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*Research Article*

# Redefining High-Risk Prostate Cancer Staging: The Role of PSMA-PET and the Promise Criteria

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***Abstract***

*Staging is a pivotal step in the management of high-risk prostate cancer. Traditionally reliant on CT and bone scans, the diagnostic landscape has evolved dramatically with the advent of prostate-specific membrane antigen positron emission tomography (PSMA-PET). This imaging modality, with superior accuracy and reduced radiation burden, not only improves detection of nodal and distant disease but also alters therapeutic strategies in a substantial proportion of patients. In parallel, the development of the PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation) criteria has introduced a standardized framework for PSMA-PET interpretation, harmonizing staging across institutions and enhancing prognostic assessments. This review integrates current evidence, including recent randomized trials and prospective registries, and explores how PSMA-PET and PROMISE are reshaping the staging and clinical management of high-risk prostate cancer.*

***Keywords***: *PSMA-PET, PROMISE criteria, prostate cancer, high-risk, miTNM, staging, imaging biomarkers*

## Introduction

Prostate cancer is among the most frequently diagnosed cancers in men worldwide, with a considerable subset classified as high-risk due to elevated PSA levels, high Gleason grade, and/or advanced local extension. Accurate initial staging in these patients is essential to determine optimal therapeutic strategies—ranging from curative-intent local therapies to systemic approaches or enrollment in clinical trials.

Conventional imaging (abdominopelvic CT and bone scintigraphy) has long been the standard; however, its limitations in sensitivity and specificity, particularly for small-volume nodal or skeletal disease, are well documented[1]. PSMA-PET imaging, using radiotracers such as 68Ga-PSMA-11 or 18F-DCFPyL, provides superior detection of prostate cancer lesions by targeting PSMA overexpression on prostate cancer cells[2]. This has revolutionized the diagnostic landscape, especially in high-risk settings.

### Diagnostic Superiority of PSMA-PET

Accurate staging in high-risk prostate cancer is essential for determining the most appropriate therapeutic strategy, whether it be local curative-intent treatment or early systemic intervention. The conventional approach, which relies on contrast-enhanced CT of the abdomen and pelvis combined with a 99mTc bone

scan, has significant limitations. These modalities often fail to detect small-volume nodal metastases or early bone lesions, leading to underestimation of disease burden.

The phase III proPSMA trial, a prospective, randomized, multicenter study involving 302 men with high-risk localized prostate cancer, directly compared PSMA-PET to conventional imaging. The study found that PSMA-PET had a significantly higher accuracy (92%) compared to conventional imaging (65%) for staging purposes[3]. Importantly, this higher accuracy was consistent across different anatomic compartments—local, nodal, and distant. Moreover, PSMA-PET showed superior inter-reader agreement, reinforcing its reproducibility in clinical settings.

Beyond diagnostic accuracy, the trial demonstrated a change in clinical management in 27% of patients based on PSMA-PET results, compared to less than 10% for those staged with conventional imaging. These changes included the decision to proceed with systemic treatment instead of surgery, modification of radiotherapy fields, or patient selection for metastasis-directed therapies. This highlights the potential of PSMA-PET not only as a diagnostic tool but as a determinant of therapeutic strategy.

An additional advantage of PSMA-PET was a significant reduction in radiation exposure, with a median dose of ~8 mSv compared to ~19 mSv with CT and bone scan combined[3]. This lower radiation burden is particularly relevant in younger patients or those undergoing repeated imaging during surveillance or response assessment.

These findings have been corroborated by multiple prospective studies and meta-analyses, including the work of Perera et al., which confirmed the robust diagnostic performance of PSMA-PET across various risk groups and clinical scenarios, consistently outperforming conventional modalities[5].

| **Aspect Evaluated** | **PSMA-PET** | **CT + Bone Scan** |
|---|---|---|
| Overall staging accuracy | 92%[3] | 65%[3] |
| Sensitivity for pelvic nodes | 85–95%[6–7] | 38–42%[4] |
| Specificity for bone metastases | 98%[6] | 82%[4] |
| Change in management | 25–28%[3] | <10%[4] |
| Radiation exposure | ~8 mSv[3] | ~19 mSv[3] |

**Table 1.** Comparison of PSMA-PET and Conventional Imaging[3–5]

These findings have been reinforced by meta-analyses, including Perera et al., confirming PSMA-PET's consistent diagnostic superiority[5].

Taken together, these data position PSMA-PET as the current gold standard for staging high-risk prostate cancer, and its integration into routine clinical practice is increasingly supported by national and international guidelines.

**The PROMISE Criteria and miTNM Staging**

One of the major challenges in the widespread adoption of PSMA-PET imaging has been the lack of standardized reporting systems that ensure consistency in interpretation across institutions and readers. To address this gap, the PROMISE criteria (Prostate Cancer Molecular Imaging Standardized Evaluation) were proposed[8]. This framework introduces a molecular imaging TNM (miTNM) classification system, designed to parallel conventional anatomical staging while incorporating functional imaging data.

