

Prostate-Specific Membrane Antigen (PSMA) PET-CT: Revolutionizing Staging, Restaging, and Treatment Response Assessment

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Cite this article: Smith T, Harper M: Prostate-Specific Membrane Antigen (PSMA) PET-CT: Revolutionizing Staging, Restaging, and Treatment Response Assessment. *Ann Urol Oncol* 2025, 8(4): 200-210. <https://doi.org/10.32948/auo.2025.12.15>

Abstract

Prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET-CT), has become the benchmark imaging tool in the management of prostate cancer, due to its unparalleled precision in staging, restaging and assessing of treatment response. Traditional imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy, suffer from subpar sensitivity, particularly in detection of small volume nodal disease and early metastatic spread. Conversely, PSMA PET-CT takes advantage of the upregulation of PSMA on prostate cancer cells to offer highly specific and sensitive molecular imaging. This review provides the contemporary overview of available literature from high-impact clinical trials, systematic reviews and meta-analyses that have described the utility of PSMA PET-CT across all stages of the prostate cancer journey. We emphasize its superior results concerning staging in the high- and intermediate-risk patients, where a better value for nodal or distant metastasis translates into individualized treatment. The review also highlights the growing importance of PSMA PET-CT imaging in biochemical recurrence, which allows early detection of recurrent disease at low prostate-specific antigen levels and individualized treatment decision making including salvage and metastasis-directed therapies. Novel applications of PSMA PET-CT in response assessment are discussed, including functional imaging biomarkers, quantitative metrics and evolving response criteria. The milestones of development and introduction of new PET tracers to support PET for PCa are also presented in the light of radiotracers, theranostics, AI and hybrid imaging. In general, PSMA PET-CT is a leap forward in prostate cancer imaging from diagnosis to treatment based on precision medicine. Continued standardization approaches and prospective evaluation will clarify its best application in a clinical context and future oncology care pathways.

Key words prostate-specific membrane antigen, PSMA PET-CT, prostate cancer imaging, biochemical recurrence, treatment response assessment

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Introduction

Prostate cancer (PCa) is still the most commonly diagnosed malignancy and the second leading cause of death from cancer in men around the world [1, 2]. In spite of progress in screening, diagnosis and treatment, clinical management of prostate cancer still faces disease heterogeneity, variability of biological behaviour and the inability to precisely characterise disease extent [3]. Accurate tumor staging at diagnosis, alternative detection of recurrence or progression and objective evaluation of therapy sensitivity are essential for therapeutic decision making. Thus, imaging is a central figure along the entire spectrum of disease, from early risk stratification to long-term follow-up [4, 5].

Other imaging techniques such as CT scan, MRI and technetium-99m bone have been commonly employed for PCa staging and restaging. However, these methods rely on morphological or surrogate functional alterations and are not sensitive for small-volume disease including lymph nodal metastases and early bone invasion [6, 7]. Lymph node staging by CT and MRI is largely based on size, which does not detect micrometastatic disease in otherwise normal-sized lymph nodes. Bone scintigraphy is also nonspecific and may not identify early bony metastases. These constraints often lead to undertreatment or delayed recognition of disease progression, both of which influence treatment planning and outcome [8].

Molecular imaging has revolutionized prostate cancer diagnosis. Of these developments, prostate-specific membrane antigen (PSMA)-targeted radiotracers for positron emission tomography (PET) has been a game changer [9]. PSMA is a type II transmembrane glycoprotein that is greatly upregulated on PCa cells, particularly in high-grade, metastatic, or castration-resistant disease but with low expression levels in most normal tissues [10]. This peculiar expression pattern promoted PSMA as a perfect target for both diagnostic imaging and therapy, heralding the advent of theranostics in prostate cancer treatment [11].

PSMA PET-CT is a new generation of nuclear and molecular imaging that significantly enhances sensitivity using CT to provide high spatial resolution for the detection of PSMA activity including anatomic changes in prostate cancers [12]. Radiotracers including ^{68}Ga -PSMA-11 and ^{18}F -labeled PSMA compounds (e.g., ^{18}F -DCFPyL and ^{34}F -PSMA-1007) have shown outstanding reliability for detection of primary tumors, nodal disease, and distant metastasis down to very low prostate-specific antigen (PSA) levels beyond the sensitivity range of standard imaging [13, 14]. This has led to the acceptance of PSMA PET-CT as a new standard in prostate cancer staging and restaging.

For initial staging, PSMA PET-CT has demonstrated high usefulness in patients with intermediate/high-risk PCa in whom evaluation of lymph node/distant metastasis is necessary for defining appropriate local/systemic treatment [15]. Several prospective trials and meta-analyses have demonstrated that PSMA PET-CT is superior to conventional imaging with respect to sensitivity and specificity for nodal and metastatic disease [16]. Significantly, this enhanced diagnostic accuracy has been demonstrated to have a direct impact on clinical management with changes in surgical planning, radiation therapy treatment volumes and systemic treatment plans [17].

