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Review

Guideline of guidelines: PSMA PET in staging newly diagnosed intermediate-risk prostate cancer

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Objective

To provide a comprehensive review and analysis of guidelines from various professional and medical organisations regarding the use of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) as a staging scan for men with newly diagnosed intermediate-risk prostate cancer (PCa).

Materials and Methods

English-language guidelines and recommendations from the following associations and societies were reviewed and critically analysed: European Association of Urology (EAU), American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE), Canadian Urological Association (CUA), American Society for Clinical Oncology (ASCO), Society for Nuclear Medicine and Medical Imaging (SNMMI).

Results

There is significant disagreement among guidelines regarding whether PSMA PET is a useful staging tool for men with a new diagnosis of intermediate-risk PCa. There is a stronger consensus that PSMA PET is useful in staging high-risk PCa.

Conclusion

Whilst there is a growing body of evidence that supports the use of PSMA PET in newly diagnosed PCa, there is significant disagreement regarding its use for men with intermediate-risk disease. Recommendations are generally weak and based on expert opinions. This is an area of considerable ongoing research, and guidelines are likely to change as new evidence emerges.

Keywords

Guidelines, Intermediate-Risk, Prostate Cancer, PSMA PET, Staging

Introduction

In 2022, the Australian government introduced Medicare item number 61563, offering a rebate to fund prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans for staging purposes in men newly diagnosed with prostate cancer (PCa) who have intermediate- or high-risk disease suitable for curative treatment. This was primarily based on the evidence of the proPSMA trial (Australian New Zealand Clinical Trials Registry [ANZCTR] number: 12617000005358) [1], which unequivocally demonstrated the superiority of PSMA PET to conventional imaging modalities (CT + bone scintigraphy) at detecting lymph nodes or distant metastases in men with newly diagnosed PCa with high-risk features. Subsequently,

numerous studies have built a strong evidence base to support the utility of PSMA PET in staging of primary PCa, with a recent systematic review and meta-analysis by Mazzone et al. [2] showing that the detection rate of nodal or metastatic disease was 15% in patients with intermediate-risk PCa and 31% in high-risk PCa.

The generous Medicare rebate has resulted in widespread availability of PSMA PET in Australia, and its adoption as part of a standard workup before definitive treatment for men with newly diagnosed PCa with International Society of Urological Pathology (ISUP) Grade Group (GG) ≥ 2 . Yet internationally, there is a high variance between guidelines regarding the use of PSMA PET within the setting of staging a newly diagnosed PCa. This likely reflects the variable

funding and availability of PSMA PET scans internationally, as well as concerns regarding the cost of the scan, and questions regarding its benefit in patients with intermediate-risk PCa. This has resulted in a lack of international consensus regarding whether patients with newly diagnosed intermediate-risk PCa should be staged with a PSMA PET scan. This review aimed to critically assess guidelines regarding the use of PSMA PET as a staging scan from major international organisations and discuss the evidence supporting their recommendations.

Prostate-Specific Membrane Antigen PET in Staging Intermediate-Risk PCa

The staging of intermediate-risk PCa is an area where there is the least consensus among the reviewed guidelines (Tables 1 and S1). Of the guidelines, only the European Association of Urology (EAU) has a weak recommendation to obtain a PSMA PET scan if available for staging of newly diagnosed ISUP GG 3 PCa. This recommendation explicitly excludes ISUP GG 2 and favourable intermediate-risk PCa. The National Comprehensive Cancer Network (NCCN) also recommends 'soft-tissue' imaging in unfavourable intermediate-risk disease. The 'soft-tissue imaging' is defined as CT chest, abdomen/pelvis, or MRI abdomen/pelvis, or PSMA-PET/CT, or PSMA-PET/MRI. This provides a soft recommendation where a PSMA PET scan can be considered as an option for staging unfavourable intermediate-risk PCa, without stating it as a preference. The NCCN also considers PSMA PET to be a suitable alternative for bone imaging. However, it only recommends considering bone imaging if regional or distant metastasis is found on soft-tissue imaging.

Conversely, the AUA guidelines state that clinicians should not routinely perform abdomino-pelvic CT or bone scans in asymptomatic men with low- and intermediate-risk PCa. The National Institute for Health and Care Excellence (NICE)

guidelines do not mention PSMA PET at all and discourage the use of bone scans in patients with low- and favourable intermediate-risk PCa, recommending CT scans only if knowledge of node or metastasis status would alter management. This is largely reflective of the lack of recent updates or revisions to the NICE guidelines, and the publishers need to review evidence regarding PSMA PET. The Society for Nuclear Medicine and Medical Imaging (SNMMI) Appropriate Use Criteria for PSMA PET also states that its use in favourable intermediate-risk PCa is rarely appropriate. However, SNMMI does support the use of PSMA PET in staging unfavourable intermediate-risk PCa, highlighting the importance of appropriate risk assessment of the primary cancer. The Canadian Urological Association (CUA) Best Practice Report and the American Society for Clinical Oncology (ASCO) guidelines do not mention the use of PSMA PET in intermediate-risk PCa. Still, given their statements on its use in high-risk disease, it can be assumed that they do not support the use of PSMA PET in intermediate-risk disease.