The miTNM system classifies findings as follows:

- miT: Local tumor extent visualized by PSMA uptake within the prostate gland and surrounding structures
- miN: Regional lymph node involvement (pelvic nodes below the aortic bifurcation)
- miM1a: Distant lymph node metastases (above aortic bifurcation or extra-pelvic nodes)
- miM1b: Bone metastases
- miM1c: Visceral metastases (lung, liver, etc.)

Unlike conventional CT-based nodal staging, which relies solely on size and morphology, PROMISE integrates both tracer uptake and anatomical localization, allowing detection of metastases in morphologically normal-sized lymph nodes or bone lesions that would otherwise go unnoticed.

The clinical utility of PROMISE lies not only in diagnostic categorization but also in its ability to enhance interdisciplinary communication, particularly in multidisciplinary tumor boards where nuclear medicine physicians, urologists, and medical/radiation oncologists must collaborate in real time to define treatment strategies[9].

Moreover, PROMISE has facilitated harmonization in patient eligibility for clinical trials, especially those involving radioligand therapy, metastasis-directed therapy, or neoadjuvant systemic approaches. Its use ensures consistent stratification of disease burden and improves reproducibility in research outcomes.

Another important dimension of PROMISE is its role in refining patient stratification in complex or "gray zone" scenarios. For example, in cases of borderline oligometastatic disease (e.g., one or two equivocal lesions), PROMISE can guide therapeutic escalation or deferral with greater confidence[8–10].

To further enhance its prognostic power, recent studies have integrated PROMISE-based miTNM into nomogram tools, such as the PPP and PPP2 models, developed through multi-institutional datasets. These models combine miTNM categories with PSA values, Gleason scores, and clinical parameters to predict outcomes such as progression-free and overall survival with greater precision than traditional risk grouping alone[11]. Early validation results have been promising, suggesting that imaging biomarkers like miTNM may soon complement or even redefine current clinical staging algorithms.

In summary, the PROMISE criteria offer a robust, reproducible, and clinically meaningful framework for interpreting PSMA-PET imaging, helping to standardize care while simultaneously advancing personalized treatment strategies.

**Clinical Implications and Applications**

The clinical value of PSMA-PET extends far beyond its superior diagnostic accuracy; it has become an active driver of therapeutic decision-making across various disease stages. By uncovering micrometastatic disease, reclassifying risk, and informing treatment intensity and modality, PSMA-PET has reshaped how high-risk prostate cancer is approached.

| Clinical Scenario | PSMA-PET Role |
|---|---|
| Initial staging of high-risk disease | Detects occult metastases → enables intensification or systemic therapy |
| PSA rise post-local therapy | Precisely localizes recurrence site, including small-volume or atypical lesions |
| Oligometastatic disease | Identifies MDT candidates; guides stereotactic RT or salvage resection; delays ADT |
| Response assessment to neoadjuvant IO | Provides early imaging biomarker of biologic response and residual tumor activity |

**Table 2.** Clinical Implications of PSMA-PET in High-Risk Prostate Cancer[12–15]

**Initial Staging and Risk Reclassification**

In newly diagnosed high-risk patients, PSMA-PET can reveal metastatic disease not visible on conventional scans. This is especially relevant in cases with rising PSA and negative CT/bone scans. Detecting miM1 disease early allows clinicians to shift from a curative local plan to a systemic or combined approach, avoiding undertreatment and inappropriate surgical interventions[12].

**Biochemical Recurrence and Site Localization**

After radical prostatectomy or radiotherapy, biochemical recurrence (BCR) is common, and locating the site of recurrence is crucial for salvage strategies. PSMA-PET has shown high sensitivity even at low PSA levels (<0.5 ng/mL), outperforming choline-PET or fluciclovine[12]. This enables precise targeting of recurrent disease—whether local, nodal, or distant—and can inform salvage radiotherapy fields or nodal dissections with curative intent.

**Oligometastatic Disease and MDT Selection**

The concept of oligometastatic prostate cancer—typically defined as ≤3–5 discrete metastatic lesions—has gained clinical importance with the advent of PSMA-PET. Trials like STOMP, ORIOLE, and EMPIRE-1 demonstrated that PSMA-PET-guided metastasis-directed therapy (MDT), such as stereotactic body radiotherapy (SBRT) or salvage lymphadenectomy, can delay progression and postpone the need for androgen deprivation therapy (ADT) in select patients[13–14]. These studies support a paradigm where PSMA-PET doesn't just detect disease but also helps tailor treatment in a way that prolongs quality of life without compromising oncologic outcomes.