In the context of metastatic prostate cancer (mPCa), the value of PSMA PET-CT is even more evident, especially in the setting of biochemical recurrence (BCR), that is, an increase in prostate-specific antigen (PSA) after definitive local treatment such as radical prostatectomy or radiotherapy [18]. Identification of the site of PSA relapse at low PSA levels is essential for early salvage treatments with the possibility to cure [19]. PSMA PET-CT has shown high detection rates with PSA below 0.5 ng/mL for early

locoregional recurrences or oligometastatic disease [20]. This capability has revolutionized the strategy of restaging, which can now be aimed at a personalized, targeted therapeutic approach.

In addition to staging and restaging, PSMA PET-CT is receiving increasing attention as a method of treatment response evaluation. Conventional anatomical change based response evaluation criteria frequently do not correlate well with biological response, for example in bone metastases or after new systemic treatments [21, 22]. PSMA PET-CT delivers functional data on tumor survival and PSMA expression, which is more sensitive for monitoring therapeutic response [23]. Novel methodologies for response assessment and also quantitative PET metrics are being developed in order to standardize the interpretation of the results and increase reproducibility both in clinical trials and routine workup [24]. The growing clinical utility of PSMA PET-CT is closely associated with improvements in the development of radiotracers and image analysis [12]. ^{18}F -labeled PSMA tracers have become available within the last years, and due to their longer half-life and excellent imaging profile they enabled broader clinical implementation as well as superior image quality. Moreover, the combination of artificial intelligence, radiomics and machine learning are providing novel strategies to extract quantitative biomarkers from PSMA PET images with potential benefits for better risk-stratification and prognostication [15, 25].

Nevertheless, several issues persist despite its fast translation into the clinic. Discrepancies in imaging protocols, choice of tracer, interpretation criteria and availability of PET-CT facilities may influence uniform findings and broad utilisation [26]. Furthermore, the position of PSMA PET-CT in certain clinical settings or situations like low-risk disease, routine follow-up and long-term follow-up is still in flux. Current research and international consensus work are focusing on these aspects, to try to define standardized recommendations of best use [27].

In this article, we present a detailed overview of evidence underpinning the application of PSMA PET-CT in prostate cancer with an emphasis on studies related to its use in primary staging, restaging post-biochemical relapse and evaluation treatment response. We review critical trials, news emergent approaches, and the horizon ahead to illuminate how PSMA PET-CT is transforming anatomic imaging of prostate cancer and pushing the envelope on precision oncology.

PSMA PET-CT in initial staging

Diagnostic accuracy of PSMA PET-CT in initial staging

Precise initial stage is one of the mainstays for prostate cancer therapy, since it is critical to risk stratification, management determination and prognosis [28]. Standard imaging techniques of CT, MRI and bone scan have historically been used for staging; however, their accuracy is not ideal, especially in the identification of small volume nodal disease and early metastatic disease spread. These limitations have led to the development of, and clinical uptake in, molecular imaging modalities including PSMA PET-CT which has shown unparalleled diagnostic sensitivity [29, 30].

PSMA PET-CT takes advantage of the high level of expression of prostate-specific membrane antigen in prostate cancer cells, resulting in excellent specific radiotracer binding and imaging of disease foci [31]. Several prospective studies, systematic reviews and meta-analyses have consistently demonstrated the superiority of PSMA PET-CT over conventional imaging in the detection of pelvic lymph node metastases as well as extrapelvic nodal disease, bone metastases and visceral disease (Table 1) [32]. Crucially, PSMA PET-CT can detect morphologically occult (normal sized) metastases undetectable by CT or MRI addressing the size-based inadequacies of standard nodal assessment [33].

Table 1. Diagnostic performance of PSMA PET-CT in initial staging.

Parameter	PSMA PET-CT	Conventional imaging (CT/MRI/Bone Scan)	Key points
Pelvic lymph node detection	High sensitivity (moderate to high depending on tumor burden)	Limited by size criteria; misses micrometastases	Detects morphologically normal metastatic nodes
Specificity for lymph nodes	>90%	Lower	Reduces false positives
Bone metastases detection	Superior, even for low-volume lesions	Lower, may miss early metastases	Avoids false positives from degenerative/inflammatory changes
Visceral metastases	Accurate localization	Often missed	Important for staging and treatment planning
Radio tracers	⁶⁸ Ga-PSMA-11, ¹⁸ F-DCFPyL, ¹⁸ F-PSMA-1007	N/A	¹⁸ F-tracers have longer half-life, better resolution
Patient subgroup impact	Intermediate- to high-risk prostate cancer	Less effective	Improved TNM staging and management decisions
Limitations	Rare PSMA-negative tumors, benign uptake	Size-dependent detection	Requires expert interpretation

Note: PSMA: Prostate-specific membrane antigen, PET-CT: Positron emission tomography-computer tomography, MRI: Magnetic resonance imaging, TNM: Tumor node metastasis classification, N/A: Not applicable.

