves, skeletal scintigraphy may yield false-negative findings during the early stages of marrow-confined metastatic dissemination prior to the development of significant osseous response. Conversely, increased tracer uptake associated with degenerative joint disease, fractures, inflammation, or other benign remodeling processes may result in false-positive interpretations [32, 33]. In a study involving 78 newly diagnosed patients, PSMA PET/CT demonstrated a metastasis detection rate of 51.2% (10 cases of regional lymph node metastases and 30 cases of distant metastases) and identified micrometastatic disease missed by conventional imaging [34, 35]. Moreover, the total number of metastatic lesions detected by PSMA PET/CT has been shown to be negatively correlated with patient prognosis [36].

PSMA PET/CT also demonstrates significant clinical impacts, leading to treatment regimen modifications in approximately 36% of patients and significantly influencing radiotherapy planning [37]. It also facilitates extended lymph node dissection in patients with lymph node metastasis, potentially improving survival outcomes [38]. Although there is controversy over its clinical significance in micrometastatic disease, growing evidence supports its value as a standard staging tool for high-risk patients [39]. The recently reported THUNDER trial further confirmed the staging value of PSMA PET/CT in newly diagnosed high-risk patients. This study showed that PSMA PET/CT resulted in disease stage reclassification in 24% of patients, leading to radiotherapy regimen modifications in approximately one-third of cases [40]. Another head-to-head study showed that ^{18}F-PSMA-1007 reclassified 15% of patients from localized to metastatic disease and detected lymph node metastases that were completely missed by CT in 20% of patients [41]. To standardize reporting, the consensus-based molecular imaging TNM (miTNM) system [42] has been proposed and increasingly adopted in clinical practice. This system provides standardized subclassifications (e.g., miN1 for regional lymph node involvement and miM1b for bone metastasis), thereby improving interobserver consistency and supporting risk stratification and treatment planning. It should be noted that existing evidence largely focuses on the impact of PSMA PET/CT on staging progression, whereas the clinical implications of imaging-detected micrometastatic disease remains controversial. In our opinion, not all micrometastases detected by PSMA PET/CT necessarily require immediate treatment intensification. For example, isolated lymph node metastases smaller than 5 mm with relatively low uptake (e.g., SUVmax <5), corresponding to low-volume miN1 disease, may represent a lower-risk subgroup, for which short-term imaging surveillance could be considered as an alternative to immediate systemic escalation [43-45]. This perspective challenges the traditional notion of “stage migration automatically leading to treatment escalation” and may help reduce overtreatment. Collectively, we hypothesize that patients with 1-3 isolated pelvic lymph nodes may be suitable for short-term surveillance, whereas those with ≥5 metastatic lesions or visceral involvement (miM1c) may require active systemic treatment. Such refined risk stratification based on miTNM parameters may potentially avoid unnecessary treatment upgrades in about 15%-20% of low-risk patients.

Currently, although mainstream guidelines mainly recommend PSMA PET/CT for high-risk patients, increasing evidence suggests that approximately 8%-15% of intermediate-risk patients may harbor occult lymph node metastasis. The 2025 update of the European Association of Urology (EAU) guidelines states that PSMA PET/CT may also be considered for staging in selected intermediate-risk patients with additional risk factors [46].

PSMA PET/CT for early localization and qualitative diagnosis of biochemical recurrence sites

PSMA PET/CT demonstrates distinct advantages in the early localization of BCR. Its detec-

tion rate increases with rising PSA levels, ranging from 11.3% at 0.01-0.2 ng/mL, 26.6% at 0.2-0.5 ng/mL, and up to 95.5% at ≥2 ng/mL, according to a retrospective study of 532 BCR patients [47]. Overall, detection rate of lymph node metastases can reach 77.9% [48]. Regarding lesion characterization, PSMA PET/CT effectively distinguishes recurrent lesions from benign lesions (e.g., postoperative alterations, inflammation) [49]. Early dynamic imaging helps differentiate prostate cancer recurrence from physiological urinary activity [49]. This approach is particularly relevant for ^{68}Ga-labeled PSMA tracers, which undergo rapid renal excretion and may result in intense bladder activity that can obscure lesions within the prostatic fossa or adjacent pelvic structures [31, 50]. Furthermore, tracers with low urinary excretion, such as ^{18}F-PSMA-1007, which are predominantly cleared through the hepatobiliary system, exhibit reduced urinary excretion and may improve lesion detectability in regions adjacent to the bladder. By minimizing urinary interference and halo artifacts, these tracers can facilitate more accurate evaluation of local recurrence in anatomically complex pelvic regions [51-53]. In addition, quantitative metabolic parameters (e.g., SUVmax) have been associated with tumor aggressiveness, which is helpful in malignancy assessment [54]. Treatment decisions for BCR patients are significantly influenced by PSMA PET/CT. Approximately 74.6% of patients thus changed their treatment regimens, with the majority (86%) transferring to targeted treatment for metastatic lesions [55]. Despite limitations such as false-positive findings and high costs [56], its central role in BCR management has increasingly recognized. Based on current evidence, we propose a refined perspective: although PSMA PET/CT detection rates increase with rising PSA levels, a negative result at PSA levels <0.5 ng/mL should not preclude further evaluation for recurrence. In selected patients, repeat PSMA PET/CT or combined multiparametric MRI at short intervals (e.g., 3 months) may be considered, as microscopic lesions may be missed due to low tracer uptake or technical limitations. However, this dynamic surveillance strategy has not yet been incorporated into mainstream guidelines and warrants prospective validation.

Mazzone et al., in a meta-analysis of 43 studies involving 8,119 patients, reported that detection rates after radiotherapy (92%) were higher than those after radical prostatectomy (60%). In the post-prostatectomy subgroup, detection rates were 48% at PSA 0.2-0.5 ng/mL, approximately 65%-70% at PSA 0.5-1.0 ng/mL, and exceeded 90% at PSA >2 ng/mL [57]. Notably, Gleason score had no significant effect on the detection rate (P = 0.08) [57], challenging the traditional notion that PSMA PET/CT should be reserved primarily for high-risk patients. This finding suggests that PSMA upregulation in recurrent disease may be driven more by tumor biological reactivation than by baseline histopathological grade, thereby supporting a lower threshold for molecular imaging across risk categories [58, 59]. A retrospective cohort study focusing on patients who had not yet met the Phoenix criteria (i.e., elevated PSA but not exceeding the lowest point + 2 ng/mL) after radiotherapy showed that 76.6% of such patients had recurrence detected by PSMA PET/CT, and 75.9% were suitable for local salvage therapy [60]. This finding provides strong evidence supporting earlier and more accurate detection of post-radiotherapy recurrence. Furthermore, a German multicenter retrospective study comparing ^{68}Ga-PSMA-11, ^{68}Ga-PSMA I&T, and ^{18}F-PSMA-1007 showed an overall detection rate of 29.6% in patients with PSA ≤0.2 ng/mL after radical prostatectomy, with detection performance correlated to PSA doubling time [61]. Collectively, these findings indicate that a negative PSMA PET/CT result cannot definitively rule out disease recurrence. Approximately 15%-20% of patients with initially negative results may demonstrate lesion detection on repeat imaging within 3-6 months. Therefore, patients with high-risk BCR (PSA doubling time <6 months, Gleason ≥8) are recommended to undergo re-examination within 3-6 months or combined evaluation with multiparametric MRI. This strategy leverages the complementary strengths of functional of anatomical imaging, potentially reducing false-negative findings caused by low PSMA expression or spatial tumor heterogeneity.

Comparison of advantages and disadvantages of PSMA PET/CT versus conventional imaging techniques

PSMA PET/CT demonstrates superior diagnostic performance compared with conventional imaging modalities (CT, bone scintigraphy, choline PET/CT) in terms of both sensitivity and

Table 1. Performance comparison of PSMA PET/CT versus conventional imaging techniques in prostate cancer

Dimension	CT	Bone scan	Choline PET/CT	PSMA PET/CT
Sensitivity for detecting lymph node metastasis	~46.1%	Not applicable	Variable data, typically lower	~71.4%
Sensitivity for detecting bone metastasis	Not sensitive to osteoblastic lesions	~72.7%	Moderate	~90.9%
Specificity for detecting bone metastasis	Low	~52.9%	Moderate	~100%
Ability to detect microscopic and micrometastatic lesions	Poor	Poor	Limited	Excellent
Detection rate in BCR (PSA <0.5 ng/mL)	Extremely low	Extremely low	Moderate	11.3%-26.6%
Resulting changes in treatment regimen (proportion)	~15%	~15%	Variable data	~28% to 36%
Cost-effectiveness	Lower costs, but with poor accuracy	Lower costs, but with poor accuracy	High costs, with moderate benefits	High initial costs, possibly superior overall cost-effectiveness

Note: PET, positron emission tomography; CT, Computed tomography; BCR, Biochemical recurrence; PSA, Prostate-Specific Antigen.

specificity. For bone metastasis detection, PSMA PET/CT achieves a sensitivity and specificity of 90.9% and 100%, respectively, compared with 72.7% and 52.9% for bone scintigraphy [62]. For lymph node metastasis evaluation, PSMA PET/CT also shows markedly improved performance compared with CT, with a sensitivity of 71.4% and specificity of 100% [63]. PSMA PET/CT is also advantageous in detecting microscopic and micrometastatic lesions, including bone marrow micro-metastases that are frequently missed by conventional imaging modalities [35, 64]. Among BCR patients, PSMA PET/CT achieves a detection rate of up to 94%, significantly higher than that of choline PET/CT (75%) [65]. This advantage promotes optimized clinical decision-making. Accordingly, the proportion of treatment modification following PSMA PET/CT (approximately 28%) is higher than that associated with traditional imaging (15%) [30]. Cost-effectiveness analysis also supports its clinical utility, as improved diagnostic accuracy may reduce unnecessary examinations and treatments [39]. Nevertheless, PSMA-targeted imaging has inherent limitations and potential interpretive pitfalls that must be recognized in clinical interpretation. From a technical perspective, lesions approaching or below the spatial resolution limits of contemporary PET systems may be affected by partial-volume effects, resulting in underestimation of tracer uptake and reduced sensitivity for very small metastatic deposits or early local recurrence [31]. In addition, an important biological limitation is observed in advanced or pretreated heavily prostate cancer, where tumor dedifferentiation or neuroendocrine transformation may result in marked downregulation or complete loss of PSMA expression [66, 67]. Under these circumstances, disease lesions may become PSMA-negative and therefore occult on PSMA PET imaging [66, 67]. Therefore, conventional anatomical imaging and ^18F-FDG PET/CT retain an important complementary role, particularly in selected high-risk or advanced disease settings, as they may identify PSMA-negative but metabolically active tumor foci that would otherwise be underestimated by PSMA-targeted imaging alone [31, 68]. In conclusion, PSMA PET/CT demonstrates clear superiority over conventional imaging in diagnostic accuracy, detection of small-volume lesions, and impact on clinical decision-making (**Table 1**). It has therefore been widely recognized as a vital tool for staging and restaging of prostate cancer.

PSMA PET/CT in guiding prostate cancer treatment decisions

PSMA PET/CT-guided target volume delineation and scope adjustment in radical treatment (surgery/radiotherapy)

In the setting of radical surgery, PSMA PET/CT enables more precise tailoring of the extent of

lymph node dissection by accurately identifying metastatic nodal involvement. In a clinical study, PSMA PET/CT detected lymph node metastases in 15.6% of patients and contributed to modifications of the planned surgical approach [38]. Beyond its role in preoperative planning, the molecular targeting capability of PSMA-directed imaging has facilitated the development of PSMA-guided radioguided surgery (RGS) and intraoperative bimodal guidance techniques combining fluorescence/radiotracer [69, 70]. Using handheld gamma probes, surgeons are able to detect and localize occult pelvic lymph node metastases smaller than 1 cm, including lesions located outside the standard extended pelvic lymph node dissection (ePLND) template in both *in vivo* and *ex vivo* settings [71, 72]. Such real-time guidance enhances the precision of metastatic lesion resection, potentially improving oncological clearance while preserving noninvolved neurovascular structures [72, 73]. In radical radiotherapy, PSMA PET/CT contributes to optimized target volume delineation. In patients with prostate cancer recurrence, the technology precisely defines the extent of recurrence, thereby facilitating escalation of tumor radiation dose while reducing irradiation of normal tissues [74, 75]. PSMA PET/CT also achieves precise targeting with controlled toxicity in the guidance of stereotactic radiotherapy for oligometastases [76]. In summary, approximately 36% of patients changed their radiotherapy regimens based on PSMA PET/CT findings [37]. We propose that the use of PSMA PET/CT in target delineation should extend to the characterization of tumor biological boundaries (i.e., regions with heterogeneous expression of PSMA) rather than limited to the localization of metastatic lymph nodes. Existing studies have overlooked the impact of spatial heterogeneity of PSMA expression within primary lesions on radiotherapy dose. We therefore suggest that future radiotherapy planning should define biological target volumes based on the metabolic volume and heterogeneity index derived from PSMA PET/CT, rather than relying solely on morphological boundaries. More specifically, quantitative PET-derived imaging biomarkers, including SUV-based tumor segmentation and radiomic characterization of intratumoral heterogeneity [77, 78], may facilitate the implementation of biologically guided dose-painting strategies. Through this approach, simultaneous integrated boost (SIB) irradiation can be selectively delivered to biologically aggressive intratumoral subregions, such as areas of high PSMA expression and/or hypoxia-associated heterogeneity [79, 80], while minimizing radiation exposure to surrounding organs at risk (OARs), including the rectum and bladder wall [31]. This strategy aims to enhance local tumor control without substantially increasing treatment-related toxicity. Collectively, this paradigm shift supports a transition from purely anatomical target definition to biologically informed radiotherapy planning.