Overall, the use of PSMA PET in staging newly diagnosed intermediate-risk PCa is not widely recommended by major international guidelines. This reflects the fact that patients with intermediate-risk PCa have a low rate of lymph node invasion and distant metastases, making PSMA PET unlikely to change therapeutic approaches or decision-making in many cases.

Prostate-Specific Membrane Antigen PET in Staging High-Risk PCa

There is considerably more support in the guidelines for use of PSMA PET in staging of high-risk PCa (Tables 1 and S1). The EAU guidelines recommend that metastatic screening should be performed with PSMA PET if available. The NCCN recommends performing bone and soft tissue imaging,

Table 1 Summary of recommendations regarding the use of PSMA PET and staging scans from various bodies.

Guideline	Intermediate-risk PCa	High-risk PCa
EAU-EANM-ESTRO-ESUR-ISUP-SIOG (2025) [5]	Perform PSMA PET for unfavourable intermediate-risk PCa if available Do not perform	Perform PSMA PET
AUA/ASTRO (2022) [6]		Perform PSMA PET if conventional imaging negative or equivocal
NCCN (2025) [7]	Perform soft-tissue imaging *PSMA imaging is considered a valid imaging modality for both bone and soft-tissue imaging	Perform bone and soft-tissue imaging
NICE [8]	Do not perform medical imaging	Perform CT if N or M staging will change management
CUA Best practice Report (2021) [9]	Not mentioned	PSMA PET may be helpful if change in management contemplated
ASCO (2020) [10]	Not mentioned	Can perform PSMA PET in patient at high risk of metastasis if conventional imaging is negative or equivocal
SNMMI Appropriate Use Criteria (2022) [11]	Favourable intermediate risk – rarely appropriate unfavourable intermediate risk – appropriate	PSMA PET appropriate

EAU, European Association of Nuclear Medicine; ESTRO, European Society for Radiotherapy and Oncology; ESUR, European Society of Urogenital Radiology; SIOG, International Society of Geriatric Oncology.

with PSMA PET being a valid option for both, making it an attractive single-scan option. In line with the NCCN, the SNMMI Appropriate Use Criteria also supports PSMA PET for primary staging of high-risk PCa. In addition, the CUA best practice report recommends using PSMA PET in staging high-risk PCa, although with the caveat that it should only be used in cases where it may alter management. In comparison, the AUA and ASCO guidelines only support the use of PSMA PET scan in patients with PCa at high risk of metastatic disease, with negative findings on conventional imaging, for further evaluation of metastases.

Overall, there is a broad consensus among international guidelines that PSMA PET is a useful staging tool for newly diagnosed high-risk PCa. This reflects the overwhelming evidence from the proPSMA trial and subsequent studies, which have demonstrated that PSMA PET has a higher overall accuracy in detecting lymph node invasion and metastatic disease in PCa compared to conventional imaging. Interestingly, both the AUA and ASCO only support their use in the case of negative or indeterminate conventional staging. Given the superior sensitivity and specificity of PSMA staging over conventional imaging, using PSMA PET as a second-line staging modality will likely introduce significant additional costs and delay to the patient's care. Centres in the United States and Europe report PSMA as being more expensive than conventional imaging [3]. However, an analysis of data from the proPSMA trial in Australia found that, within the Australian context, PSMA PET had a lower direct comparative cost than conventional imaging [4]. Given the comparatively poorer sensitivity of conventional imaging with CT and bone scan, there is a strong case that it is far more economical to perform a PSMA PET scan as the first choice for initial staging, rather than doing it only after conventional imaging is negative or equivalent, as the AUA and ASCO suggest.

Is there a Use for PSMA PET in Intermediate-Risk PCa?

Although there is a lack of consensus in the current guidelines regarding the use of PSMA PET in staging intermediate-risk PCa, a growing body of evidence suggests it may have some utility. As discussed, up to 15% of patients with intermediate-risk PCa have extraprostatic disease detected on PSMA PET imaging [2]. Given the lower sensitivity, it is unlikely that these patients will be staged accurately by conventional imaging. The alternative to staging with imaging is via pelvic lymph node dissection at the time of radical prostatectomy, which is a highly morbid procedure associated with complications such as lymphocele, infection and venous thromboembolism [12]. Given its morbidity and lack of proven oncological benefit, it is mainly reserved for patients at high risk of lymph node invasion as determined by preoperative nomograms. Therefore, PSMA PET presents

an attractive non-invasive alternative for staging patients with intermediate-risk PCa. A systematic review and meta-analysis found that the negative predictive value of a PSMA PET scan is much higher in patients with a low risk of lymph node metastases [13]. This suggests that patients with a low or borderline risk of lymph node invasion, as determined by nomograms, may be safely excluded from lymph node dissection based on PSMA PET scanning. Given that these patients would largely fall into the intermediate-risk PCa cohort, PSMA PET should be considered a useful tool when selecting which patients can be safely excluded from lymph node dissection.