The available meta-analytical data showed that PSMA PET-CT has high specificity (often >90%) for lymph node involvement and moderate to high sensitivity according to tumour load and disease risk category [34]. Although sensitivity is likely compromised for micrometastatic nodal disease smaller than the spatial resolution of PET imaging, PSMA PET-CT has a markedly higher performance compared to anatomic imaging with CT and MRI alone [35]. For bone involvement, PSMA PET-CT has demonstrated higher accuracy when compared with bone scintigraphy for early or low-volume lesions and decreased false-positive readings of degenerative or inflammatory changes [36].

The diagnostic accuracy of PSMA PET-CT imaging has been demonstrated with various radiotracers, such as ⁶⁸Ga-PSMA-11 and ¹⁸F-labeled tracers including ¹⁸F-DCFPyL and ¹⁸F-PSMA-1007 [13]. Although all are highly sensitive, ¹⁸F-labelled tracers provide a longer half-life in addition to an improved spatial resolution and lower urinary excretion (where applicable) that may be helpful for better visualization of pelvic-based lesions. Comparative analyses indicate an overall uniform accuracy of tracers, while tracer choice may impact detection patterns in certain areas as revealed by the factor scores [14].

Notably, the performance of PSMA PET-CT is even more striking among men with intermediate and high risk PCa in whom the prevalence of metastatic disease is greater [37]. In these subgroups, the PSMA PET-CT assists in a more accurate delineation of disease extension prospecting nap for accurate Tumor-LNode-Metastasis (TNM) staging [38]. Prostatic cancer Prospective trials, such as the key randomized studies, have shown that PSMA PET-CT conspicuously raises staging accuracy versus conventional imaging with higher diagnostic confidence and fewer equivocal findings [27].

There are some limitations of the high accuracy. PSMA can be heterogeneously expressed and rare prostate cancer subtypes may have low expression of PSMA, thus leading to false-negative findings [39]. Furthermore, nontumoral tissues and benign processes like ganglia, fractures or inflammatory lesions can show physiological or not otherwise specified PSMA uptake, requiring

expert reading [40]. Nonetheless, when used in the right clinical setting, PSMA PET-CT is the most accurate imaging technique for primary staging of prostate cancer to date [12].

Clinical implications

Beyond accuracy, the clinical relevance of PSMA PET-CT manifests in impact on patient management. Greater staging precision also increases the level of information available to guide treatment, and permits customization of therapy in response to actual disease burden. Various series have shown that PSMA PET-CT impacts upon clinical management to a large extent if used as initial staging, especially in intermediate-high-risk prostate cancer [27, 41].

By far the most important clinical consequence of a positive PSMA PET-CT, is its effect on planning local therapy [42]. Precise determination of pelvic lymph node involvement can impact on a decision to carry out or not an extended pelvic lymphadenectomy as part of radical prostatectomy and to adapt the radiotherapy fields according to involved nodal regions [43]. On the other hand, avoidance of overtreatment by ruling out metastatic disease may lead to less unnecessary aggressive surgical or radiation therapy and subsequent morbidity [44].

PSMA PET-CT is also crucial for detecting occult distant metastases, which can alter management from curative local therapy to systemic strategies [20]. The recognition of oligometastatic disease (ie, few metastases) has led to change in therapeutic approach and the introduction of treatment strategies such as metastasis-directed therapy by means of stereotactic body radiotherapy or focal surgical resection [45]. In selected patients, PSMA PET-CT may lead to a tailored and possibly aggressive treatment approach through precise identification of sites of metastatic disease [27].

Prospective trial findings suggest that PSMA PET-CT-directed staging leads to management changes in a significant proportion of men, frequently > 20–30% when contrasted against conventional imaging [46]. These modifications may involve changes in

the surgical technique, radiation planning, commencement of systemic therapy, or participation in clinical trials. Critically, PSMA PET-CT steers clear of uncertainty and further imaging which is widespread in the staging process - it narrows down a diagnosis and kicks treatment options into gear [27].

From a multidisciplinary point of view, PSMA PET-CT can contribute to optimal communication and equipoise among urologists, radiation oncologists, medical oncologists and nuclear medicine physicians [47]. The comprehensive genomic and fusion-guided anatomical information enabled by PSMA PET-CT underpins consensus-driven decision-making, especially in difficult situations where traditional imaging is inconclusive [48].

There is also a growing body of evidence to support the prognostic utility of PSMA PET-CT staging [49]. Burden and Distribution of PSMA-Avid Disease Have a Strong Impact on Oncologic Outcomes, Such as PFS and BCR [50]. Quantitative PET parameters and whole-body tumor burden measures from PSMA PET-CT are currently evaluated as potential candidates for risk stratification, which suggests that the clinical assessment using PSMA-PET CT may go beyond the mere detection of lesions [51].