PSMA PET/CT for identification of oligometastatic patients suitable for metastasis-directed treatment

PSMA PET/CT is a critical imaging modality for identifying patients with oligometastatic prostate cancer (typically ≤5 metastatic lesions) and guiding metastasis-directed therapy (MDT). Importantly, the adoption of PSMA PET/CT has redefined the conceptual framework of oligometastatic disease, shifting patient classification from an anatomy-based definition toward a molecular imaging-driven paradigm [81]. Owing to its superior sensitivity in detecting otherwise occult metastatic deposits, PSMA PET/CT frequently leads to stage migration and facilitates the exclusion of patients with higher metastatic burden than initially recognized on conventional imaging [30, 82, 83]. As a result, candidates selected for MDT more likely to represent a biologically more homogeneous subgroup characterized by genuinely low-volume and spatially restricted disease, which may improve the consistency of therapeutic outcomes [84]. PSMA PET/CT accurately detects both synchronous or metachronous oligometastatic lesions [85], with SUVmax values correlating with disease aggressiveness [86].

PSMA PET/CT-guided targeted therapies for metastases (e.g., stereotactic radiotherapy) have demonstrated clinical efficacy, including reductions in PSA levels in a substantial proportion of patients and prolongation of progression-free survival. In some patients, it can even delay the start of systemic therapy, such as androgen deprivation therapy (ADT) [86, 87]. The number of metastatic lesions detected by PSMA PET/CT correlates with prognosis, with fewer lesions indicating better outcomes [88].

PSMA PET/CT can be used for treatment response assessment, where decreased tracer uptake after therapy indicates effective treatment [89].

Shekar et al. reported a single-center retrospective study on PSMA PET/CT-guided stereotactic radiotherapy involving 67 patients with oligometastatic prostate cancer [90]. In this cohort, 93 PSMA PET/CT-detected oligometastatic lesions were treated, with a median follow-up of 18.8 months. The median biochemical progression-free survival was 22.1 months, and the median time to next intervention was 28.8 months; the median PSA decline reached 68.9%, with 55.2% of patients achieving a PSA50 response and 43% achieving complete metabolic remission. Multivariate analysis identified lower initial T stage and longer interval to multidisciplinary treatment decision-making as factors associated with improved biochemical progression-free survival. This study complements previous data derived from European cohorts and supports the real-world applicability of PSMA PET/CT-guided stereotactic radiotherapy in oligometastatic prostate cancer.

Grün et al. investigated the feasibility of an "early and repetitive" stereotactic radiotherapy strategy in patients with oligorecurrent prostate cancer. The study included 67 patients with lymph node recurrence, detected by ^{18}F or ^{68}Ga-labeled PSMA PET/CT, who did not receive concurrent ADT, with a median PSA level of 2.175 ng/mL. All metastatic lesions were treated with stereotactic radiotherapy, and 32 patients underwent ≥1 course of stereotactic radiotherapy, with a maximum of four treatment courses [91]. The results showed a median biochemical progression-free survival of 9.5 months, a median stereotactic radiotherapy progression-free survival of 19.5 months, and a median ADT-free survival of up to 35 months [92]. These findings suggest that repeated stereotactic radiotherapy strategy may enable selected patients to defer initiation of ADT for nearly three years. Importantly, no grade ≥2 treatment-related toxicities were observed, indicating a favorable safety profile in rigorously selected patients with low-burden lymph node oligorecurrence. From a biological standpoint, the integration of early and repeated metastasis-directed interventions supports the emerging view that oligorecurrent prostate cancer may represent a clinically controllable disease state rather than a uniformly progressive systemic condition [81, 84, 93]. Serial PSMA PET/CT surveillance facilitates the timely identification of newly emerging metastatic lesions that may remain amenable to metastasis-directed therapy, thereby enabling an adaptive treatment strategy guided by evolving disease burden [93]. This iterative use of focal ablative therapy may delay systemic disease progression and postpone the initiation of systemic ADT [81]. In turn, such an approach may help reduce the metabolic and cardiovascular toxicities associated with long-term hormonal treatment and may reduce the evolutionary pressure that contributes to the development of aggressive castration-resistant prostate cancer (CRPC) [94].

PSMA PET/CT for guiding systemic therapy selection and efficacy assessment

In mCRPC patients, PSMA PET/CT can be used to screen patients suitable for PSMA-targeted radioligand therapy (e.g., 177Lu-PSMA-617). Clinical studies suggest that over 90% of patients may be suitable for this treatment [95]. In routine clinical practice, eligibility assessment is largely guided by quantitative PET metrics, with adequate PSMA expression typically defined as lesion uptake substantially exceeding physiological liver uptake [96, 97]. To further refine patient selection, a dual-tracer imaging paradigm combining PSMA PET/CT with ^{18}F-FDG PET/CT is increasingly being adopted [68]. This complementary approach facilitates the detection of PSMA-negative but FDG-positive discordant lesions, which are frequently associated with biologically aggressive tumor subclones, including dedifferentiated or neuroendocrine-transformed tumor subclones [98]. Because such lesions often exhibit reduced uptake of ^{177}Lu-PSMA radioligands, their identification provides important information on intrapatient spatial heterogeneity and may help avoid administering PSMA-targeted therapy to patients with limited expected benefit [99, 100]. Beyond patient selection, PSMA PET/CT may also provide supportive information for predicting response to systemic therapies, including androgen receptor pathway inhibitors [95]. Regarding treatment response assessment, PSMA PET/CT enables early visu-

alization of metabolic changes. After androgen deprivation therapy (ADT) or PSMA-targeted radioligand therapy, reductions in tracer uptake may indicate partial or complete response [95, 101]. Conversely, increasing or newly emerging lesions on PSMA PET/CT may signal disease progression and prompt timely modification of systemic treatment strategies [102]. To improve objectivity in response evaluation, standardized molecular imaging response frameworks, such as the Response Evaluation Criteria in PSMA PET/CT (RECIP 1.0) and the PSMA PET Progression (PPP) criteria, have been developed [103, 104]. These systems incorporate quantitative imaging biomarkers, such as longitudinal changes in total tumor volume (TTV), as well as the appearance of new PSMA-avid lesions, thereby enabling more reproducible assessment of treatment response and disease progression [103-105]. Their application is particularly valuable in differentiating true disease progression from transient PSA flare responses, which may occur following initiation of taxane-based chemotherapy or second-generation hormonal therapies. As a result, treatment decisions can be guided by objective imaging evidence rather than short-term biochemical fluctuations, thereby reducing the risk of premature discontinuation of effective therapy [106, 107].

PSMA PET/CT drives the evolution of clinical decision-making paradigms and facilitates integrated diagnosis and treatment

PSMA PET/CT enables the transition from conventional anatomical staging to molecular imaging-based staging

PSMA PET/CT has driven a paradigm shift in prostate cancer staging from anatomy-based imaging to molecular imaging-based staging. By enabling the detection of micrometastatic disease frequently missed by conventional methods (CT/bone scintigraphy), PSMA PET/CT significantly improves overall staging accuracy. Consequently, stage migration is commonly observed, with disease upstaging in approximately 23.9% of patients and downstaging in 8.9%, leading to corresponding modifications in treatment strategies [108-110]. The clinical value of PSMA PET/CT has been increasingly recognized in authoritative guidelines and is now recommended for staging patients with high-risk prostate cancer and BCR [111].

PSMA PET/CT-based "integrated diagnosis and treatment": application of targeted radioligand therapy

"Integrated diagnosis and treatment" represents one of the core advantages of PSMA PET/CT. Diagnostic PSMA PET/CT is used not only to identify patients eligible for PSMA-targeted radioligand therapy (e.g., 177Lu-PSMA-617), but also to predict treatment efficacy via the evaluation of baseline PSMA expression levels [112]. Post-therapeutic PSMA PET/CT further enables direct visualization of therapeutic response and disease progression through dynamic changes in tracer uptake, thereby facilitating precision disease monitoring throughout the treatment course [113-115]. Existing patient selection criteria for PSMA-targeted radioligand therapy, including fixed PSMA expression thresholds, have certain limitations. We therefore propose a hypothesis that quantitative measures of intratumoral heterogeneity (e.g., the ratio of SUVmax to SUVmean) and spatial uptake inhomogeneity within lesions may provide superior predictive value for treatment response than a single SUV threshold. From a radiobiological standpoint, substantial intratumoral heterogeneity implies the coexistence of highly PSMA-avid tumor regions alongside poorly differentiated subregions with reduced PSMA expression [66, 67, 116].

Given that β-emitting radionuclides such as ^{177}Lu exert therapeutic effects partly through cross-fire irradiation of neighboring tumor cells, marked spatial heterogeneity in tracer uptake may lead to heterogeneous radiation dose distribution within individual lesions [117, 118]. Consequently, regions with low PSMA expression may receive sublethal radiation doses, allowing survival and subsequent expansion of resistant tumor subclone that contribute to disease progression and therapeutic resistance [66]. Notably, such clinically relevant spatial heterogeneity is often obscured when tumor characterization relies exclusively on global uptake metrics such as SUVmax, highlighting the limitations of conventional semiquantitative assessment [103]. Furthermore, in patients with disease progression after PSMA-targeted treatment, a decrease or loss of PSMA expression on repeat PSMA PET/CT (PSMA-negative progression) may indicate biological dedifferentiation, and in such patients, a switch

to alternative systemic therapies (such as chemotherapy or immunotherapy) should be considered. Although this dynamic decision-making framework has not yet been incorporated into guidelines, it represents a promising direction for future clinical translation.

The Phase 3 PSMAfore trial (n = 468) demonstrated that among taxane-naïve patients with mCRPC, the median overall survival (OS) was 24.48 months in the ^{177}Lu-PSMA-617 group versus 23.13 months in the ARPI-switch group (HR = 0.91, P = 0.20). Notably, the crossover rate in the ARPI group reached 60.3%, and after crossover-adjusted analysis, the weighted HR after crossover adjustment was 0.59, indicating that the apparent survival benefit may have been underestimated in the unadjusted analysis. In terms of safety, the incidence of grade ≥3 adverse events was lower in the ^{177}Lu-PSMA-617 group than the ARPI-switch group [119]. These findings support an earlier positioning of ^{177}Lu-PSMA-617 in the treatment sequence of mCRPC, particularly after progression on androgen receptor pathway inhibitors.

In addition, a large-scale real-world analysis from France's Early Access Program evaluating ^{177}Lu-PSMA-617 between December 2021 and April 2025 included a total of 3,709 patients with mCRPC [66]. The results of the study showed that over time, the enrolled patients showed a trend toward older age, lower baseline PSA levels, and a decreasing proportion of patients with highly PSMA-positive lesions. Concurrently, treatment patterns evolved, with fewer patients receiving multiple prior lines of chemotherapy or androgen receptor pathway inhibitors. Specifically, the proportion of patients receiving ≥2 lines of chemotherapy decreased from 65.7% in the earlier cohort to 24.6% in the 2025 cohort, while the proportion receiving ≥2 androgen receptor pathway inhibitors declined from 68.1% to 41.9%. These trends reflect the progressive integration of ^{177}Lu-PSMA-617 into earlier treatment lines and provide complementary evidence to clinical trials by including underrepresented populations, such as elderly patients, those with renal impairment, and patients with specific genomic alterations.

However, approximately 30%-40% of patients with mCRPC were primarily resistant to ^{177}Lu-PSMA-617, defined as a PSA decline of less than 50% following treatment initiation. The core mechanisms underlying resistance are multifactorial [120, 121]: (1) Downregulation or loss of PSMA expression, known as "PSMA-negative progression"; approximately 15%-20% of patients with progressive disease experience a significant decline in PSMA expression during treatment, and in such cases, continu ed PSMA-targeted therapy is no longer effective; (2) Reactivation of androgen receptor pathway, whereby tumor cells reactivate the androgen receptor signaling pathway through AR-V7 splice variants or androgen receptor enhancer mutations; (3) Acquired mutations in DNA damage repair pathways, leading to increased tolerance to radiation-induced DNA damage. To address potential mechanisms underlying resistance to β-emitting radioligand therapy, including heterogeneous target expression and insufficient radiation dose delivery, targeted alpha therapy (TAT) using radionuclides such as ^{225}Ac-PSMA-617 has emerged as a promising therapeutic strategy [122, 123]. In contrast to β-emitting radionuclides, α-particles possess a markedly higher linear energy transfer (LET) and a very short tissue penetration range (<100 μm), enabling highly localized energy deposition within tumor cells [124]. These characteristics lead to the induction of complex, clustered DNA double-strand breaks that are challenging to repair, thereby enhancing cytotoxic potency at the cellular level [124, 125]. Owing to these distinctive radiobiological properties, α-emitting radioligand therapies may maintain antitumor activity in a subset of lesions that demonstrate reduced sensitivity to ^{177}Lu-based treatment [122, 126].