**Response Assessment and Neoadjuvant Trials**

Although not yet standard in guidelines, PSMA-PET is emerging as a promising tool for treatment response evaluation, particularly in the context of neoadjuvant systemic therapy. Since it detects viable tumors based on molecular expression, rather than merely anatomical size, it can serve as an early biomarker of therapeutic efficacy. This application is especially relevant in trials exploring immune checkpoint inhibitors or AR pathway inhibitors before prostatectomy, where early imaging response might correlate with pathological complete response or minimal residual disease[15].

In summary, PSMA-PET is no longer just a staging tool—it is increasingly integral to clinical decision-making. Its utility spans from risk classification and personalized salvage strategies to guiding MDT and assessing biologic response in the era of neoadjuvant therapy.

| Study / Author (Ref) | Study Type | Population / Setting | Key Findings | Clinical Impact |
|---|---|---|---|---|
| Hofman et al. (2020) [1] | Phase III RCT (proPSMA) | 302 high-risk PCa patients | PSMA-PET: 92% accuracy vs. 65%; 27% change in management | Established PSMA-PET as new diagnostic standard |
| Eiber et al. (2018) [7] | Consensus framework (PROMISE) | International expert panel | Introduced miTNM system for structured PSMA-PET reporting | Standardized interpretation and improved interdisciplinary communication |
| Perera et al. (2016) [4] | Meta-analysis | >1300 prostate cancer patients | PSMA-PET superior in sensitivity and specificity vs. conventional imaging | Confirmed PSMA-PET's diagnostic advantage |
| Ost et al. (2018) [12] | Phase II RCT (STOMP) | Oligometastatic prostate cancer | MDT guided by PSMA-PET delayed progression | Supported MDT in low-volume metastatic disease |
| Calais et al. (2019) [2] | Prospective impact study | Biochemical recurrence | PSMA-PET changed therapeutic management in ~30% of cases | Validated clinical utility in real-world practice |
| Emmett et al. (2022) [9] | Prospective response evaluation | Neoadjuvant systemic therapy | PSMA-PET identified early imaging biomarker of response | Suggested role in monitoring treatment response |
| PPP2 Consortium (2025) [10] | Nomogram validation | Localized & metastatic prostate cancer | miTNM-based models predicted PFS and OS | Toward individualized prognostication |
| Afshar-Oromieh et al. (2020) [11] | Tracer comparison study | BCR after local therapy | Ga-68 and F-DCFPyL equally effective | Supported broader tracer availability |

| | | | | |
|---|---|---|---|---|
| Schmidkonz et al. (2020) [14] | Observational study | Advanced PCa under therapy | PSMA uptake correlated with clinical response | Reinforced role in treatment follow-up |
| Rowe et al. (2020) [8] | Real-world miTNM application | Mixed-risk prostate cancer | Validated clinical implementation of miTNM | Translated PROMISE into practice |
| Phillips et al. (2020) [13] | Phase II RCT (ORIOLE) | Oligometastatic PCa | MDT reduced progression vs. observation | Evidence for benefit of targeted intervention |
| Clarke et al. (2024) [18] | Expert review | High-risk PCa | Guidance on implementing PPP nomograms | Facilitated imaging-based prognostic modeling |

***Abbreviations: PCa = prostate cancer; PSMA-PET = prostate-specific membrane antigen positron emission tomography; MDT = metastasis-directed therapy; miTNM = molecular imaging TNM classification; RCT = randomized controlled trial; BCR = biochemical recurrence; PFS = progression-free survival; OS = overall survival.***

**Table 3.** Summary of Key Clinical Studies Supporting the Role of PSMA-PET Imaging and PROMISE Criteria in Prostate Cancer

**Future Perspectives and Limitations**

As the adoption of PSMA-PET accelerates worldwide, it is increasingly positioned to become the default imaging modality for initial staging, recurrence assessment, and treatment guidance in prostate cancer. However, several limitations and considerations must be acknowledged before its universal implementation.

1. **Cost and Access Disparities**

The infrastructure required for PSMA-PET—radioisotope production, PET/CT scanners, and trained nuclear medicine personnel—can be prohibitive in low- and middle-income countries (LMICs), and even in under-resourced institutions within high-income settings. Furthermore, availability of specific tracers (such as 68Ga-PSMA-11 or 18F-DCFPyL) depends on regulatory approvals and local radiopharmacy capacity. These disparities may widen the gap in diagnostic equity, reinforcing the need for global initiatives to support access.

**2. False-Positives and Non-Specific Uptake**

Although PSMA expression is highly specific to prostate cancer, it is not exclusive to malignant tissue. Uptake may occur in benign conditions such as inflammation, granulomatous disease, or ganglia, potentially leading to false-positive results. This is particularly important when interpreting equivocal findings in bone or lymph nodes. Experienced readers and, when needed, correlation with MRI or biopsy are essential to avoid misclassification[16].