However, the implementation of PSMA PET-CT in the routine clinical care needs to be balanced against its costs and availability in addition to need for specialized skills [52]. Although a cost-effectiveness analysis universally favours PSMA PET-CT once inappropriately selected patients because of associated management change, access to PSMA remains heterogeneous between health provider organisations. Moreover, standardized reporting and interpretation system are needed to guarantee a uniform performance of a technique [53].

PSMA PET-CT in restaging and detection of recurrence

PSMA PET-CT in biochemical recurrence

Introduction Biochemical recurrence (BCR) is a major clinical problem in the management of prostate cancer and occurs in many patients after definitive local therapy, such as radical prostatectomy

and radiotherapy [54]. BCR is usually characterized by an increase in the prostate-specific antigen (PSA) level, whereas no clinical or radiographic signs of disease have been detected [18]. Recurrence disease clearly needs to be identified early, and precisely as possible because there may still be a potential curative effect or postponement of treatment among salvage treatments [54]. However, traditional imaging is less sensitive in this population especially at low PSA levels and may result in deferred or empiric treatments [55].

PSMA PET-CT is the most sensitive imaging modality for detection of recurrence of prostate cancer and has revolutionised the diagnostic paradigm in BCR. Due to the fact that PC expresses the PSMA in excessive amounts, a special opportunity is open: with the help of PSMA PET-CT one can see the disease in a PSA far below those values at which CT, MRI or bone scintigraphy are sensitive enough [12, 56]. A number of reports have shown high detection rates even among patients with a PSA 80% for PSA >2.0 ng/mL [57]. This early sensitivity results in localization of recurrence, frequently predate the appearance of symptoms or later extensive disease and permits more accurate and earlier treatment intervention [58].

Anatomical patterns of recurrence PSMA PET-CT has a greater potential for detecting local recurrence in the prostatic bed, pelvic lymph node metastases, extraprostatic nodal disease and bone or visceral metastases [59]. Importantly, some of these lesions are small and could be overlooked according to size criteria for imaging. The success of PSMA PET-CT at identifying oligometastatic disease has revolutionized clinical thinking regarding recurrence and the popular contention that a proportion of patients may benefit from targeted, metastasis-directed therapy rather than early systemic therapy [45].

The efficacy of PSMA PET-CT in BCR has been demonstrated using a variety of radiotracers, including ⁶⁸Ga-PSMA-11 and ¹⁸F-based agents [60]. ¹⁸F-labelled tracers have advantages regarding image resolution and even better biodistribution, with potential enhanced detection of lesions in selected regions [61]. Although variations in detection rates were observed, diagnostic

Table 2. Impact of PSMA PET-CT on management in biochemical recurrence (BCR).

Clinical scenario	Role of PSMA PET-CT	Effect on management	Evidence / Notes
Salvage radiotherapy	Identifies local recurrence & pelvic nodes	Adjusts target volumes, escalates doses, avoids unnecessary irradiation	Improves biochemical control
Oligometastatic recurrence	Detects limited metastatic lesions	Guides metastasis-directed therapy (MDT) like stereotactic radiotherapy or surgery	Delays systemic therapy, preserves QoL
Extensive/distant metastases	Identifies systemic spread	Initiates appropriate systemic therapy (ADT, AR inhibitors, chemotherapy)	Avoids futile local salvage treatments
Overall management change	N/A	30–60% of patients with BCR	Includes surgery, radiation, systemic therapy, trial eligibility
Prognostic utility	PSMA-avid lesion burden & distribution	Risk stratification for progression-free survival and CRPC	Quantitative PET parameters under study
Limitations	Low PSMA expression, neuroendocrine differentiation, false positives	Requires careful interpretation with clinical context	Standardization ongoing

Note: PSMA: Prostate-specific membrane antigen, PET-CT: Positron emission tomography-computer tomography, BCR: Biochemical recurrence, MDT: Multi-disciplinary treatment, ADT: Androgen-deprivation therapy, CRPC: Castration-resistant prostate cancer, QoL: Quality of life, N/A: Not applicable.