From a clinical management perspective, dynamic monitoring-based monitoring is essential. Baseline and follow-up PSMA PET/CT scans can be used to evaluate changes in PSMA expression and treatment response. In patients demonstrating "PSMA-negative progression", a timely switch to non-PSMA-targeted systemic therapies, such as chemotherapy (taxanes or docetaxel) or immunotherapy based on FDG PET/CT assessment, is recommended. A recent real-world cohort study published in 2025 analyzed the efficacy of ^{177}Lu-PSMA-617 in combination with an androgen receptor pathway inhibitor. This study showed that approximately 60% of patients received concomitant

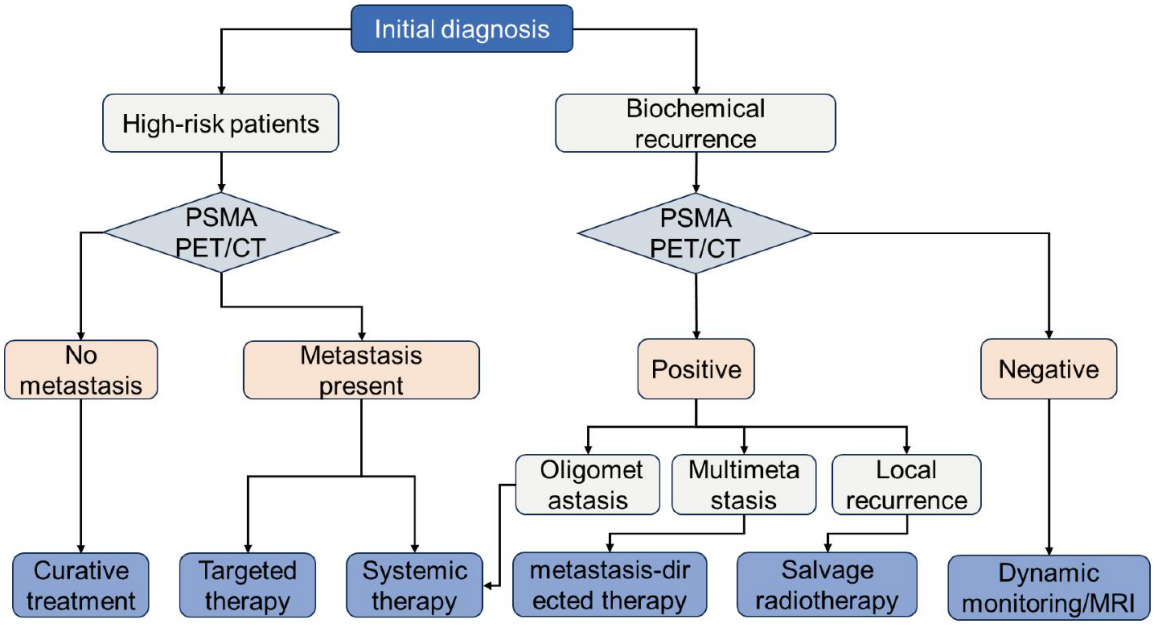

Figure 2. Flowchart of PSMA PET/CT-guided prostate cancer diagnosis and treatment decision-making. For newly diagnosed high-risk patients, PSMA PET/CT enables stratification of metastatic status, thereby guiding radical treatment (for patients without metastasis) or systemic/targeted therapy (for patients with metastasis). For patients with biochemical recurrence, PSMA PET/CT results serve as the guidance for subsequent management: a negative result indicates the need for dynamic monitoring or MRI; a positive result requires further classification into local recurrence (rescue therapy), oligometastasis (targeted therapy for metastatic lesions), or multiple metastases (systemic therapy). Notes: PSMA, Prostate-specific membrane antigen; PET/CT, positron emission tomography (PET)/computed tomography (CT); MRI, multiparametric magnetic resonance imaging.

AR pathway inhibition. Compared with patients not receiving combination therapy, those treated with the combination demonstrated a higher PSA50 response rate (65% vs. 49%) and an improvement in progression-free survival of approximately 3 months, although the difference in overall survival was not statistically significant [127]. In addition, an early-stage clinical trial investigating the combination of PARP inhibitors with ^{177}Lu-PSMA-617 is ongoing (NCT05881850). The biological rationale is that PARP inhibitors impair DNA repair, thereby potentiating the lethal effect of PSMA-targeted radiotherapy-induced DNA double-strand breaks, leading to synthetic lethality in tumor cells with compromised genomic stability.

The core role of PSMA PET/CT in multidisciplinary diagnosis and treatment

Due to the high-resolution molecular imaging information provided by PSMA PET/CT, it is increasingly regarded a cornerstone of multidisciplinary diagnosis and treatment (MDT)-based decision-making. It facilitates integration across different disciplines and plays a crucial role in the management of complex clinical scenarios, including differential diagnoses, biopsies guidance, and individualized treatment planning (selection and/or combination of surgery, radiotherapy, and systemic therapies) [83, 128]. The application of PSMA PET/CT has been deeply integrated into contemporary MDT workflows for prostate cancer and has influenced both clinical guideline development and the design of prospective clinical trials [111, 129].

Based on the evidence summarized above, we propose a comprehensive clinical decision-making algorithm that incorporates PSMA PET/CT findings into routine clinical practice, as illustrated in **Figure 2**.

Current challenges, limitations, and future prospects of PSMA PET/CT technology

Technical limitations and interpretation challenges of current PSMA PET/CT

Currently, PSMA PET/CT technology still faces certain technical limitations, including false-

positive results, inconsistent interpretation criteria, and controversies regarding health economics. False positive results are mainly caused by PSMA expression in normal tissues (e.g., salivary glands, kidneys) and benign lesions (e.g., inflammation, sarcoidosis [130]). A study involving 101 patients demonstrated a false-positive rate of 5% for detecting bone metastases [131]. A further challenge lies in the lack of standardized interpretation criteria. The use of different systems, including EANM, PROMISE, and PSMA-RADS, may lead to variability in diagnostic conclusions [131]. Notably, when PSMA-RADS was used, interobserver agreement for bone metastasis interpretation was only 0. moderate ($\kappa = 0.495$) [131]. The substantial interobserver variability observed in skeletal assessment is partly attributable to nonspecific tracer a range of benign osseous and neural structures [132-134]. For example, benign lesions associated with increased bone turnover, including degenerative osteophytes, healing fractures, fibrous bone lesions, and vertebral hemangiomas, may demonstrate mild-to-moderate PSMA uptake due to osteoblastic activity, inflammatory processes, and associated neovascularization [132]. In addition, physiological uptake in the dorsal root ganglia represents a well-recognized interpretive pitfall. Given their anatomical proximity to the vertebral foramina, these structures may be misinterpreted as adjacent osseous lesions on PSMA PET imaging, thereby contributing to diagnostic uncertainty and reduced interobserver agreement in skeletal assessment [133, 135, 136].

From the perspective of health economics, the controversy regarding PSMA PET/CT technology primarily centers on examination costs and health insurance reimbursement policies. For example, in Australia, a single PSMA PET/CT scan costs approximately AUD 1,203, which is lower than the cost of traditional imaging examinations (about AUD 1,412), but was historically not covered by health insurance. Despite this, its superior diagnostic accuracy demonstrates better overall cost-effectiveness [39]. In many countries, PSMA PET/CT remains excluded from health insurance coverage, which increases the financial burden on patients. Kunst et al. adopted a combined approach of decision tree and Markov models to simulate lifetime health outcomes and medical costs among 1,000 patients with BCR (median age: 66 years) [131]. The analysis showed that a PSMA PET-based strategy yielded the highest quality-adjusted life years (QALYs) (7.12 vs. 6.55), but also incurred higher average costs (451,000 vs. 351,000), resulting in an incremental cost-effectiveness ratio (ICER) of 172,000 per QALY, exceeding the pre-specified willingness-to-pay threshold of 150,000 per QALY. However, subgroup analysis demonstrated more favorable cost-effectiveness in patients with PSA <2 ng/mL, in whom the ICER dropped to 113,000/QALY, within the acceptable threshold range [131]. The model further suggested a potential gain of up to 15,747 QALYs through improved diagnostic stratification and information acquisition [131].

A recent systematic review (2025-2026) including seven health economics evaluations involving public and private health systems [148] indicated that PSMA PET/CT is cost-effective within the willingness-to-pay threshold across different countries compared to existing imaging technologies or standard treatment practices. However, the review also emphasized substantial heterogeneity across regions due to differences in healthcare resource, cost structures, disease prevalence, and clinical practice patterns. Therefore, PSMA PET/CT is likely to be most cost-effective in specific patient subgroups (e.g., patients with PSA <2 ng/mL, low metastatic burden, or those suitable for salvage therapy); however, its universal application in all patients with BCR remains controversial.

Moreover, the high costs of PET/CT equipment and radioligand preparation limit the widespread adoption of PSMA PET/CT in primary medical institutions [111]. It should be noted that although PSMA is also expressed in the neovascularization of other solid tumors, such as renal and liver cancers, the relevant clinical evidence is largely based on small-scale studies and is insufficient to support routine clinical application in these malignancies. From a biological perspective, this off-target uptake is predominantly attributed not to tumor cell themselves, but to PSMA (glutamate carboxypeptidase II, GCPII) expression in tumor-associated endothelial cells [137, 138], which is closely linked to angiogenesis and regulated by hypoxia-driven pro-angiogenic signaling path-

ways [139, 140]. Despite these limitations, the clinical utility of PSMA PET/CT is gradually expanding with ongoing optimization of interpretation frameworks and reductions in costs. The introduction of standardized reporting systems such as the E-PSMA guidelines has improved interobserver consistency [141], while novel tracers such as ^{18}F-PSMA-1007 have contributed to reduced examination costs [25]. The integration of artificial intelligence-based technology is expected to enhance detection accuracy and reduce interobserver variability [27]. With the development of technology, many current limitations of PSMA PET/CT are expected to be progressively mitigated, further expanding its clinical applications [142].

Progress in the development of novel PSMA tracers

To address the current limitations, the development of novel tracers and the application of artificial intelligence technologies are driving this field forward. The novel small-molecule ligand ^{18}F-PSMA-1007 exhibits a longer half-life and higher tracer uptake rate, which facilitate the detection of smaller metastatic lesions. In a study involving 195 patients, lesion detection rates at 2 hours post-injection were significantly higher than those at 1 hour, with improved identification of pelvic lymph node and bone metastases [25]. Another tracer, ^{18}F-DCFPyL, demonstrates high PSMA affinity and rapid pharmacokinetics, resulting in improved tumor-to-background contrast and enhanced lesion conspicuity [26]. More recently, first-in-human proof-of-concept studies of ^{18}F-siPSMA-14 were reported in 2025. This tracer features a simplified, scalable production process that avoids the more complex nucleophilic or electrophilic fluorination steps required for conventional tracers. Reported dosimetric data indicate an effective dose of $1.95\times10^{-2} \pm 0.25\times10^{-2}$ mSv/MBq, comparable to other ^{18}F and ^{68}Ga-labeled PSMA tracers. In addition, ^{18}F-siPSMA-14 enables high-quality imaging without mandatory forced diuresis, thereby improving patient compliance. Dynamic imaging further demonstrated time-dependent increases in tracer uptake between 60 and 120 minutes post-injection, with local lesion SUVmax increasing from 10.6 to 14.0 for primary lesions ($P = 0.01$) and from 17.7 to 20.6 for metastatic lesions ($P = 0.01$) [143].

A head-to-head comparative study involving 37 patients with BCR showed comparable detection rates between ^{18}F-AlF-PSMA-HBED-CC and ^{18}Ga-PSMA-11 (46% vs. 49%) [144]. However, subgroup analyses revealed site-specific differences: for bone metastases, ^{18}F-AlF-PSMA-11 yielded a significantly higher SUVmax (8.6 vs. 6.6, $P<0.001$) along with superior lesion-to-background contrast, whereas ^{68}Ga-PSMA-11 showed a slight advantage in SUVmax for lymph node and primary prostatic lesions [144]. From an imaging physics perspective, the superior performance of ^{18}F-labeled tracers in skeletal imaging can be largely attributable to the favorable nuclear characteristics of fluorine-18 [145-147]. Compared with ^{68}Ga, ^{18}F emits positrons with a substantially lower maximum energy (0.63 MeV versus 1.90 MeV), resulting in a markedly shorter positron range in tissue [145, 146]. This reduced positron travel distance minimizes image blurring before annihilation and improves the intrinsic spatial resolution of PET imaging. In the setting of small skeletal metastases and complex trabecular bone architecture, these characteristics help mitigate partial-volume effects and enhance lesion detectability and contrast recovery [42, 146, 147]. Taken together, these findings suggest that different PSMA tracers may may have complementary clinical roles rather than a universal superiority. For example, ^{18}F-labeled tracers may be preferable in patients with a high burden of bone metastases, while ^{68}Ga-based tracers may remain advantageous for certain pelvic lesions requiring optimal soft-tissue delineation.

In terms of dual-target tracers, recent studies have reported both preclinical and first-in-human studies of a novel PSMA/fibroblast activation protein (FAP) bispecific tracer (labeled with ^{68}Ga and Al^{18}F) [148]. FAP is highly expressed in cancer-associated fibroblasts in the tumor microenvironment, with possible expression in PSMA-negative or low-expression areas (approximately 5%-15% of the tumor volume) in prostate cancer. Therefore, dual-target tracers are hypothesized to partially overcome intratumoral heterogeneity of PSMA expression. Preclinical data showed that these bispecific tracers exhibit high tumor affinity, prolonged intratumoral retention, and significantly reduced renal uptake. The reduction in physiological renal accumulation has important impli-

cations for both PSMA-targeted imaging and radioligand therapy [149-151]. Conventional monovalent PSMA tracers often exhibit substantial renal cortical accumulation, which may obscure lesions located near the renal hilum or collecting system and simultaneously designates the kidneys as critical organs at risk in PSMA-targeted radioligand therapy [149, 150]. By optimizing biodistribution through the incorporation of a FAP-targeting moiety, these heterobivalent tracers may enhance tumor retention while reducing renal exposure, thereby improving the tumor-to-kidney uptake ratio [152-154]. Collectively, these findings suggest a potentially favorable dosimetric profile of PSMA/FAP bispecific tracers, supporting their potential role in the development of next-generation theranostic strategies [153, 154].