**3. Need for Longitudinal Validation in Diverse Populations**

Many of the current validation studies for PSMA-PET and PROMISE-based nomograms have been conducted in select academic centers or homogeneous populations. There remains a pressing need to validate these models across broader, more diverse cohorts, including patients from different ethnicities, socioeconomic backgrounds, and healthcare systems. Long-term outcomes—such as metastasis-free survival and overall survival—linked to PSMA-based staging and treatment algorithms must be confirmed prospectively.

**4. Integration with Genomic and Molecular Profiling**

The future of prostate cancer management lies at the intersection of imaging and molecular biology. PSMA-PET provides a real-time visualization of biologically active disease, but its full potential may be realized when integrated with genomic classifiers such as Decipher, Prolaris, or Oncotype DX, which offer prognostic information on tumor aggressiveness. Combining molecular imaging with genomic risk profiling could enable unprecedented levels of precision in selecting candidates for adjuvant therapy, active surveillance, or trial enrollment.

Despite these limitations, the convergence of advanced imaging and molecular classification tools represents a paradigm shift. PSMA-PET, especially when interpreted using standardized frameworks like PROMISE, moves prostate cancer management away from a "one-size-fits-all" approach toward true personalized oncology. As evidence continues to accumulate, and as access improves, PSMA-PET is set to become not only a diagnostic cornerstone but a strategic instrument in redefining risk, monitoring therapy, and guiding individualized treatment.

## Discussion

The integration of PSMA-PET imaging and the PROMISE criteria into the diagnostic and therapeutic landscape of high-risk prostate cancer marks a significant advancement in the pursuit of precision oncology. This review confirms the superior diagnostic performance of PSMA-PET compared to conventional imaging, particularly in detecting nodal and distant metastatic disease, with clear implications for treatment intensification, clinical trial eligibility, and individualized care planning[3–5].

Several pivotal studies, most notably the proPSMA trial[3], have demonstrated that PSMA-PET not only improves staging accuracy but also drives clinically meaningful changes in management strategies. These findings underscore the evolving role of imaging as a biomarker, capable of guiding risk stratification, predicting outcomes, and informing therapeutic decisions across the disease continuum[13–14].

The introduction of the PROMISE criteria[8] has provided a much-needed framework to standardize PSMA-PET interpretation, facilitating interdisciplinary communication and consistent reporting across clinical practice and research. By adopting a miTNM-based classification, PROMISE bridges the gap between molecular imaging and conventional staging systems, enabling a more granular understanding of tumor burden and distribution. This has particular relevance in "gray zone" cases such as oligometastatic disease, where treatment decisions depend heavily on precise characterization of lesion number, location, and biological behavior[9–10].

From a practical standpoint, the clinical utility of PSMA-PET is already being felt in several scenarios: guiding salvage therapy in biochemical recurrence[12], informing metastasis-directed therapy (MDT) in oligometastatic settings[13–14], and even emerging as a potential tool for assessing early response to neoadjuvant or systemic therapies[15]. As such, PSMA-PET is transitioning from a diagnostic test to a decision-making platform.

Nevertheless, several barriers must still be addressed before PSMA-PET becomes universally accessible. The cost and complexity of implementation, disparities in tracer availability, and variability in interpretation across institutions may limit equitable access to this transformative technology. Moreover, while early data on PROMISE-based nomograms (such as PPP and PPP2) are promising[11], longitudinal studies in diverse patient populations are needed to validate their prognostic power and generalizability.

Another key area for future research lies in the integration of PSMA-PET with molecular and genomic classifiers. Combining functional imaging with tools like Decipher or Prolaris may unlock a new dimension in prostate cancer characterization—one that transcends morphology and embraces biologic heterogeneity.

In conclusion, the convergence of PSMA-based molecular imaging and standardized interpretative criteria represents a decisive step forward in the staging and management of high-risk prostate cancer. As clinical experience grows and evidence deepens, these tools will likely become indispensable elements of modern uro-oncologic practice, driving more informed, personalized, and effective care for patients worldwide.

**Key Messages**

- PSMA-PET is superior to conventional imaging in detecting nodal and distant metastases.
- It changes management in 25–30% of high-risk patients.
- PROMISE criteria offer a reproducible and harmonized staging system.
- Clinical applications include staging, recurrence localization, MDT selection, and early treatment response evaluation.
- Its incorporation into guidelines is ongoing, with ASCO, EAU, and NCCN already supporting its use in specific settings[17–18].

## Conclusion

The integration of PSMA-PET and the PROMISE criteria into the management of high-risk prostate cancer is transforming staging into a precision-driven process. It enhances detection, guides individualized therapy, and introduces a language that unifies disciplines. As adoption widens and evidence accumulates, PSMA-based imaging is set to become a cornerstone of modern prostate cancer care.

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