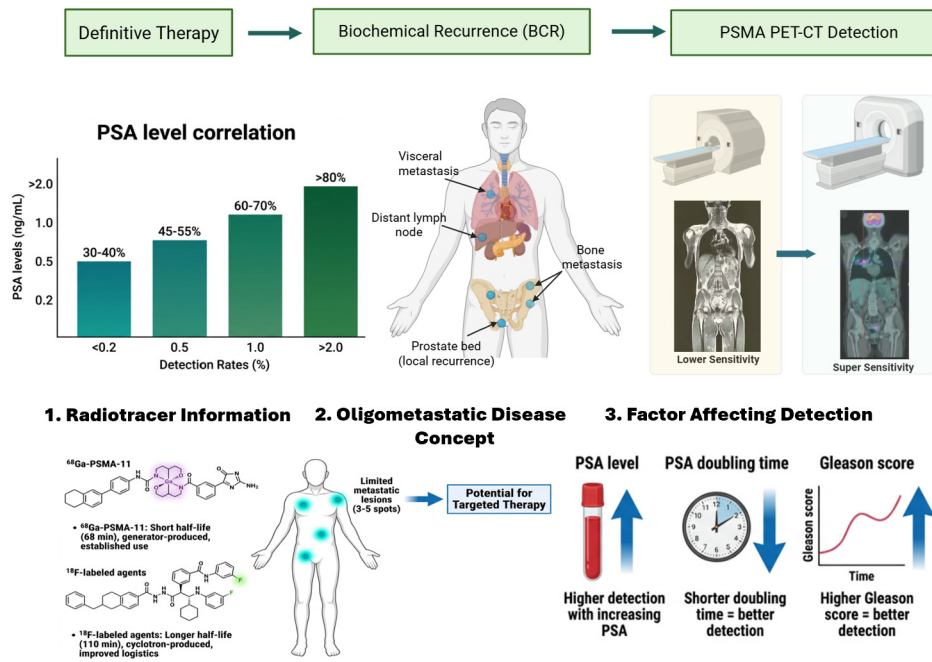


Figure 1. PSMA PET-CT in guiding prostate cancer recurrence management. Flow diagram for the use of PSMA PET-CT in the assessment of biochemical recurrence following definitive treatment for prostate cancer. The model demonstrates how PSA drives imaging choice, with PSMA PET-CT having greater sensitivity than traditional imaging for local and metastatic recurrence. The detection rate increases with increasing PSA-value, shorter PSA doubling time, and higher Gleason score. Identification of oligometastatic disease (3-5 lesions) allows for personalized treatment modalities.

performance is well maintained for all tracers tested and highlights the strength of PSMA-targeted imaging (e.g. imaging) at time of recurrence [62].

PSMA PET-CT has its inherent limitations notwithstanding its impressive features. False-negative can be seen in low expression of PSMA or neuroendocrine differentiation, while false-positive sites are reactive lymph nodes, fractures or inflammatory alterations independent of a treatment response [40, 63]. However, when correlated with clinical and biochemical parameters, PSMA PET-CT is unequalled in terms of diagnostic confidence in the BCR context (Figure 1) [64].

Impact of PSMA PET-CT on clinical management in biochemical recurrence

More so than its diagnostic advantage, the greatest advantage of PSMA PET-CT in biochemical recurrence is that it guides patient’s clinical management directly. By accurately identifying the site of disease recurrence, PSMA PET-CT permits personalized salvage treatment regimen based on patterns and burden of recurrence rather than utilizing a blanket approach based only on PSA kinetics [65]. As summarized in Table 2, this imaging directly affects clinical decision-making across several key scenarios.

Management issues One of the major implications regarding management would be to salvage radiotherapy. The correct diagnosis of local recurrence and pelvic nodal involvement enables radiation oncologists to adjust the target volumes, to intensify doses to PSMA-avid lesions as well as to minimize unnecessary irradiation of non-involved areas [66]. It has been demonstrated

that PSMA PET-CT findings have resulted in changes of salvage radiotherapy plans in a significant number of patients with a resultant improvement in biochemical control on follow-up [67].

PSMA PET-CT has also paved the way for metastasis-directed therapy (MDT) of oligometastatic recurrence [68]. When few metastatic lesions are found by PSMA PET-CT, stereotactic body radiotherapy or surgical metastasectomy can be applied. Initial clinical data indicates that PSMA PET-CT directed MDT has the potential to sustain use of androgen deprivation therapy, maintain QoL and affect cancer related outcomes in the appropriate patient population [47].

If PSMA PET-CT demonstrates widespread or distant metastatic disease, treatment options are typically focused on systemic therapy, such as androgen deprivation therapy, androgen receptor pathway inhibitors, or chemotherapy [69]. In this regard, PSMA PET-CT can spare inappropriate local salvage therapies and facilitate prompt commencement of suitable systemic treatment. Critically, this stratified strategy reduces over-treatment while ensuring that treatment intensity is congruent with the disease burden [70].

Numerous studies have demonstrated that PSMA PET-CT affects management in 30–60% of patients with BCR. These include modifications in radiation fields, surgical planning, institution or deferral of systemic therapy, and candidacy for clinical trials [64]. This level of impact to management illustrates the clinical significance of PSMA PET-CT, beyond the diagnostic performance.

In terms of prognostication, imaging with PSMA PET-CT has been correlated clinically with survival outcomes such as progression-free and time to develop castrate-resistant disease.

The volume and pattern of PSMA-avid lesions and the quantitative PET parameters are under evaluation as potential biomarkers, which can be used to inform risk-adapted treatment approaches [71].

A risk of integration with PSMA PET-CT is its disruptive impact, and there are ongoing efforts to deconvolute evolving BCR management algorithms [65]. Heterogeneity in imaging protocols, reporting, and treatment thresholds may act as confounders of clinical decision making. There are current international efforts to create consensus guidelines and reporting standards for uniform interpretation and application between institutions [72].