Application prospects and latest progress of artificial intelligence in PSMA

PSMA PET/CT technology has significantly changed the diagnostic and therapeutic pathway for prostate cancer. In newly diagnosed high-risk patients, PSMA PET/CT has replaced conventional CT and bone scintigraphy as the standard staging tool [155]. In a study involving 302 patients, PSMA PET/CT technology resulted in treatment regimen changes in approximately 28% of patients, with 41 patients subsequently receiving metastatic-directed therapy [30]. PSMA PET/CT technology can detect recurrence in patients with BCR even at a low PSA level of <0.5 ng/mL, thereby providing a critical imaging basis for early salvage treatment decision-making [56].

Based on accumulating evidence, the EAU guidelines have designated PSMA PET/CT as the standard staging method for high-risk prostate cancer, and the National Cancer Comprehensive Network (NCCN) guidelines also support its use in the evaluation of biochemical recurrence. In addition, PSMA PET/CT-guided metastasis-directed treatment for oligometastatic disease has been incorporated into treatment guidelines. Despite ongoing debates on costs and false-positive findings, an increasing number of evidence supports the role of PSMA PET/CT as a standard diagnostic tool. Moreover, PSMA PET/CT contributes to precision medicine in prostate cancer by enabling patient stratification based on biological characteristics (e.g., high PSMA expression), as well as also by facilitating longitudinal treatment response assessment and dynamic adjustment of therapeutic strategies throughout the disease course [156]. PSMA PET/CT technology will undoubtedly play an increasingly crucial role in the diagnosis and treatment of prostate cancer with continuous technological advancements, providing patients with more precise and individualized treatment strategies [157].

The application of artificial intelligence improves the diagnostic accuracy of PSMA PET/CT. Deep learning-based algorithms automatically segment tumor lesions and calculate SUV values, which reduces human-related measurement errors [27]. In lesion detection tasks, deep learning algorithms have achieved a detection rate of 80% for lesions, showing a detection rate of 93% for lesions with SUVmax >5.0 [27].

Constantino et al. systematically evaluated the performance of a deep learning-based maximum intensity projection (MIP) approach for automatic segmentation of ^{68}Ga-PSMA PET/CT lesions [158]. The study employed a three-dimensional U-Net architecture and included whole-body ^{68}Ga-PSMA PET/CT scans from 355 prostate cancer patients (285 for training, 70 for testing). The results demonstrated that ^{68}Ga-PSMA PET/CT already achieved excellent lesion detectability under the standard deep learning algorithm; however, additional enhancement using MIP failed to provide incremental benefit. In contrast, the application of similar AI to ^{18}F-FDG PET/CT yielded more pronounced improvements, with the false-positive detection rate dropping from 12% to 0%, and the consistency of lesion characteristics improving from an ICC of 0.42-0.94 to 0.80-0.94 [158]. These findings suggest that the inherently high tumor-to-background contrast and favorable image quality of PSMA PET/CT may reduce the marginal gain achievable through additional AI-based enhancement for lesion segmentation.

Trägårdh et al. applied AI to fully automated lesion detection and quantification in ^{18}F-PSMA-1007 PET/CT [159]. The AI-based approach achieved sensitivities of 85% for primary prostate tumors/recurrences, 91% for lymph node metastases, and 61% for bone

metastases, compared to 82%, 86%, and 70%, respectively, for manual interpretation. Corresponding positive predictive values were 85%, 83%, and 58% for AI versus 63%, 86%, and 39% for manual interpretation, respectively. The reported improvement in positive predictive value for skeletal lesion classification underscores the potential of deep convolutional neural networks to leverage high-order spatial and textural features embedded within PET imaging data [160]. Unlike conventional visual interpretation, these models integrate multiscale imaging features and capture subtle spatial heterogeneity that may not be readily appreciable to the human eye. This capability may contribute to improved differentiation between true skeletal metastases and benign uptake associated with degenerative changes, trauma-related remodeling, or other non-neoplastic bone processes, ultimately reducing false-positive interpretations [161, 162].

Looking forward, the role of artificial intelligence in PSMA PET imaging is increasingly extending beyond automated lesion detection and segmentation toward prognostic assessment and treatment-response prediction [163, 164]. Emerging end-to-end multimodal deep learning architectures, including Vision Transformers (ViTs), are being trained on longitudinal whole-body PSMA PET/CT datasets to enable automated quantification of total tumor volume (TTV) and characterization of disease distribution patterns [164]. By integrating radiomic signatures of tumor heterogeneity with complementary clinical biomarkers, such as PSA doubling time and genomic risk stratification, these models have shown potential in predicting biochemical progression, identifying patients most likely to benefit from ^{177}Lu-based radioligand therapy, and improving risk stratification for long-term clinical outcomes [165]. As these approaches continue to mature and undergo prospective validation, artificial intelligence is expected to evolve from an image-analysis tool into a clinically integrated decision-support component within precision oncology workflows for personalized cancer management [164].

Application prospects of PSMA PET/CT in other cancers

Unlike prostate cancer, in which PSMA is highly and homogeneously expressed on the tumor cell membrane, PSMA expression in other cancers is primarily confined to tumor angiogenesis, with lower overall density and greater heterogeneity. This biological difference explains why PSMA PET/CT has become a central tool in prostate cancer management, whereas its application in other tumor types remains largely investigational.

Despite the aforementioned biological limitations, emerging evidence suggests its promising potential in several non-prostatic malignancies, particularly renal cell carcinoma (RCC), hepatocellular carcinoma (HCC). Among these, RCC represents one of the most extensively studied indications. PSMA uptake can be observed in lesions of clear cell RCC, a finding primarily attributed to PSMA expression in the endothelial cells of tumor neovasculature [166]. Nevertheless, interpretation of PSMA avidity in non-prostatic genitourinary malignancies remains challenging [167, 168]. Physiological tracer accumulation within the renal cortex, hepatic parenchyma, and, in some cases, the urinary collecting system may reduce lesion conspicuity, resulting in relatively modest tumor-to-background ratios (TBRs) for neovasculature-associated uptake [167, 168]. Consequently, accurate lesion characterization often requires a multiparametric approach that integrates PET findings with anatomical imaging, semiquantitative parameters, and relevant clinical information. In selected settings, dynamic imaging and kinetic analysis may provide additional value in distinguishing tumor-related uptake from physiological or nonspecific background tracer distribution [31, 169]. A multicenter study (n = 78) showed that PSMA PET/CT exhibited a notably higher detection rate for distant metastasis of RCC than CT, and resulted in changes in treatment strategy in some patients [170]. A study performed on 40 HCC patients demonstrated that PSMA PET/CT detected distant metastasis in 20% of patients and contributed to treatment regimen adjustments in 47.5% of patients [108]. In addition, PSMA PET/CT can also detect PSMA expression levels in prostate neuroendocrine tumors to guide treatment decisions [171, 172]. Although current evidence remains limited and largely derived from small-scale or retrospective studies, these findings collectively suggest that PSMA PET/CT may have broader oncologic applications beyond prostate cancer.

Table 2. Summary of key prospective trials and meta-analyses on PSMA PET/CT in prostate cancer (2024-2025)

Study/Trial	Patient population	Intervention/comparison	Key findings
THUNDER trial	High-risk, planned radiotherapy	PSMA PET/CT vs conventional imaging	Upstaging 24%; radiotherapy changed in ~33%
^{18}F-PSMA-1007 staging study	High-risk	^{18}F-PSMA-1007 vs ^{18}F-NaF PET/CT	15% reclassified to metastatic; 20% CT-occult nodes
Mazzone meta-analysis	BCR after definitive treatment	PSMA PET/CT detection rates	Post-RT detection 92%; post-RP detection 60% (PSA-dependent)
van Altena cohort	Post-RT BCR (pre-Phoenix)	PSMA PET/CT before Phoenix criteria	76.6% positive, 75.9% local/regional
German multi-center	BCR with PSA ≤0.2 ng/mL	Three PSMA tracers	Overall detection 29.6%; PSA-DT <6 mo predictor
Shekar SBRT study	Oligometastatic, ADT-naïve	PSMA-PET-guided SBRT	Median bPFS 22.1 mo; ADT-free survival not reached
Ganswindt repeat SBRT	Nodal oligorecurrence	Early and repetitive SBRT	Median ADT-free survival 35 mo; zero grade ≥2 toxicity
PSMAfore (final OS)	Taxane-naïve mCRPC	^{177}Lu-PSMA-617 vs ARPI switch	mOS 24.5 vs 23.1 mo (HR 0.91); crossover adjusted HR 0.59
French EAP real-world	mCRPC	^{177}Lu-PSMA-617 early access	Confirms VISION/PSMAfore benefits; includes underrepresented subgroups
Kunst cost-effectiveness	BCR	PSMA-PET vs conventional	ICER 172k/QALYoverall; 172k/QALYoverall; 113k/QALY for PSA <2

Note: PET, positron emission tomography; CT, Computed tomography; BCR, Biochemical recurrence; PSA, Prostate-Specific Antigen; ADT, Androgen Deprivation Therapy; PSA-DT, Prostate-Specific Antigen Doubling Time; mCRPC, Metastatic Castration-Resistant Prostate Cancer; SBRT, Stereotactic Body Radiotherapy; QALY, Quality-Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio.

Table 2 summarizes key prospective trials and meta-analyses published between 2024 and 2025, which form the current evidence base for PSMA PET/CT in prostate cancer. These studies collectively confirm its high diagnostic accuracy, clinical impact on treatment decisions, and an emerging role in therapeutic medicine, while also highlighting persistent challenges related to cost-effectiveness and optimal patient selection.

Conclusion

PSMA PET/CT technology has transitioned from a research tool to a mainstream clinical approach, playing an increasingly central role in the precise staging, recurrence detection, treatment decision-making, and integrated diagnosis and treatment of prostate cancer. This review systematically integrates existing evidence and proposes new perspectives on the stratification of the clinical significance of PSMA-detected micrometastases, dynamic surveillance strategies in patients with negative imaging findings, the potential refinement of biologically informed target volume delineation, and a dynamic treatment decision-making framework.

In the future, with the continued advances in novel tracers, artificial intelligence-assisted image analysis, and health economics, PSMA PET/CT is expected to achieve a three-stage leap from “precision imaging” to “precision prognosis prediction” and then to “precision treatment guidance”. Therefore, further prospective studies are warranted to validate the clinical impact of these emerging strategies and to facilitate their integration into standardized management pathways, thereby advancing the progress of personalized diagnosis and treatment of prostate cancer.

Disclosure of conflict of interest

None.

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References

[1] Aziz N, Nabi W, Khan M, Gulzar AHB, Rath S, Ansab M, Kumar D and Bhat A. Trends and dis-

