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Clinical Medicine GUIDELINE

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Practical guideline for prostate specific membrane antigen positron emission tomography / computed tomography in prostate cancer

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Prostate cancer (PCa) remains a leading cause of cancer-related morbidity and mortality in men. Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein highly overexpressed in most prostate adenocarcinoma cells, is an ideal molecular imaging target. PSMA-targeted positron emission tomography / computed tomography (PET/CT) has become a transformative diagnostic tool for PCa. This practical guideline synthesizes current best evidence and provides standardized recommendations for the use of PSMA PET/CT in PCa, graded according to Oxford Centre for Evidence-Based Medicine and EAU-EANM 2024 criteria.

PSMA-TARGETED RADIOTRACERS

PSMA PET radiotracers (e.g., ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-I&T, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{18}F-rhPSMA-7, and ^{64}Cu-SAR-bisPSMA) differed by radionuclide and excretion route.[1] ^{18}F-labeled ligands offer superior spatial resolution (0.6 mm mean positron range) than ^{68}Ga-labeled tracers (3.5 mm range), while ^{64}Cu-labeled agents facilitate 24-hour delayed imaging for occult micrometastases. Renal-excreted tracers (e.g., ^{68}Ga-PSMA-11) often generate urinary artifacts masking local recurrence in prostatic fossa, whereas hepatobiliary tracers like ^{18}F-PSMA-1007 risk non-specific bone uptake due to defluorination of the ^{18}F label. Thus, renal-excreted tracers are preferred for systemic staging, hepatobiliary agents for detecting localized recurrence near the bladder, and ^{64}Cu-labeled agents or delayed imaging for micro-metastases with ultra-low PSA (<0.5 ng/mL).

GENERAL USE CRITERIA FOR PSMA PET/CT IMAGING

PSMA PET/CT has no absolute contraindications when clinically indicated, but its use requires consideration of clinical scenario, disease stage, management impact, and cost-effectiveness.[2,3] Importantly, PSMA PET/CT is indicated only if findings may guide or change therapy, and not warranted when simpler measures suffice (e.g., routine follow-up with undetectable PSA post-radical prostatectomy), nor when no further treatment options exist.

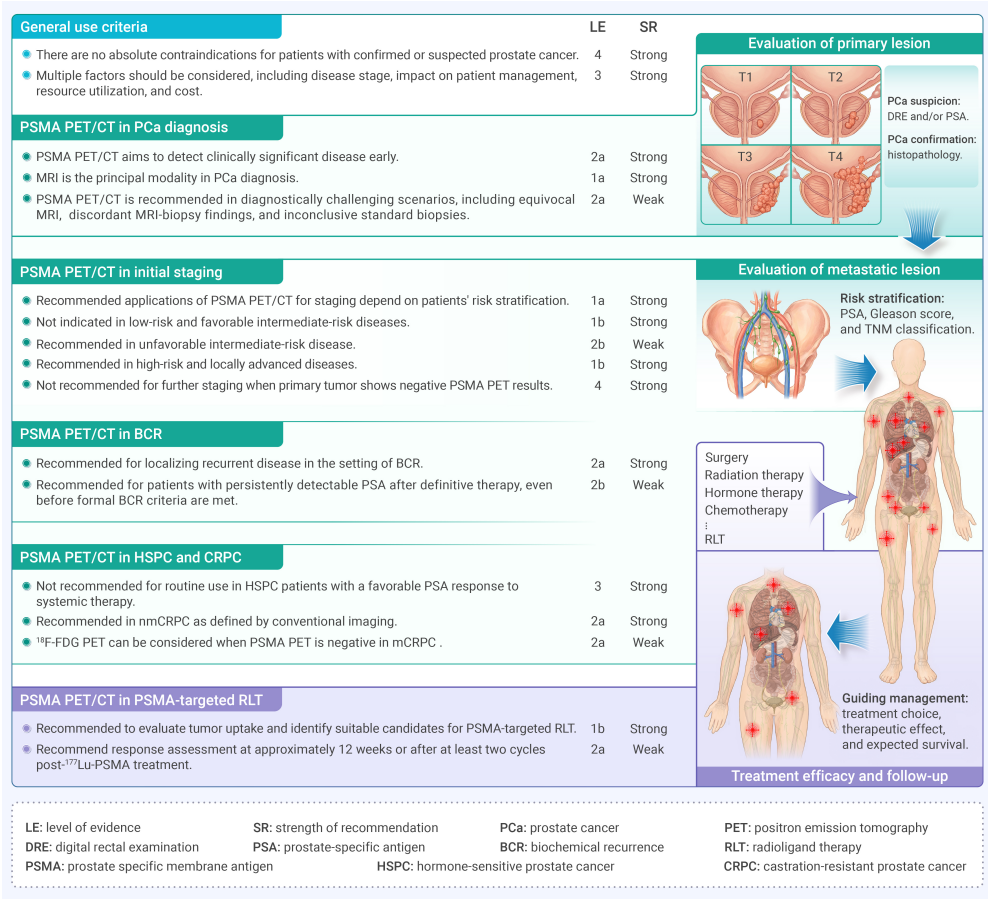

Figure 1. Suggested practical guideline for PSMA PET/CT in prostate cancer.