Treatment response assessment

Current status of PSMA PET-CT in treatment response assessment

Monitoring treatment response is essential to prostate cancer care, which helps clinical decision-making and provides a predictor of prognosis [73]. Historically, serum prostate-specific antigen (PSA) levels, anatomic imaging and clinical symptoms have been used as measures of response. Yet these measures have significant shortcomings [74]. PSA kinetics may not accurately represent tumor load in all situations, particularly during novel systemic agents and conventional imaging has difficulty distinguishing viable tumour from treatment-induced changes, especially in bone metastases [75]. In this setting PSMA PET-CT has become appealing, being a functional imaging modality potentially able to offer relevant biological information about therapy response.

PSMA PET-CT provides the doctrine of the visualization of vital tumor, which is defined by PSMA expression but not size or morphology based assessment. This attribute is of particular relevance in mCRPC, where lesions may appear stabilization in size despite biological progression or response [76]. The early clinical trials have shown that, in many cases, the variation of PSMA uptake on PET-CT is known to precede anatomical changes which can be used as an indicator of early therapeutic response (or failure) using PSMA PET-CT [77].

The use of PSMA PET-CT has been investigated with regard to different treatment options, including androgen deprivation therapy (ADT), ARPI, chemotherapy, radiotherapy and PSMA anticancer radioligand [78]. In patients on systemic hormonal therapy, PSMA uptake may decrease in responding lesions, whereas stable or increased uptake can signify resistant disease. Transient increases in PSMA expression, the so-called “flare phenomenon,” which regularly occur early after ADT initiation have also been described and should be considered when interpreting serial imaging results [77, 79].

In the radiotherapy context, PSMA PET-CT has been shown to have value in differentiating residual or recurrent disease from post-treatment fibrosis or inflammation. This isn't always possible to be seen with standard imaging and makes a big difference in how we plan next steps [80]. In addition, in patients receiving chemotherapy, changes on PSMA PET parameters have been associated with clinical response indicating a potential role in early treatment monitoring [81].

PSMA PET-CT has also become increasingly important in the era of PSMA-targeted radioligand therapy, where imaging is used diagnostically and predictively [82]. Base-line PSMA PET-CT ensures the expression of target before therapy; follow-up imaging can reflect the efficacy and heterogeneity of disease. Response patterns on PSMA PET-CT has been related with survival, emphasizing its importance as a prognostic marker [83].

However, despite these encouraging results, the number of studies of PSMA PET-CT for treatment response assessment is relatively limited, and it has not yet become a widespread clinical application [84]. One issue is the absence of an accepted response

criteria. Classical approaches such as RECIST are not readily applicable to molecular imaging, and in particular for bone-dominant disease. Therefore, the interpretation of PSMA PET-CT response is currently varied by qualitative assessment or institution specific quantitative cut-off values [85].

Emerging criteria, quantitative metrics, and future directions

Acknowledging the lack of standardized response evaluation, several attempts for PSMA PET-specific response criteria are emerging[21]. These frameworks seek to address variations in PSMA uptake, lesion number and whole-body tumour load to standardize more reliable treatment response assessment [21]. In this context, progression rules and emerging criteria (eg RECIP [Response Evaluation Criteria in PSMA Imaging for Prostate Cancer]) are important steps toward standardization [86].

Quantitative PSMA PET-CT parameters, such as SUV, PSMA tumor volume and total lesion PSMA expression are increasingly being studied as potential surrogates for response. Such parameters may instigate development beyond binary categorization (response-vs-progression) and might support a more differential evaluation of treatment effects [70]. The latter (ie, changes in PSMA uptake above the threshold of normal tissue) has been demonstrated to be associated with improved progression-free and overall survival, indicating its prognostic significance [87].

Imaging analysis techniques (radiomics and artificial intelligence) continue to broaden the scope of how PSMA PET-CT can be used in response assessment. Radiomic-features derived from PSMA PET images could have the potential to represent intratumoral heterogeneity and treatment-related alterations below the level of detection by visual assessment [88, 89]. Machine-learning algorithms that incorporate PSMA PET imaging with clinical and genomic data are being constructed to predict response to treatment and personalize therapy choice [90].

An additional possible utility of PSMA PET-CT is adaptive treatment planning. By localizing sites of residual PSMA-avid disease during or after treatment, oncologists could adapt intensity of therapy details such as dose escalation to refractory locations or more expeditious changes in systemic therapy at an earlier stage[65]. This personalized adaptive mechanism is consistent with the principles of precision cancer therapy and may offer benefit in terms of response without undue toxicity [91].

However, many hurdles must still be overcome before PSMA PET-CT is integrated in regular treatment response evaluations [21]. It remains critical to standardize acquisition protocols, moment for follow-up scans and reporting criteria to obtain consistency among institutions and clinical trials [92]. Furthermore, the biological variance of PSMA expression, especially under treatment selection pressure, needs to be taken into account to prevent misinterpretation of imaging results [93].