parities in prostate cancer mortality in the united states (1999-2020). Clin Genitourin Cancer 2025; 23: 102298.
[2] Qi JL, Wang LJ, Zhou MG, Liu YN, Liu JM, Liu SW, Zeng XY and Yin P. Disease burden of prostate cancer among men in China, from 1990 to 2013. Zhonghua Liu Xing Bing Xue Za Zhi 2016; 37: 778-782.
[3] Guzman-Esquivel J, Murillo-Zamora E, Ortiz-Mesina M, Galvan-Salazar HR, De-Leon-Zaragoza L, Casarez-Price JC, Delgado-Enciso J and Delgado-Enciso I. Regional and national burden of prostate cancer: incidence, mortality, years of life lost, and disability-adjusted life years, in Mexico and Latin America from 1990 to 2019. Int Urol Nephrol 2023; 55: 2155-2160.
[4] Kania E, Janica M, Nesterowicz M, Modzelewski W, Cybulski M and Janica J. Advances and challenges in prostate cancer diagnosis: a comprehensive review. Cancers (Basel) 2025; 17: 2137.
[5] Fonteyne V, Tree A, Castro E, Touijer K and Walz J. Prostate cancer. Lancet 2026; 407: 622-636.
[6] Sharma S, Zapatero-Rodríguez J and O'Kennedy R. Prostate cancer diagnostics: clinical challenges and the ongoing need for disruptive and effective diagnostic tools. Biotechnol Adv 2017; 35: 135-149.
[7] Yamoah K, Asamoah FA, Abrahams AOD, Awasthi S, Mensah JE, Dhillon J, Mahal BA, Gueye SM, Jalloh M, Farahani SJ, Lal P, Rebbeck TR and Yarney J. Prostate tumors of native men from West Africa show biologically distinct pathways-A comparative genomic study. Prostate 2021; 81: 1402-1410.
[8] Damaj N, Najdi T, Seif S, Nakouzi N and Kattan J. Zoledronic acid in metastatic castrate-sensitive prostate cancer: a state-of-the-art review. J Bone Oncol 2025; 51: 100667.
[9] Finianos A and Aragon-Ching JB. Zoledronic acid for the treatment of prostate cancer. Expert Opin Pharmacother 2019; 20: 657-666.
[10] Brea L and Yu J. Tumor-intrinsic regulators of the immune-cold microenvironment of prostate cancer. Trends Endocrinol Metab 2025; 36: 855-866.
[11] Carll J, Bonaddio J, Woon D, Perera M, Lawrentschuk N and Chengodu T. Prostate specific membrane antigen (PSMA) as a biomarker in early and localized advanced prostate cancer: a narrative review. Can J Urol 2026; 33: 21-34.
[12] Tayara O, Poletajew S, Malewski W, Kunikowska J, Pełka K, Kryst P and Nyk Ł. Prostate-specific membrane antigen expression in patients with primary prostate cancer: diagnostic and prognostic value in positron emission tomography-prostate-specific membrane antigen. Curr Oncol 2024; 31: 4165-4177.
[13] Jang A, Kendi AT and Sartor O. Status of PSMA-targeted radioligand therapy in prostate cancer: current data and future trials. Ther Adv Med Oncol 2023; 15: 17588359231157632.
[14] Maurice Dror C, Chi KN and Khalaf DJ. Finding the optimal treatment sequence in metastatic castration-resistant prostate cancer-a narrative review. Transl Androl Urol 2021; 10: 3931-3945.
[15] Chen M, Cai L, Xiang Y, Zhong L and Shi J. Advances in non-radioactive PSMA-targeted small molecule-drug conjugates in the treatment of prostate cancer. Bioorg Chem 2023; 141: 106889.
[16] Basu S and Alavi A. PET-based personalized management in clinical oncology: an unavoidable path for the foreseeable future. PET Clin 2016; 11: 203-207.
[17] Miyahira AK, Pienta KJ, Morris MJ, Bander NH, Baum RP, Fendler WP, Goeckeler W, Gorin MA, Hennekes H, Pomper MG, Sartor O, Tagawa ST, Williams S and Soule HR. Meeting report from the prostate cancer foundation PSMA-directed radionuclide scientific working group. Prostate 2018; 78: 775-789.
[18] Miyahira AK and Soule HR. The 24th annual prostate cancer foundation scientific retreat report. Prostate 2018; 78: 867-878.
[19] Parghane R and Basu S. Small cell transformation of metastatic prostate adenocarcinoma diagnosed by dual-tracer PET/CT ((68)Ga-PSMA and (18)F-FDG): potential clinical utility in therapeutic decision making and treatment monitoring. J Nucl Med Technol 2019; 47: 85-87.
[20] Miyahira AK, Pienta KJ, Babich JW, Bander NH, Calais J, Choyke P, Hofman MS, Larson SM, Lin FI, Morris MJ, Pomper MG, Sandhu S, Scher HI, Tagawa ST, Williams S and Soule HR. Meeting report from the prostate cancer foundation PSMA theranostics state of the science meeting. Prostate 2020; 80: 1273-1296.
[21] Suman S, Parghane RV, Joshi A, Prabhash K, Bakshi G, Talole S, Banerjee S and Basu S. Therapeutic efficacy, prognostic variables and clinical outcome of (177)Lu-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. Br J Radiol 2019; 92: 20190380.
[22] Assadi M, Jokar N, Ghasemi M, Nabipour I, Gholamrezanezhad A and Ahmadzadehfar H. Precision medicine approach in prostate cancer. Curr Pharm Des 2020; 26: 3783-3798.
[23] Esen B, Seymen H, Tarim K, Koseoglu E, Bolukbasi Y, Falay O, Selçukbiricik F, Molinas Mandel N, Kordan Y, Demirkol MO, Tilki D and Esen T. Diagnostic performance of (68)Ga-PSMA-11 positron emission tomography/computed to-

mography to monitor treatment response in patients with metastatic prostate cancer: the concordance between biochemical response and prostate-specific membrane antigen results. Eur Urol Focus 2023; 9: 832-837.
[24] Dias AH, Jochumsen MR, Zacho HD, Munk OL and Gormsen LC. Multiparametric dynamic whole-body PSMA PET/CT using [(68)Ga]Ga-PSMA-11 and [(18)F]PSMA-1007. EJNMMI Res 2023; 13: 31.
[25] Hvittfeldt E, Bitzén U, Minarik D, Oddstig J, Olsson B and Trägårdh E. PET/CT imaging 2 h after injection of [(18)F]PSMA-1007 can lead to higher staging of prostate cancer than imaging after 1 h. Eur J Hybrid Imaging 2023; 7: 9.
[26] Chan TH, Haworth A, Wang A, Osanlouy M, Williams S, Mitchell C, Hofman MS, Hicks RJ, Murphy DG and Reynolds HM. Detecting localised prostate cancer using radiomic features in PSMA PET and multiparametric MRI for biologically targeted radiation therapy. EJNMMI Res 2023; 13: 34.
[27] Xu Y, Klyuzhin I, Harsini S, Ortiz A, Zhang S, Bénard F, Dodhia R, Uribe CF, Rahmim A and Lavista Ferres J. Automatic segmentation of prostate cancer metastases in PSMA PET/CT images using deep neural networks with weighted batch-wise dice loss. Comput Biol Med 2023; 158: 106882.
[28] Hötker AM, Mühlematter U, Beintner-Skawran S, Ghafoor S, Burger I, Huellner M, Eberli D and Donati OF. Prediction of pelvic lymph node metastases and PSMA PET positive pelvic lymph nodes with multiparametric MRI and clinical information in primary staging of prostate cancer. Eur J Radiol Open 2023; 10: 100487.
[29] Klingenberg S, Jochumsen MR, Ulhøi BP, Fredsøe J, Sørensen KD, Borre M and Bouchelouche K. (68)Ga-PSMA PET/CT for primary lymph node and distant metastasis NM staging of high-risk prostate cancer. J Nucl Med 2021; 62: 214-220.
[30] Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, Rutherford N, Martin JM, Frydenberg M, Shakher R, Wong LM, Taubman K, Ting Lee S, Hsiao E, Roach P, Nottage M, Kirkwood I, Hayne D, Link E, Marusic P, Matera A, Herschtal A, Iravani A, Hicks RJ, Williams S and Murphy DG. 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 2020; 395: 1208-1216.
[31] Fendler WP, Eiber M, Beheshti M, Bomanji J, Calais J, Ceci F, Cho SY, Fanti S, Giesel FL, Goffin K, Haberkorn U, Jacene H, Koo PJ, Kopka K, Krause BJ, Lindenberg L, Marcus C, Mottaghy FM, Oprea-Lager DE, Osborne JR, Piert M, Rowe SP, Schöder H, Wan S, Wester HJ, Hope TA and Herrmann K. PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. Eur J Nucl Med Mol Imaging 2023; 50: 1466-1486.
[32] Jabeen N, Rasheed R, Rafique A and Murtaza G. The established nuclear medicine modalities for imaging of bone metastases. Curr Med Imaging Rev 2019; 15: 819-830.
[33] Tombal B and Lecouvet F. Modern detection of prostate cancer's bone metastasis: is the bone scan era over? Adv Urol 2012; 2012: 893193.
[34] Ergül N, Yilmaz Güneş B, Yücetaş U, Toktaş MG and Çermik TF. 68Ga-PSMA-11 PET/CT in newly diagnosed prostate adenocarcinoma. Clin Nucl Med 2018; 43: e422-e427.
[35] Anttinen M, Ettala O, Malaspina S, Jambor I, Sandell M, Kajander S, Rinta-Kiikka I, Schildt J, Saukko E, Rautio P, Timonen KL, Matikainen T, Noponen T, Saunavaara J, Löyttyniemi E, Taimen P, Kemppainen J, Dean PB, Blanco Sequeiros R, Aronen HJ, Seppänen M and Boström PJ. A prospective comparison of (18) F-prostate-specific membrane antigen-1007 positron emission tomography computed tomography, whole-body 1.5 T magnetic resonance imaging with diffusion-weighted imaging, and single-photon emission computed tomography/computed tomography with traditional imaging in primary distant metastasis staging of prostate cancer (PROSTAGE). Eur Urol Oncol 2021; 4: 635-644.
[36] Simsek DH, Sanli Y, Engin MN, Erdem S and Sanli O. Detection of metastases in newly diagnosed prostate cancer by using 68Ga-PSMA PET/CT and its relationship with modified D'Amico risk classification. Eur J Nucl Med Mol Imaging 2021; 48: 1639-1649.
[37] Onal C, Torun N, Akyol F, Guler OC, Hurmuz P, Yildirim BA, Cağlar M, Reyhan M and Ozyigit G. Integration of 68Ga-PSMA-PET/CT in radiotherapy planning for prostate cancer patients. Clin Nucl Med 2019; 44: e510-e516.
[38] van Kalmthout LWM, van Melick HHE, Lavalaye J, Meijer RP, Kooistra A, de Klerk JMH, Braat AJAT, Kaldeway HP, de Bruin PC, de Keizer B and Lam MGEH. Prospective validation of gallium-68 prostate specific membrane antigen-positron emission tomography/computerized tomography for primary staging of prostate cancer. J Urol 2020; 203: 537-545.
[39] de Feria Cardet RE, Hofman MS, Segard T, Yim J, Williams S, Francis RJ, Frydenberg M, Lawrentschuk N, Murphy DG and De Abreu Lourenco R. Is prostate-specific membrane antigen positron emission tomography/computed tomography imaging cost-effective in prostate cancer: an analysis informed by the proPSMA trial. Eur Urol 2021; 79: 413-418.

[40] Kleiburg F, Dirix P, Fonteyne V, Bral S, De Troyer B, Sautois B, Lamande M, Liefhooghe N, Grisay G, Meersschout S, Vandermeulen A, Jullian N, Staelens L, Poelaert F, Strijbos M, Verschueren J, Goffin K, Withofs N and Ost P. Stage migration on prostate-specific membrane antigen positron emission tomography/computed tomography in comparison to conventional imaging in patients with high-risk prostate cancer referred for radiation therapy: results from the phase 2/3 THUNDER trial. Eur Urol Oncol 2025; 8: 1333-1339.

[41] Talavera Cobo V, Yanez Ruiz CA, Tapia Tapia MD, Calva Lopez A, Munoz Bastidas CA, Ancizu Marckert FJ, Torres Roca M, Huerta LL, Sanchez Zalabardo D, Diez-Caballero Alonso FJ, Guillen-Grima F, Robles Garcia JE and Minana-Lopez B. Diagnostic accuracy of PSMA-PET/CT vs. mpMRI in primary staging of intermediate- and high-risk prostate cancer. Med Sci (Basel) 2026; 14: 64.

[42] Eiber M, Herrmann K, Calais J, Hadaschik B, Giesel FL, Hartenbach M, Hope T, Reiter R, Maurer T, Weber WA and Fendler WP. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-Ligand PET/CT. J Nucl Med 2018; 59: 469-478.

[43] Ozman O, Veerman H, Contieri R, Droghetti M, Donswijk ML, Hagens MJ, Van Leeuwen PJ, Vis AN and van der Poel HG. Staging accuracy and prognostic value of prostate-specific membrane antigen PET/CT strongly depends on lymph node tumor burden. J Clin Med 2024; 13: 6534.

[44] Kim IH, Chong Y, Yun JK, Choi S, Kim HR, Kim YH, Kim DK, Park SI and Lee GD. Analysis of lymph node metastasis based on consolidation tumor ratio and maximum standardized uptake value in clinical stage IA non-small cell lung cancer. J Thorac Dis 2025; 17: 944-958.

[45] Muraglia L, Mattana F, Zuccotti G, Collamati F, Luzzago S, Travaini LL, Musi G and Ceci F. Prostate-specific membrane antigen (PSMA) radioguided surgery in prostate cancer: an overview of current application and future perspectives. Clinical and Translational Imaging 2023; 11: 255-261.

[46] Carll J, Shi W, Perera M, Lawrentschuk N, Chengodu T and Woon D. Guideline of guidelines: PSMA PET in staging newly diagnosed intermediate-risk prostate cancer. BJU Int 2025; 136: 800-804.

[47] Meredith G, Wong D, Yaxley J, Coughlin G, Thompson L, Kua B and Gianduzzo T. The use of (68) Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. BJU Int 2016; 118 Suppl 3: 49-55.

[48] Rauscher I, Maurer T, Beer AJ, Graner FP, Haller B, Weirich G, Doherty A, Gschwend JE, Schwaiger M and Eiber M. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med 2016; 57: 1713-1719.

[49] Uprimny C, Kroiss AS, Decristoforo C, Fritz J, Warwitz B, Scarpa L, Roig LG, Kendler D, von Guggenberg E, Bektic J, Horninger W and Virgolini IJ. Early dynamic imaging in (68)Ga-PSMA-11 PET/CT allows discrimination of urinary bladder activity and prostate cancer lesions. Eur J Nucl Med Mol Imaging 2017; 44: 765-775.

[50] Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, Holland-Letz T, Hadaschik BA, Giesel FL, Debus J and Haberkorn U. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2014; 41: 11-20.

[51] Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, Kesch C, Tolstov Y, Singer S, Grabe N, Duensing S, Schäfer M, Neels OC, Mier W, Haberkorn U, Kopka K and Kratochwil C. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging 2017; 44: 678-688.

[52] Rahbar K, Afshar-Oromieh A, Seifert R, Wagner S, Schäfers M, Bögemann M and Weckesser M. Diagnostic performance of (18)F-PSMA-1007 PET/CT in patients with biochemical recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2018; 45: 2055-2061.

[53] Awenat S, Piccardo A, Carvoeiras P, Signore G, Giovanella L, Prior JO and Treglia G. Diagnostic role of 18F-PSMA-1007 PET/CT in prostate cancer staging: a systematic review. Diagnostics 2021; 11: 552.