PSMA PET/CT IN DIAGNOSING PCA

The diagnostic process aims for timely detection of clinically significant PCa.[3] Suspicion of PCa arises from digital rectal examination and/or prostate-specific antigen (PSA) levels, while definitive diagnosis by histopathology. MRI is the principal imaging modality to indicate the presence of cancer, guide targeted biopsies and local staging. PSMA PET/CT is a valuable adjunct to MRI for more sensitive and specific detection of primary PCa. It is recommended for navigating diagnostic challenges, including clarifying equivocal MRI (PI-RADS 3), resolving discrepancies between positive MRI (PI-RADS > 3) and negative biopsy, and guiding biopsies when standard approaches yield inconclusive results.[4]

PSMA PET/CT IN INITIAL STAGING OF PCA

MRI remains the primary modality for local staging of newly diagnosed PCa. Systemic staging decisions should be risk-adapted based on PSA, ISUP Grade Groups (GG), and clinical stage.[3] For low-risk (PSA < 10 ng/mL and GG 1) and favorable intermediate-risk (GG 2 with PSA < 10 ng/mL, or GG 1 with PSA 10–20 ng/mL) disease, PSMA PET/CT is generally not indicated due to extremely low metastatic yield. In unfavorable intermediate-risk disease (GG 3, or GG 2 with PSA 10–20 ng/mL), PSMA PET/CT may be considered if available to improve staging accuracy. For high-risk (PSA > 20 ng/mL, GG 4/5, or cT2c) and locally advanced (cT3–4) disease, PSMA PET/CT is strongly recommended as the preferred first-line staging modality. However, small lymph node metastases (< 5 mm) may be false-negative. Notably, if PSMA PET is negative for the primary tumor, its utility for systemic staging is limited, and alternative imaging (e.g., ^{18}F-FDG PET) should be performed.

PSMA PET/CT IN BIOCHEMICAL RECURRENCE OF PCA

Biochemical recurrence (BCR) is a rise in PSA levels after definitive treatment, such as surgery (>0.2 ng/ml) or radiation therapy (>2 ng/ml), indicating local or metastatic recurrence. PSMA PET/CT is recommended as the primary imaging modality for localizing recurrent disease in BCR. Its detection rate correlates with PSA levels, PSA doubling time, Gleason score, and primary tumor PSMA expression.[3] For patients with persistently detectable PSA after definitive therapy for PCa, even without meeting formal BCR criteria, PSMA PET/CT remains a valuable adjunct, but its use should balance diagnostic yield against clinical urgency for intervention.

PSMA PET/CT IN HORMONE SENSITIVE PCA AND CASTRATION-RESISTANT PCA

For hormone-sensitive PCa (HSPC) receiving androgen deprivation therapy, PSMA PET/CT should generally be avoided within the first three months due to potential PSMA upregulation (flare phenomenon). Routine use is not recommended in patients demonstrating a favorable PSA response to systemic therapy, particularly if no treatment modification is planned.

For castration-resistant PCa (CRPC), PSMA PET/CT is recommended for patients with non-metastatic (nmCRPC) on conventional imaging, as it detects occult metastatic lesions in most cases.[2] This reclassification enables personalized management. Oligometastatic disease (1-3 lesions) allows for metastasis-directed therapy, which improves metastasis-free survival and delays intensified systemic treatment. Conversely, polymetastatic findings (≥5 lesions) identify high-risk subgroups with shorter overall survival, justifying earlier systemic escalation.

PSMA PET/CT IN RADIOLIGAND THERAPY OF PCA

PSMA-targeted radioligand therapy (RLT), most commonly ^{177}Lu-PSMA therapy, has been increasingly used in PCa. PSMA PET is mandatory to evaluate tumoral uptake and identify eligible candidates. Lower pretreatment PET SUVmean, higher lesion count, and bone and/or liver metastases are associated with worse prognosis.[5] Response assessment is suggested at approximately 12 weeks (after at least two cycles) after ^{177}Lu-PSMA treatment, to better avoid flare phenomena and capture stable response. PSMA-specific criteria (RECIP 1.0 and PPP) offer superior prognostic value over traditional anatomical (e.g., RECIST 1.1) or adapted (e.g., aPCWG3/aPERCIST) frameworks, as the latter often overcall progression or fail to evaluate non-measurable bone-dominant disease.

RECOGNITION AND MANAGEMENT OF PITFALLS

Clinical practicality of PSMA PET/CT requires distinguishing PSMA-avid benign findings from malignancy. False-positive uptake in fractures, Paget's disease, or infection requires mandatory correlation with co-registered CT, in which structural features (e.g., fracture lines) or cortical thickening are diagnostic. Benign ganglia are identified by location and absence of masses. Indeterminate bone lesions (PSMA-RADS 3) may require MRI or 3-month follow-up PET to assess stability. Notably, PSMA can be highly expressed in the neovascular endothelium of various solid tumors (e.g., lung cancer). False-negative results typically stem from micrometastases (<5 mm) or PSMA-negative phenotypes. For advanced disease with discordant low PSA, a PSMA-negative/FDG-positive mismatch indicates dedifferentiation or neuroendocrine transformation, necessitating FDG PET/CT and neuroendocrine markers (e.g., NSE).

CONCLUSION

PSMA PET/CT has revolutionized PCa management, offering high clinical value in primary staging, biochemical recurrence localization, and advanced disease burden assessment (Figure 1). This practical guideline supports the rational and individualized use of PSMA PET/CT to guide management decisions, while acknowledging cost-effectiveness and resource-aware implementation.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.