Whilst PSMA PET can detect extraprostatic disease in as many as 31% of high-risk patients, within the intermediate-risk cohort, it is much lower, ~15% [2]. More importantly, within the intermediate-risk PCa subgroup, there is a negligible rate of extra-pelvic disease (<1%) [2]. This raises the possibility of significant stage migration within the intermediate-risk group due to the increased sensitivity of PSMA PET, and any perceived oncological benefits being attributable to the 'Will Rogers phenomenon'. Small pelvic lymph nodes previously undetectable on conventional imaging would either be identified at the time of pelvic lymph node dissection or treated with radiotherapy in cases of biochemical recurrence after primary treatment. Earlier detection with PSMA PET imaging may lead to a perceived improvement in outcomes, as some intermediate-risk PCa are re-classified from N0 to so-called 'molecular imaging N1' (miN1) disease. These patients, who would otherwise be classified as clinical N0 on conventional imaging, have demonstrated decreased biochemical progression-free survival [14,15]. This suggests that earlier detection of N1 disease with PSMA PET may lead to stage migration, and a potential false improvement in oncological outcomes, as re-classification with more sensitive imaging results in a healthier cohort of both N0 and N1 patients. This phenomenon is known as the Will Rogers phenomenon and has previously been described in PCa in relation to MRI-targeted biopsies and updates to the Gleason classification system [16]. Whether a similar effect will be observed with the introduction of PSMA PET remains to be seen but is likely based on early data regarding biochemical recurrences. The potential oncological benefits of staging intermediate-risk PCa with PSMA and detecting miN1 disease remain uncertain. This uncertainty regarding oncological benefits from earlier detection and treatment of N1 disease in patients with intermediate-risk PCa is an argument against the routine use of PSMA staging within this cohort.

Another potential application of PSMA PET in intermediate-risk PCa is the detection of cancers that may have been under-graded on the original biopsy. PCa diagnosed on an MRI-targeted biopsy is not always reflective of the actual grade of disease on the final specimen. An estimated 23% of patients have their tumours upgraded to a higher Gleason score on a

radical prostatectomy specimen [17]. This is particularly relevant in intermediate-risk PCa, as favourable intermediate-risk disease can be suitable for active surveillance rather than immediate radical treatment. Therefore, accurate grading of the initial cancer is crucial to inform decision-making. There is a growing body of evidence that suggests features on PSMA PET can be associated with higher-risk disease. A systematic review found that a higher maximum standardised uptake value (SUV_{max}) on PSMA PET is associated with adverse pathological features, such as a higher GG and extraprostatic disease [18]. This suggests that PSMA PET may be a useful tool in identifying patients who have been undergraded on the original biopsy. This is an area of intense interest, given the expansion of active surveillance to include favourable intermediate-risk cancers, making correct grading essential. This has led to several trials examining the potential utility of PSMA PET as a tool to enhance active surveillance [19–21]. Whilst the clinical utility of PSMA PET in staging intermediate-risk PCa is not widely agreed upon currently, there may yet be a role for it in risk assessing the primary PCa and selecting patients suitable for active surveillance.

Conclusion

There is a growing consensus among international guidelines that PSMA PET is a valuable tool in staging high-risk PCa due to its superior sensitivity in detecting nodal and metastatic disease. However, there is significant variance among guidelines regarding the use of PSMA PET in intermediate-risk PCa. There is increasing support for its use in unfavourable intermediate-risk PCa; however, this is far from universal. There is currently no support in guidelines for the use of PSMA PET in favourable intermediate-risk PCa. This reflects the current state of evidence and uncertainty regarding the potential for PSMA PET to alter management or provide oncological benefit in a cohort of patients already at low risk of having lymph node invasion or metastatic disease. Recommendations from bodies to use PSMA PET in staging intermediate-risk PCa are weak and based on expert consensus rather than a broad base of evidence. However, a growing body of literature suggests that PSMA PET may have a variety of uses within this cohort. There is evidence showing that it can be a useful tool in excluding patients that may otherwise have undergone a pelvic lymph node dissection, and that it can provide useful information regarding the primary tumour, potentially detecting lesions that have been under-graded on biopsy. This is a rapidly evolving field of research, and recommendations are likely to change as guidelines are updated to reflect new and emerging evidence.

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Disclosure of Interests

Jonathon Carll—No conflicts exist. Weiwei Shi—No conflicts exist. Marlon Perera—No conflicts exist. Nathan Lawrentschuk declares the following conflicts: Proctor for both Robotic Surgery (Device Technologies Australia) and Focal Therapy with Nanoknife (Getz healthcare Australia). Thilakavathi Chengodu—No conflicts exist. Dixon Woon—No conflicts exist.

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Abbreviations: ASCO, American Society for Clinical Oncology; CUA, Canadian Urological Association; EAU, European Association of Urology; GG, Grade Group; ISUP, International Society of Urological Pathology; miN1, molecular imaging N1; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PCa, prostate cancer; PSMA PET, prostate-specific membrane antigen positron emission tomography; SNMMI, Society for Nuclear Medicine and Medical Imaging.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Full recommendations regarding the use of staging scans from various bodies.