[54] Vinsensia M, Chyoke PL, Hadaschik B, Holland-Letz T, Moltz J, Kopka K, Rauscher I, Mier W, Schwaiger M, Haberkorn U, Mauer T, Kratochwil C, Eiber M and Giesel FL. (68)Ga-PSMA PET/CT and volumetric morphology of PET-positive lymph nodes stratified by tumor differentiation of prostate cancer. J Nucl Med 2017; 58: 1949-1955.

[55] Grubmüller B, Baltzer P, D'Andrea D, Korn S, Haug AR, Hacker M, Grubmüller KH, Goldner GM, Wadsak W, Pfaff S, Babich J, Seitz C, Fajkovic H, Susani M, Mazal P, Kramer G, Shariat SF and Hartenbach M. (68)Ga-PSMA 11 ligand PET imaging in patients with biochemical recurrence after radical prostatectomy - di-

agnostic performance and impact on therapeutic decision-making. Eur J Nucl Med Mol Imaging 2018; 45: 235-242.

[56] Kranzbühler B, Nagel H, Becker AS, Müller J, Huellner M, Stolzmann P, Muehlematter U, Guckenberger M, Kaufmann PA, Eberli D and Burger IA. Clinical performance of (68)Ga-PSMA-11 PET/MRI for the detection of recurrent prostate cancer following radical prostatectomy. Eur J Nucl Med Mol Imaging 2018; 45: 20-30.

[57] Mazzone E, Thomson A, Chen DC, Cannoletta D, Quarta L, Pellegrino A, Gandaglia G, Moon D, Eapen R, Lawrentschuk N, Montorsi F, Siva S, Hofman MS, Chiti A, Briganti A, Perera ML and Murphy DG. The role of prostate-specific membrane antigen positron emission tomography for assessment of local recurrence and distant metastases in patients with biochemical recurrence of prostate cancer after definitive treatment: a systematic review and meta-analysis. European Urology 2025; 88: 129-141.

[58] Abghari-Gerst M, Armstrong WR, Nguyen K, Calais J, Czernin J, Lin D, Jariwala N, Rodnick M, Hope TA, Hearn J, Montgomery JS, Alva A, Reichert ZR, Spratt DE, Johnson TD, Scott PJH and Piert M. A comprehensive assessment of (68)Ga-PSMA-11 PET in biochemically recurrent prostate cancer: results from a prospective multicenter study on 2,005 patients. J Nucl Med 2022; 63: 567-572.

[59] Christensen MT, Jochumsen MR, Klingenberg S, Sørensen KD, Borre M and Bouchelouche K. Evaluation of predictors of biochemical recurrence in prostate cancer patients, as detected by (68)Ga-PSMA PET/CT. Diagnostics (Basel) 2022; 12: 195.

[60] van Altena EJE, Jansen BHE, Korbee ML, Knol RJJ, Luining WI, Nieuwenhuijzen JA, Oprea-Lager DE, van der Pas SL, van der Voort van Zyp JRN, van der Zant FM, van Leeuwen PJ, Wondergem M and Vis AN. Prostate-specific membrane antigen positron emission tomography before reaching the phoenix criteria for biochemical recurrence of prostate cancer after radiotherapy: earlier detection of recurrences. Eur Urol Oncol 2025; 8: 417-424.

[61] Burgard C, Frei M, Blickle A, Hartrampf PE, Hoffmann MA, Schreckenberger M, Schmid HP, Unterrainer L, Rogasch J and Galler M. PSMA PET/CT in biochemical recurrence of prostate cancer with PSA levels ≤0.2 ng/mL: a German multicenter analysis of conventional PSMA tracers, including [68Ga] Ga-PSMA-11, [68Ga] Ga-PSMA I&T, and [18F] PSMA-1007. Eur J Nucl Med Mol Imaging 2025; 52: 4368-4376.

[62] Uslu-Beşli L, Sağer S, Akgün E, Asa S, Şahin OE, Demirdağ Ç, Güner E, Khosroshahi BR, Karayel E, Pehlivanoğlu H, Aygün A, Uslu İ, Talat Z and Sönmezoğlu K. Comparison of Ga-68 PSMA positron emission tomography/computerized tomography with Tc-99m MDP bone scan in prostate cancer patients. Turk J Med Sci 2019; 49: 301-310.

[63] Pepe P and Pennisi M. Should 68Ga-PSMA PET/CT Replace CT and bone scan in clinical staging of high-risk prostate cancer? Anticancer Res 2022; 42: 1495-1498.

[64] Pianou NK, Stavrou PZ, Vlontzou E, Rondogianni P, Exarhos DN and Datseris IE. More advantages in detecting bone and soft tissue metastases from prostate cancer using (18)F-PSMA PET/CT. Hell J Nucl Med 2019; 22: 6-9.

[65] Van Damme J, Tombal B, Collette L, Van Nieuwenhove S, Pasoglou V, Gérard T, Jamar F, Lhommel R and Lecouvet FE. Comparison of (68)Ga-prostate specific membrane antigen (PSMA) positron emission tomography computed tomography (PET-CT) and whole-body magnetic resonance imaging (WB-MRI) with diffusion sequences (DWI) in the staging of advanced prostate cancer. Cancers (Basel) 2021; 13: 5286.

[66] Bakht MK and Beltran H. Biological determinants of PSMA expression, regulation and heterogeneity in prostate cancer. Nat Rev Urol 2025; 22: 26-45.

[67] Aggarwal R, Wei X, Kim W, Small EJ, Ryan CJ, Carroll P, Cooperberg M, Evans MJ and Hope T. Heterogeneous flare in prostate-specific membrane antigen positron emission tomography tracer uptake with initiation of androgen pathway blockade in metastatic prostate cancer. Eur Urol Oncol 2018; 1: 78-82.

[68] Kratochwil C, Fendler WP, Eiber M, Hofman MS, Emmett L, Calais J, Osborne JR, Iravani A, Koo P, Lindenberg L, Baum RP, Bozkurt MF, Delgado Bolton RC, Ezziddin S, Forrer F, Hicks RJ, Hope TA, Kabasakal L, Konijnenberg M, Kopka K, Lassmann M, Mottaghy FM, Oyen WJG, Rahbar K, Schoder H, Virgolini I, Bodei L, Fanti S, Haberkorn U and Hermann K. Joint EANM/SNMMI procedure guideline for the use of (177)Lu-labeled PSMA-targeted radioligandtherapy ((177)Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging 2023; 50: 2830-2845.

[69] Maurer T, Robu S, Schottelius M, Schwamborn K, Rauscher I, van den Berg NS, van Leeuwen FWB, Haller B, Horn T, Heck MM, Gschwend JE, Schwaiger M, Wester HJ and Eiber M. (99m)technetium-based prostate-specific membrane antigen-radioguided surgery in recurrent prostate cancer. Eur Urol 2019; 75: 659-666.

[70] Robu S, Schottelius M, Eiber M, Maurer T, Gschwend J, Schwaiger M and Wester HJ. Preclinical evaluation and first patient application of 99mTc-PSMA-I&S for SPECT imaging and radioguided surgery in prostate cancer. J Nucl Med 2017; 58: 235-242.

[71] Rauscher I, Horn T, Eiber M, Gschwend JE and Maurer T. Novel technology of molecular radioguidance for lymph node dissection in recurrent prostate cancer by PSMA-ligands. World J Urol 2018; 36: 603-608.

[72] Mazzone E, Gandaglia G, Ploussard G, Marra G, Valerio M, Campi R, Mari A, Minervini A, Serni S, Moschini M, Marquis A, Beauval JB, van den Bergh R, Rahota RG, Soeterik T, Roumiguiè M, Afferi L, Zhuang J, Guo H, Mattei A, Gontero P, Cucchiara V, Stabile A, Fossati N, Montorsi F and Briganti A. Risk stratification of patients candidate to radical prostatectomy based on clinical and multiparametric magnetic resonance imaging parameters: development and external validation of novel risk groups. Eur Urol 2022; 81: 193-203.

[73] Schottelius M, Viertl D, Buckle T, Koch H, Martin S, Litvinenko A, Patt M, van Willigen DM, van Leeuwen FWB, Wester HJ, Weckermann D, Liebich A, Gäble A, Reitsam NG, Märkl B, Enke JS, Brosch-Lenz J and Lapa C. [(99m)Tc]Tc-PSMA-HSG for PSMA-targeted Hybrid Surgical Guidance: a new addition to the PSMA-I&S/I&T family. Eur J Nucl Med Mol Imaging 2026; 53: 2974-2993.

[74] Sonni I, Dal Pra A, O'Connell DP, Ells Z, Benz M, Nguyen K, Yoon SM, Deng J, Smith C, Grogan T, Nickols NG, Cao M, Kishan AU and Calais J. (68)Ga-PSMA PET/CT-based atlas for prostate bed recurrence after radical prostatectomy: clinical implications for salvage radiation therapy contouring guidelines. J Nucl Med 2023; 64: 902-909.

[75] Singh M, Katdare A, Ghosh S, Choudhury S, Phurailatpam R, Patil D, Tiwari M, Anaz M, Chougle NH, Sable N, Agrawal A, Pawar A, Rangarajan V, Maitre P and Murthy V. PSMA-PET-guided intraprostatic boost in prostate SBRT (PROBE): a phase 2 trial. Int J Radiat Oncol Biol Phys 2026; 125: 203-213.

[76] Li M, Fan Y, Trapp C, Schmidt-Hegemann NS, Ma J, Buchner A, Lu S, Xu B, Stief C, Wang X, Zhou C, Belka C and Rogowski P. Elective nodal radiotherapy with a gapless radiation field junction for oligorecurrent prostate cancer after previous radiotherapy. Clin Transl Radiat Oncol 2023; 39: 100571.

[77] Zamboglou C, Fassbender TF, Steffan L, Schiller F, Fechter T, Carles M, Kiefer S, Rischke HC, Reichel K, Schmidt-Hegemann NS, Ilhan H, Chirindel AF, Nicolas G, Henkenberens C, Derlin T, Bronsert P, Mavroidis P, Chen RC, Meyer PT, Ruf J and Grosu AL. Validation of different PSMA-PET/CT-based contouring techniques for intraprostatic tumor definition using histopathology as standard of reference. Radiother Oncol 2019; 141: 208-213.

[78] Zamboglou C, Carles M, Fechter T, Kiefer S, Reichel K, Fassbender TF, Bronsert P, Koeber G, Schilling O, Ruf J, Werner M, Jilg CA, Baltas D, Mix M and Grosu AL. Radiomic features from PSMA PET for non-invasive intraprostatic tumor discrimination and characterization in patients with intermediate- and high-risk prostate cancer - a comparison study with histology reference. Theranostics 2019; 9: 2595-2605.

[79] Bettermann AS, Zamboglou C, Kiefer S, Jilg CA, Spohn S, Kranz-Rudolph J, Fassbender TF, Bronsert P, Nicolay NH, Gratzke C, Bock M, Ruf J, Benndorf M and Grosu AL. [(68)Ga-]PSMA-11 PET/CT and multiparametric MRI for gross tumor volume delineation in a slice by slice analysis with whole mount histopathology as a reference standard - implications for focal radiotherapy planning in primary prostate cancer. Radiother Oncol 2019; 141: 214-219.

[80] Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, Polat B, Hildebrandt G, Müller AC, Plasswilm L, Papachristofilou A, Schär C, Sumila M, Zaugg K, Guckenberger M, Ost P, Reuter C, Bosetti DG, Khanfir K, Gomez S, Wust P, Thalmann GN and Aebersold DM. Dose-intensified versus conventional-dose salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: the SAKK 09/10 randomized phase 3 trial. Eur Urol 2021; 80: 306-315.

[81] Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, Rowe SP, Ross AE, Gorin MA, Deville C, Greco SC, Wang H, Denmeade SR, Paller CJ, Dipasquale S, DeWeese TL, Song DY, Wang H, Carducci MA, Pienta KJ, Pomper MG, Dicker AP, Eisenberger MA, Alizadeh AA, Diehn M and Tran PT. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol 2020; 6: 650-659.

[82] Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, Wong JYC, Pantel AR, Cho SY, Gage KL, Piert M, Iagaru A, Pollard JH, Wong V, Jensen J, Lin T, Stambler N, Carroll PR and Siegel BA. Diagnostic performance of (18)F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. Clin Cancer Res 2021; 27: 3674-3682.

[83] Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, Saperstein L, Preston MA, Alva AS, Patnaik A, Durack JC, Stambler N, Lin T, Jensen J, Wong V, Siegel BA and Morris MJ. A

phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with (18)F-DCFPyL in prostate cancer patients (OSPREY). J Urol 2021; 206: 52-61.

[84] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, Lambert B, Delrue L, Bultijnck R, Claeys T, Goetghebeur E, Villeirs G, De Man K, Ameye F, Billiet I, Joniau S, Vanhaverbeke F and De Meerleer G. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018; 36: 446-453.

[85] Hurmuz P, Onal C, Ozyigit G, Igdem S, Atalar B, Sayan H, Akgun Z, Kurt M, Ozkok HB, Selek U, Oymak E, Tilki B, Guler OC, Mustafayev TZ, Saricanbaz I, Rzazade R and Akyol F. Treatment outcomes of metastasis-directed treatment using (68)Ga-PSMA-PET/CT for oligometastatic or oligorecurrent prostate cancer: turkish society for radiation oncology group study (TROD 09-002). Strahlenther Onkol 2020; 196: 1034-1043.

[86] Onal C, Ozyigit G, Akgun Z, Atalar B, Igdem S, Oymak E, Agaoglu F, Selek U, Guler OC, Hurmuz P, Mustafayev TZ and Akyol F. Oligometastatic bone disease in castration-sensitive prostate cancer patients treated with stereotactic body radiotherapy using 68Ga-PSMA PET/CT: TROD 09-004 Study. Clin Nucl Med 2021; 46: 465-470.