The prospective trials underway are poised to critically validate the PSMA PET-based response criteria and define their role in predicting with PSA response versus survival end points [77]. As the data definition evolves, PSMA PET-CT will likely be included in response assessment algorithms for advanced and heavily pre-treated patients with prostate cancer (Figure 2) [94].

Radio tracer advances and emerging techniques

The success of PSMA PET-CT in (prostate cancer) is partly due to the rapid technological developments within each imaging modality and regarding radiopharmaceuticals [95]. Early clinical application was primarily based on ⁶⁸Ga-labeled PSMA ligands, which presented high affinity toward PSMA and good diagnostic performance in PET imaging of prostate cancer [96]. The clinical studies of these tracers were crucial in the

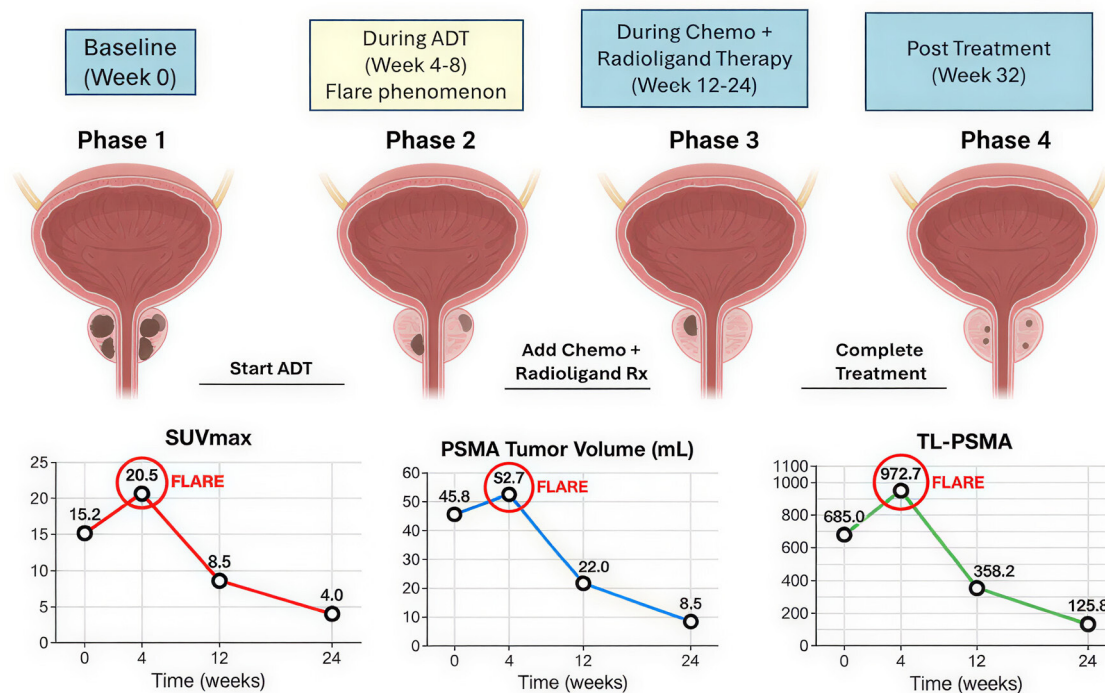


Figure 2. PET-CT in treatment response assessment. Sequential PSMA PET-CT scans and quantitative parameters at baseline, during, and after various treatments in a patient with PCa treated with ADT, chemotherapy, and/or radioligand therapy. The heat maps show PSMA uptake (red-yellow, high; blue, low). SUVmax, PSMA tumor volume and TL-PSMA reflect the change of tumour burden. A temporary “flare phenomenon” is detected after initiation of ADT, and then lesion response. Persistent uptake indicates resistant lesions.

development of PSMA PET-CT as a clearly superior modality than standard imaging modalities for both staging and restaging. Yet short half-life, limited amounts of radioactivity available for production and high urinary excretion have initiated the search for alternative tracers and technological improvements permitting improved clinical use [23]. ^{18}F -labeled PSMA tracers are the largest breakthrough in this context. Because of a longer half-life and higher positron yield, agents for PET based on ^{18}F can be produced centrally, sold over a larger area and show better resolution [15]. Tracers with diagnostic performance that is comparable to, and in some settings better than, ^{68}Ga -PSMA-11 have been shown for ^{18}F -DCFPyL and ^{18}F -PSMA-1007. These agents have enabled wider dissemination of clinical PSMA PET-CT and increased consistency between the imaging centers [97]. Noteworthy is the low urinary excretion of ^{18}F -PSMA-1007 allowing for better delineation of both the prostate bed and pelvic structures; however, its uptake in benign bone lesions underscores the necessity for cautious image interpretation [98].