[87] Artigas C, Flamen P, Charlier F, Levillain H, Wimana Z, Diamand R, Albisinni S, Gil T, Velthoven RV, Peltier A, Gestel DV, Roumeguere T and Otte FX. (68)Ga-PSMA PET/CT-based metastasis-directed radiotherapy for oligometastatic prostate cancer recurrence after radical prostatectomy. World J Urol 2019; 37: 1535-1542.

[88] Werensteijn-Honingh AM, Wevers AFJ, Peters M, Kroon PS, Intven M, Eppinga WSC and Jürgenliemk-Schulz IM. Progression-free survival in patients with (68)Ga-PSMA-PET-directed SBRT for lymph node oligometastases. Acta Oncol 2021; 60: 1342-1351.

[89] Metz R, Rauscher A, Vaugier L, Supiot S, Drouet F, Campion L and Rousseau C. Comparison of hormone-sensitive oligorecurrent prostate cancer patients based on routine use of choline and/or PSMA PET/CT to guide metastasis-directed therapy. Cancers (Basel) 2023; 15: 1898.

[90] Shekar S, Crumbaker M, Joshua A, Yam A, Stricker P, Yuen C, Ende D, Namdarian B, Thompson J, Kooner R, O'Neill G, Mo J, Sim HW, Hruby G, Kasraei F, Ho A and De Leon J. Real-world clinical outcomes of oligometastatic prostate cancer using SBRT: an Australian experience. BJUI Compass 2025; 6: e70055.

[91] Grün A, Cumaoglu S, Kluge A, Schlomm T, Böhmer D, Miller K, Heidenreich H, Zips D and Kalinauskaite G. Early and repetitive novel-tracer PET-guided stereotactic body radiotherapy for nodal oligorecurrent prostate cancer after definitive first-line therapy. Strahlenther Onkol 2025; 201: 36-46.

[92] Hotta M, Gafita A, Czernin J and Calais J. Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with (177)Lu-PSMA therapy: a multicenter retrospective analysis. J Nucl Med 2022; 63: 1484-1488.

[93] Tang H, Wang H, Fang Y, Zhu JY, Yin J, Shen YX, Zeng ZC, Jiang DX, Hou YY, Du M, Lian CH, Zhao Q, Jiang HJ, Gong L, Li ZG, Liu J, Xie DY, Li WF, Chen C, Zheng B, Chen KN, Dai L, Liao YD, Li K, Li HC, Zhao NQ and Tan LJ. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy for locally advanced esophageal squamous cell carcinoma: a prospective multicenter randomized clinical trial. Ann Oncol 2023; 34: 163-172.

[94] Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, Gandaglia G, Gillessen S, Grivas N, Henry AM, Lardas M, van Leenders G, Liew M, Linares Espinos E, Oldenburg J, van Oort IM, Oprea-Lager DE, Ploussard G, Roberts MJ, Rouvière O, Schoots IG, Schouten N, Smith EJ, Stranne J, Wiegel T, Willemse PM and Tilki D. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer-2024 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2024; 86: 148-163.

[95] Tseng JR, Chang SH, Wu YY, Fan KH, Yu KJ, Yang LY, Hsiao IT, Liu FY and Pang ST. Impact of three-month androgen deprivation therapy on [68Ga]Ga-PSMA-11 PET/CT indices in men with advanced prostate cancer-results from a pilot prospective study. Cancers (Basel) 2022; 14: 1329.

[96] Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH, Beer TM, Armour A, Pérez-Contreras WJ, DeSilvio M, Kpamegan E, Gericke G, Messmann RA, Morris MJ and Krause BJ. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385: 1091-1103.

[97] Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, Pattison DA, Tan TH, Kirkwood ID, Ng S, Francis RJ, Gedye C, Rutherford NK, Weickhardt A, Scott AM, Lee ST, Kwan EM,

Azad AA, Ramdave S, Redfern AD, Macdonald W, Guminski A, Hsiao E, Chua W, Lin P, Zhang AY, McJannett MM, Stockler MR, Violet JA, Williams SG, Martin AJ and Davis ID. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 2021; 397: 797-804.

[98] Michalski K, Ruf J, Goetz C, Seitz AK, Buck AK, Lapa C and Hartrampf PE. Prognostic implications of dual tracer PET/CT: PSMA ligand and [(18)F]FDG PET/CT in patients undergoing [(177)Lu]PSMA radioligand therapy. Eur J Nucl Med Mol Imaging 2021; 48: 2024-2030.

[99] Hamy AS, Bonsang-Kitzis H, De Croze D, Laas E, Darrigues L, Topciu L, Menet E, Vincent-Salomon A, Lerebours F, Pierga JY, Brain E, Feron JG, Benchimol G, Lam GT, Laé M and Reyal F. Interaction between molecular subtypes and stromal immune infiltration before and after treatment in breast cancer patients treated with neoadjuvant chemotherapy. Clin Cancer Res 2019; 25: 6731-6741.

[100] Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG and Sandhu S. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018; 19: 825-833.

[101] Pan J, Wei Y, Zhang T, Liu C, Hu X, Zhao J, Gan H, Liu W, Zhu B, Wu J, Wang B, Song S, Ye D and Zhu Y. Stereotactic radiotherapy for lesions detected via (68)Ga-prostate-specific membrane antigen and (18)F-fluorodexyglucose positron emission tomography/computed tomography in patients with nonmetastatic prostate cancer with early prostate-specific antigen progression on androgen deprivation therapy: a prospective single-center study. Eur Urol Oncol 2022; 5: 420-427.

[102] Hirmas N, Leyh C, Sraieb M, Barbato F, Schaarschmidt BM, Umutlu L, Nader M, Wedemeyer H, Ferdinandus J, Rischpler C, Herrmann K, Costa PF, Lange CM, Weber M and Fendler WP. (68)Ga-PSMA-11 PET/CT improves tumor detection and impacts management in patients with hepatocellular carcinoma. J Nucl Med 2021; 62: 1235-1241.

[103] Gafita A, Djaileb L, Rauscher I, Fendler WP, Hadaschik B, Rowe SP, Herrmann K, Calais J, Rettig M, Eiber M, Weber M, Benz MR and Farolfi A. Response Evaluation Criteria in PSMA PET/CT (RECIP 1.0) in metastatic castration-resistant prostate cancer. Radiology 2023; 308: e222148.

[104] Michalski K, Klein C, Brueggemann T, Meyer PT, Jilg CA and Ruf J. Assessing Response to [(177)Lu]PSMA radioligand therapy using modified PSMA PET progression criteria. J Nucl Med 2021; 62: 1741-1746.

[105] Seifert R, Herrmann K, Kleesiek J, Schäfers M, Shah V, Xu Z, Chabin G, Grbic S, Spottiswoode B and Rahbar K. Semiautomatically quantified tumor volume using (68)Ga-PSMA-11 PET as a biomarker for survival in patients with advanced prostate cancer. J Nucl Med 2020; 61: 1786-1792.

[106] Armstrong AJ, Garrett-Mayer E, Ou Yang YC, Carducci MA, Tannock I, de Wit R and Eisenberger M. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. J Clin Oncol 2007; 25: 3965-3970.

[107] Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW and Armstrong AJ. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 2016; 34: 1402-1418.

[108] Esen T, Falay O, Tarim K, Armutlu A, Koseoglu E, Kilic M, Seymen H, Sarikaya AF, Kiremit MC, Balbay MD, Canda AE, Baydar DE, Kordan Y, Demirkol MO and Tilki D. (68)Ga-PSMA-11 positron emission tomography/computed tomography for primary lymph node staging before radical prostatectomy: central review of imaging and comparison with histopathology of extended lymphadenectomy. Eur Urol Focus 2021; 7: 288-293.

[109] Ma TM, Gafita A, Shabsovich D, Juarez J, Grogan TR, Thin P, Armstrong W, Sonni I, Nguyen K, Lok V, Reiter RE, Rettig MB, Steinberg ML, Kupelian PA, Yang DD, Muralidhar V, Chu C, Feng F, Savjani R, Deng J, Parikh NR, Nickols NG, Elashoff D, Czernin J, Calais J and Kishan AU. Identifying the best candidates for prostate-specific membrane antigen positron emission tomography/computed tomography as the primary staging approach among men with high-risk prostate cancer and negative conventional imaging. Eur Urol Oncol 2022; 5: 100-103.

[110] Shaygan B, Zukotynski K, Bénard F, Ménard C, Kuk J, Sistani G, Bauman G, Veit-Haibach P and Metser U. Canadian urological association best practice report: prostate-specific membrane antigen positron emission tomography/

computed tomography (PSMA PET/CT) and PET/magnetic resonance (MR) in prostate cancer. Can Urol Assoc J 2021; 15: 162-172.
[111] Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, Hauser S, Feldmann G, Essler M and Ahmadzadehfar H. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with 177Lu-PSMA-617. J Nucl Med 2017; 58: 312-319.
[112] Roll W, Bode A, Weckesser M, Bögemann M and Rahbar K. Excellent Response to 177Lu-PSMA-617 radioligand therapy in a patient with advanced metastatic castration resistant prostate cancer evaluated by 68Ga-PSMA PET/CT. Clin Nucl Med 2017; 42: 152-153.
[113] Will L, Sonni I, Kopka K, Kratochwil C, Giesel FL and Haberkorn U. Radiolabeled prostate-specific membrane antigen small-molecule inhibitors. Q J Nucl Med Mol Imaging 2017; 61: 168-180.
[114] Fendler WP, Reinhardt S, Ilhan H, Delker A, Böning G, Gildehaus FJ, Stief C, Bartenstein P, Gratzke C, Lehner S and Rominger A. Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. Oncotarget 2017; 8: 3581-3590.
[115] Fizazi K, Chi KN, Shore ND, Herrmann K, de Bono JS, Castellano D, Piulats JM, Fléchon A, Wei XX, Mahammedi H, Roubaud G, Fleming M, Haas T, Ghebremariam S, Kreisl TN, Rajagopalan S, Sartor O and Morris MJ. Final overall survival and safety analyses of the phase III PSMAfore trial of [(177)Lu]Lu-PSMA-617 versus change of androgen receptor pathway inhibitor in taxane-naive patients with metastatic castration-resistant prostate cancer. Ann Oncol 2025; 36: 1319-1330.
[116] Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C, Ferreira A, Lambros MBK, Seed G, Yuan W, Dolling D, Welti JC, Neeb A, Sumanasuriya S, Rescigno P, Bianchini D, Tunariu N, Carreira S, Sharp A, Oyen W and de Bono JS. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol 2019; 76: 469-478.
[117] Sgouros G, Roeske JC, McDevitt MR, Palm S, Allen BJ, Fisher DR, Brill AB, Song H, Howell RW, Akabani G, Bolch WE, Brill AB, Fisher DR, Howell RW, Meredith RF, Sgouros G, Wessels BW and Zanzonico PB. MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. J Nucl Med 2010; 51: 311-328.
[118] Plyku D, Hobbs RF, Wu D, Garcia C, Sgouros G and Van Nostrand D. I-124 PET/CT image-based dosimetry in patients with differentiated thyroid cancer treated with I-131: correlation of patient-specific lesional dosimetry to treatment response. Ann Nucl Med 2022; 36: 213-223.
[119] Massard V, Bailly C, Vija L, Giraudet A, Roubaud G, Girault S, Lacourtoisie SA, Viala C, Flechon A and Godbert Y. 2389P final analysis of patients treated with [177Lu]Lu-PSMA-617 in early access program in metastatic castration-resistant prostate cancer (mCRPC) in France. Annals of Oncology 2025; 36: S1299.
[120] Ayzman A, Pachynski RK and Reimers MA. PSMA-based therapies and novel therapies in advanced prostate cancer: the now and the future. Curr Treat Options Oncol 2025; 26: 375-384.
[121] Muniz M, Sartor O, Orme JJ, Koch RM, Scharf Z, Heath EI, Zarka JG, Kase AM, Riaz IB, Andrews JR, Thorpe MP, Tuba Kendi A, Bilgin GB, Johnson GB, Kwon ED and Childs DS. Outcomes for [(177)Lu]Lu-PSMA-617 with and without concurrent use of androgen receptor pathway inhibitors in patients with metastatic castration-resistant prostate cancer. Eur Urol Oncol 2025; 8: 1087-1093.
[122] Sathekge M, Bruchertseifer F, Knoesen O, Reyneke F, Lawal I, Lengana T, Davis C, Mahapane J, Corbett C, Vorster M and Morgenstern A. (225)Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study. Eur J Nucl Med Mol Imaging 2019; 46: 129-138.
[123] Kratochwil C, Bruchertseifer F, Rathke H, Hohenfellner M, Giesel FL, Haberkorn U and Morgenstern A. Targeted α-therapy of metastatic castration-resistant prostate cancer with (225)Ac-PSMA-617: swimmer-plot analysis suggests efficacy regarding duration of tumor control. J Nucl Med 2018; 59: 795-802.
[124] Sgouros G, Bodei L, McDevitt MR and Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov 2020; 19: 589-608.
[125] Pouget JP, Navarro-Teulon I, Bardiès M, Chouin N, Cartron G, Pèlegrin A and Azria D. Clinical radioimmunotherapy--the role of radiobiology. Nat Rev Clin Oncol 2011; 8: 720-734.
[126] Khreish F, Ebert N, Ries M, Maus S, Rosar F, Bohnenberger H, Stemler T, Saar M, Bartholomä M and Ezziddin S. (225)Ac-PSMA-617/(177)Lu-PSMA-617 tandem therapy of metastatic castration-resistant prostate cancer: pilot experience. Eur J Nucl Med Mol Imaging 2020; 47: 721-728.
[127] Elhaie M, Koozari A and Khademi MR. Prostate puzzle: Unconventional prostatic STUMP findings in a middle-aged patient prompt closer

examination. Radiol Case Rep 2025; 20: 882-885.
[128] Albisinni S, Artigas C, Aoun F, Biaou I, Grosman J, Gil T, Hawaux E, Limani K, Otte FX, Peltier A, Sideris S, Sirtaine N, Flamen P and van Velthoven R. Clinical impact of (68) Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. BJU Int 2017; 120: 197-203.
[129] Braga Ribeiro AM, Nascimento TMD and Lima ENP. Extrapleural solitary fibrous tumor evidenced by (68)Ga-prostate-specific membrane antigen positron emission tomography/computed tomography study in the staging of a high-risk prostate cancer patient. World J Nucl Med 2020; 19: 425-427.
[130] Karahan Şen NP, Aksu A, Bozkurt O, Tuna EB and Çapa Kaya G. Interreader agreement in evaluation of 68Ga-PSMA PET/CT at the time of initial staging: comparison of the three evaluation criteria in the pretreatment risk groups. Nucl Med Commun 2022; 43: 86-91.
[131] Kunst N, Long JB, Sprenkle PC, Kim IY, Saperstein L, Rabil M, Ghaffar U, Karnes RJ, Ma X, Gross CP, Wang SY and Leapman MS. Cost-effectiveness and evidence gaps surrounding PSMA-PET for recurrent prostate cancer evaluation. JAMA Netw Open 2025; 8: e2539250.
[132] Sheikhbahaei S, Afshar-Oromieh A, Eiber M, Solnes LB, Javadi MS, Ross AE, Pienta KJ, Allaf ME, Haberkorn U, Pomper MG, Gorin MA and Rowe SP. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. Eur J Nucl Med Mol Imaging 2017; 44: 2117-2136.
[133] Rauscher I, Düwel C, Haller B, Rischpler C, Heck MM, Gschwend JE, Schwaiger M, Maurer T and Eiber M. Efficacy, predictive factors, and prediction nomograms for (68)Ga-labeled prostate-specific membrane antigen-ligand positron-emission tomography/computed tomography in early biochemical recurrent prostate cancer after radical prostatectomy. Eur Urol 2018; 73: 656-661.
[134] Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S and Herrmann K. (68)Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 2017; 44: 1014-1024.
[135] Rischpler C, Maurer T, Schwaiger M and Eiber M. Intense PSMA-expression using (68)Ga-PSMA PET/CT in a paravertebral schwannoma mimicking prostate cancer metastasis. Eur J Nucl Med Mol Imaging 2016; 43: 193-194.
[136] Kroenke M, Mirzoyan L, Horn T, Peeken JC, Wurzer A, Wester HJ, Makowski M, Weber WA, Eiber M and Rauscher I. Matched-pair comparison of (68)Ga-PSMA-11 and (18)F-rhPSMA-7 PET/CT in patients with primary and biochemical recurrence of prostate cancer: frequency of non-tumor-related uptake and tumor positivity. J Nucl Med 2021; 62: 1082-1088.
[137] Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS and Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res 1999; 59: 3192-3198.
[138] Silver DA, Pellicer I, Fair WR, Heston WD and Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 1997; 3: 81-85.
[139] Nomura N, Pastorino S, Jiang P, Lambert G, Crawford JR, Gymnopoulos M, Piccioni D, Juarez T, Pingle SC, Makale M and Kesari S. Prostate specific membrane antigen (PSMA) expression in primary gliomas and breast cancer brain metastases. Cancer Cell Int 2014; 14: 26.
[140] Wernicke AG, Edgar MA, Lavi E, Liu H, Salerno P, Bander NH and Gutin PH. Prostate-specific membrane antigen as a potential novel vascular target for treatment of glioblastoma multiforme. Arch Pathol Lab Med 2011; 135: 1486-1489.
[141] Ceci F, Oprea-Lager DE, Emmett L, Adam JA, Bomanji J, Czernin J, Eiber M, Haberkorn U, Hofman MS, Hope TA, Kumar R, Rowe SP, Schwarzenboeck SM, Fanti S and Herrmann K. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 2021; 48: 1626-1638.
[142] Rafiei Alavi N, Rahmani M, Gupta A and Yaghmai V. PSMA-RADS to improve evaluation and management of prostate cancer. Abdom Radiol (NY) 2025; 50: 3272-3283.
[143] Miksch J, Yousefzadeh-Nowshahr E, Hardiansyah D, Glatting G, Solbach C, Bolenz C, Zengerling F, Wiegel T, Beer M, Prasad V, Wester HJ, Beer AJ and Thaiss W. First clinical application of silicon-based [^{18}F]siPSMA-14 in prostate cancer patients: a proof-of-concept study. Nuklearmedizin 2025; 64: 285-293.
[144] dos Santos Loureiro GG, Duarte Couto P, Gambini Gonzalez JP and Alonso Nuñez O. 18F-AlF-PSMA-HBED-CC as a novel tracer for the evaluation of prostate cancer patients with biochemical relapse: intraindividual compari-

son with 68Ga-PSMA-HBED-CC. World Journal of Urology 2025; 43: 597.
[145] Conti M. State of the art and challenges of time-of-flight PET. Phys Med 2009; 25: 1-11.
[146] Giesel FL, Knorr K, Spohn F, Will L, Maurer T, Flechsig P, Neels O, Schiller K, Amaral H, Weber WA, Haberkorn U, Schwaiger M, Kratochwil C, Choyke P, Kramer V, Kopka K and Eiber M. Detection efficacy of (18)F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med 2019; 60: 362-368.
[147] Dietlein F, Kobe C, Neubauer S, Schmidt M, Stockter S, Fischer T, Schomäcker K, Heidenreich A, Zlatopolskiy BD, Neumaier B, Drzezga A and Dietlein M. PSA-stratified performance of (18)F- and (68)Ga-PSMA PET in patients with biochemical recurrence of prostate cancer. J Nucl Med 2017; 58: 947-952.
[148] Wang X, Wang M, Chen Y, Jian R, Yu H, Zhang X, Zhang J, Yao S, Du J and Cui M. Preclinical evaluation and first-in-human study of (68)Ga- and Al(18)F-Labeled PSMA/FAP bispecific tracers for prostate cancer imaging. Eur J Nucl Med Mol Imaging 2026; 53: 2489-2501.
[149] Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A and Bal C. Post-therapeutic dosimetry of 177Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer. Nucl Med Commun 2017; 38: 91-98.
[150] Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K and Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-Labeled PSMA-617. J Nucl Med 2016; 57: 1170-1176.
[151] Ballal S, Yadav MP, Moon ES, Rösch F, ArunRaj ST, Agarwal S, Tripathi M, Sahoo RK and Bal C. First-in-human experience with 177Lu-DOTA-GA.(SA.FAPi)2 therapy in an uncommon case of aggressive medullary thyroid carcinoma clinically mimicking as anaplastic thyroid cancer. Clin Nucl Med 2022; 47: e444-e445.
[152] Ballal S, Yadav MP, Satapathy S, Raju S, Tripathi M, Damle NA, Sahoo RK and Bal C. Long-term survival outcomes of salvage [(225)Ac]Ac-PSMA-617 targeted alpha therapy in patients with PSMA-expressing end-stage metastatic castration-resistant prostate cancer: a real-world study. Eur J Nucl Med Mol Imaging 2023; 50: 3777-3789.
[153] Loktev A, Lindner T, Burger EM, Altmann A, Giesel F, Kratochwil C, Debus J, Marmé F, Jäger D, Mier W and Haberkorn U. Development of fibroblast activation protein-targeted radiotracers with improved tumor retention. J Nucl Med 2019; 60: 1421-1429.
[154] Lindner T, Loktev A, Giesel F, Kratochwil C, Altmann A and Haberkorn U. Targeting of activated fibroblasts for imaging and therapy. EJNMMI Radiopharm Chem 2019; 4: 16.
[155] Ravi Kumar AS, Lawrentschuk N and Hofman MS. Prostate-specific membrane antigen PET/computed tomography for staging prostate cancer. Curr Opin Urol 2020; 30: 628-634.
[156] Cysouw MCF, Jansen BHE, van de Brug T, Oprea-Lager DE, Pfaehler E, de Vries BM, van Moorselaar RJA, Hoekstra OS, Vis AN and Boellaard R. Machine learning-based analysis of [(18)F]DCFPyL PET radiomics for risk stratification in primary prostate cancer. Eur J Nucl Med Mol Imaging 2021; 48: 340-349.
[157] Satapathy S, Singh H, Kumar R and Mittal BR. Diagnostic accuracy of (68)Ga-PSMA PET/CT for initial detection in patients with suspected prostate cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 2021; 216: 599-607.
[158] Constantino CS, Oliveira FPM, Machado M, Vinga S and Costa DC. The use of maximum-intensity projections and deep learning adds value to the fully automatic segmentation of lesions avid for [(18)F]FDG and [(68)Ga]Ga-PSMA in PET/CT. J Nucl Med 2025; 66: 795-801.
[159] Trägårdh E, Ulén J, Enqvist O, Larsson M, Valind K, Minarik D and Edenbrandt L. A fully automated AI-based method for tumour detection and quantification on [(18)F]PSMA-1007 PET-CT images in prostate cancer. EJNMMI Phys 2025; 12: 78.
[160] Iravani A and Hicks RJ. Imaging the cancer immune environment and its response to pharmacologic intervention, part 2: the role of novel PET agents. J Nucl Med 2020; 61: 1553-1559.
[161] Chunyu H, Chen Y, Xue S, Zhang X, Miao Y, Guo R, Li B and Shi K. Clinical evaluation of deep learning-based CT-free PET reconstruction image: a dual-center study. Eur J Nucl Med Mol Imaging 2026; 53: 2592-2603.
[162] Tapper W, Carneiro G, Mikropoulos C, Thomas SA, Evans PM and Boussios S. The application of radiomics and ai to molecular imaging for prostate cancer. J Pers Med 2024; 14: 287.
[163] Liu M, Li L, Rais-Bahrami S, Hemal AK, Atala A and Zhang Y. Artificial intelligence in prostate cancer: navigating the new frontier of precision uro-oncology. Am J Clin Exp Urol 2025; 13: 348-359.
[164] Zang S, Meng Q, Li X, Guo T, Zhang L, Zhao Z, Yu F, Zhang P, Wu W, Ni Y, Shi Y, Shao G, Feng Y, Hu L, Jia R, Civelek AC, Guo H and Wang F. Fully automated volumetric assessment of tumor burden using artificial intelligence on (68)Ga-PSMA-11 PET predicts survival after (177)

Lu-PSMA therapy in metastatic Castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2026; 53: 1913-1926.
[165] Yazdani E, Geramifar P, Karamzade-Ziarati N, Sadeghi M, Amini P and Rahmim A. Radiomics and artificial intelligence in radiotheranostics: a review of applications for radioligands targeting somatostatin receptors and prostate-specific membrane antigens. Diagnostics (Basel) 2024; 14: 181.
[166] Sadaghiani MS, Baskaran S, Gorin MA, Rowe SP, Provost JC, Teslenko I, Bilyk R, An H and Sheikhbahaei S. Utility of PSMA PET/CT in staging and restaging of renal cell carcinoma: a systematic review and metaanalysis. J Nucl Med 2024; 65: 1007-1012.
[167] Rowe SP, Gorin MA and Pomper MG. Imaging of prostate-specific membrane antigen with small-molecule PET radiotracers: from the bench to advanced clinical applications. Annu Rev Med 2019; 70: 461-477.
[168] Treglia G, Annunziata S, Pizzuto DA, Giovanella L, Prior JO and Ceriani L. Detection rate of (18) F-labeled PSMA PET/CT in biochemical recurrent prostate cancer: a systematic review and a meta-analysis. Cancers (Basel) 2019; 11: 710.
[169] Werner RA, Bundschuh RA, Bundschuh L, Javadi MS, Leal JP, Higuchi T, Pienta KJ, Buck AK, Pomper MG, Gorin MA, Lapa C and Rowe SP. Interobserver agreement for the standardized reporting system PSMA-RADS 1.0 on (18) F-DCFPyL PET/CT imaging. J Nucl Med 2018; 59: 1857-1864.
[170] Tariq A, Pearce A, Rhee H, Kyle S, Raveenthiran S, Pelecanos A, Gan CL, Goh JC, Wong D, McBean R, Marsh P, Goodman S, Dunglison N, Esler R, Navaratnam A, Yaxley JW, Thomas P, Pattison DA and Roberts MJ. The role of prostate-specific membrane antigen positron emission tomography/computed tomography in primary staging of selected renal tumours: initial experience in a multicentre cohort. Eur Urol Focus 2024; 10: 770-778.
[171] Cohen D, Hazut Krauthammer S, Fahoum I, Kesler M and Even-Sapir E. PET radiotracers for whole-body in vivo molecular imaging of prostatic neuroendocrine malignancies. Eur Radiol 2023; 33: 6502-6512.
[172] Pomykala KL, Fendler WP, Vermesh O, Umutlu L, Herrmann K and Seifert R. Molecular imaging of lymphoma: future directions and perspectives. Semin Nucl Med 2023; 53: 449-456.