The development of radiolabelled tracers has in addition contributed to the implementation of PSMA PET-CT into theranostic concepts and thereby established an interconnection between diagnostic imaging and targeted radionuclide treatment [11]. PSMA PET-CT is central for selecting patients who are eligible to undergo PSMA-targeted radioligand therapy as it verifies adequate target expression and imaging of disease site [82]. Radio-ligand therapies with beta-emitting isotopes (e.g., ^{177}Lu -PSMA) have shown strong systemic treatment benefits in metastatic castration-resistant prostate cancer, and PSMA PET-CT plays a key role in patient selection, therapy monitoring, and dosimetry [99]. The advent of alpha-emitting monoclonal PSMA targeted agents have further broadened therapeutic options,

especially in CRPC; however, dosing, and safety is still evolving as a field [100].

PSMA PET-CT has also been improved with the development of technological innovations in PET imaging systems. Facility of digital PET detectors, better time-of-flight technology and new reconstruction algorithms has led to superior spatial resolution, improved lesion detection and lower acquisition duration [101]. These enhancements have improved the ability to detect micrometastases, and could pave the way for a reduction in radiotracer dose without sacrificing image quality. Thus metal artefact reduced (MAR) PSMA PET-CT has also become more effective and better tolerated, remaining accurate systematically [17, 102].

Simultaneously, quantitative imaging and artificial intelligence have broadened the analytical horizon of PSMA PET-CT. Semi-quantitative parameters measured on PSMA PET/CT, such as SUVmax, PSMA-derived tumor volume and whole-body tumor burden, are being more accepted as potential quantitative biomarkers for disease characterization and therapy response evaluation [103]. Radiomics and machine-learning techniques complexify the identification of imaging features that reflect tumor heterogeneity, biological activity beyond visual assessment. Integration of data derived from PSMA PET and more traditional clinical, biochemical and genomics-based information appears particularly promising for prognostication and personalized treatment [104].

Combining PSMA PET with other imaging modalities and clinical workflows constitutes a second key area of innovation [105]. Molecular-sensitive with excellent soft-tissue characterization, hybrid approaches such as PET-MRI hold promise for local staging and pelvic disease assessment. In

addition, PSMA PET-CT findings are incorporated more frequently into radiation therapy planning, surgical navigation and adaptive treatment strategies highlighting the increasing role of this modality in precision oncology [48].

Nevertheless, obstacles persist for the broader applicability of the new PSMA PET-CT techniques. Variable radiotracer availability, imaging protocols and interpretation criteria can influence reproducibility and clinical symmetry [27]. Currently work is ongoing to develop and validate standard acquisition protocols, reporting schemes and quantitative measures to ensure consistent application at various sites [106]. Furthermore, biological variability of the PSMA expression, particularly under therapeutic pressure needs to be taken into account upon interpreting imaging results and making treatment decisions [93].

Conclusion and future perspective

PSMA PET-CT has revolutionized imaging in prostate cancer by fundamentally changing the paradigms of disease staging, restaging and treatment response evaluation. This approach overcomes the limitations of conventional imaging by focusing on the biological characteristic of PSMA overexpression, and facilitates exact identification of disease at all levels. An expanding body of literature uniformly shows that PSMA PET-CT surpasses conventional imaging in diagnostic accuracy, risk classification and impact on management.

In the primary diagnostic setting, PSMA PET-CT has emerged as the most accurate tool for detection of nodal and metastatic disease, especially for patients with intermediate to high-risk prostate cancer. It has allowed the identification of clinically relevant metastases, which would have otherwise been missed, contributed to better treatment planning, and reduced the uncertainty characterizing the diagnostic phase. Likewise, in BCR, PSMA PET-CT allows a timely visualization of recurrent disease at low PSA levels for individualized salvage and metastasis directed therapies and to avoid an unnecessary or highly ineffective treatment.

In addition to the role in disease detection, PSMA PET-CT is increasingly being considered for evaluation of treatment response. With standardized response criteria still in development, preliminary evidence suggests that PSMA PET-derived measures can serve as functional biomarkers that capture tumor biology and treatment response better than traditional results. Quantitative analysis, radiomics, and artificial intelligence further contribute to the increasingly strong role of PSMA PET-CT imaging for precision oncology and adaptive therapeutic decisions.

Technological development such as with new radiotracers, theranostic approaches, improved imaging systems further extend the clinical utility of PSMA PET-CT. These developments are not only driving diagnostic accuracy and accessibility, but also fostering greater linkage between imaging and image-guided therapeutic strategies in a manner that underpins the personalized model of prostate cancer care.

Such enthusiasm has not come without challenges, however, namely lack of imaging biostandardization (imaging protocol harmonization), interpretation criteria and access to PSMA PET-CT. Continued prospective trials, consensus programs and interaction among multidisciplinary teams will be necessary to refine the clinical indications and establish evidence based guidelines for its best utilization.

In conclusion, PSMA PET-CT is a new milestone in the imaging of prostate cancer which links diagnostics, treatment and prognostication. With progressive development of clinical data and technological capacity, PSMA PET-CT is set to assume a central role in tailoring personalized care and improving outcomes for patients with prostate cancer.

Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

TS contributed to design of the work, data collection, and drafting the article. MH revised the draft manuscript and approved the final submission.

Competing interests

The author declares no competing interests.

Funding

None.

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