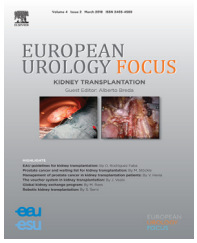
EUROPEAN UROLOGY FOCUS 7 (2021) 951–954

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Mini Review – Prostate Cancer

Clinical Translation of Positive Metastases Identified on Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging in the Management of De Novo Synchronous Oligometastatic Prostate Cancer

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Article info

Article history:
Accepted December 5, 2020

Associate Editor: Derya Tilki

Keywords:
Prostate cancer
Prostate-specific membrane antigen
Positron emission tomography
Computed tomography
^{68}Ga-labelled radiotracer
Metabolic tumour parameters
Treatment response
Metastasectomy
Stereotactic ablative therapy
Whole-body tumour burden

Abstract

Recent evidence from randomised trials supports the diagnostic superiority of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) over conventional imaging in the detection of distant occult metastasis in men with newly diagnosed high-risk prostate cancer. This may result in a rise in the detection of de novo synchronous hormone-sensitive "oligometastatic" prostate cancer. We outline the evidence supporting PSMA PET/CT imaging in primary staging. We also discuss the translation of positive areas with a high probability of distant metastasis into clinical therapeutic targets for metastasis-directed interventions. Finally, we highlight the role of PSMA PET/CT as an imaging biomarker. This may have future utility in disease monitoring and prediction of response to systemic, local cytoreductive and metastasis-directed interventions.

Patient summary: A new whole-body scan can accurately detect cancer deposits in men in whom distant prostate cancer spread is suspected. This may be useful for monitoring and predicting response to drug therapy, treatments to the prostate, and cancer deposits.

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https://doi.org/10.1016/j.euf.2020.12.002

1. Introduction

Recent evidence from randomised trials supports the diagnostic superiority of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) over conventional imaging (abdominopelvic CT and bone scintigraphy) in the detection of distant occult metastasis in men with newly diagnosed high-risk prostate cancer [1,2]. This may result in a rise in the diagnosis of de novo synchronous oligometastatic prostate cancer. Oligometastatic prostate cancer is a controversial clinically defined state characterised in terms of numerical lesion-based criteria for the metastatic burden (eg, <3 or <5 bone lesions) without international consensus [3,4]. It is hypothesised that men in this state derive additional oncological benefit from local cytoreductive treatment and metastasis-directed therapy (MDT) [3,4].

Here we review the trial evidence supporting PSMA PET/CT and the impact of its integration in primary staging of high-risk prostate cancer, the subsequent translation of positive distant lesions into clinical therapeutic targets for MDT, and the potential utility in disease monitoring.

2. PSMA PET/CT in the primary staging of high-risk prostate cancer

PSMA-targeted radiotracers for PET/CT have been evaluated in diagnosing distant disease in two trials recruiting men with high-risk prostate cancer [1,2]. First, the prospective multicentre proPSMA study (ANZCTR12617000005358) randomised 302 men with biopsy-proven prostate cancer and high-risk features awaiting radical prostatectomy or radiotherapy to first-line conventional imaging (n = 152) or [^{68}Ga]-PSMA PET/CT (n = 150) [1]. The primary outcome was the accuracy of first-line imaging in identifying either pelvic nodal or distant metastatic disease (defined in terms of the receiver operating characteristic curve using a predefined reference standard including histopathology, imaging, and biochemistry at 6-mo follow-up). Overall, PSMA PET/CT had 27% (95% confidence interval [CI] 23–31%) greater accuracy than conventional imaging alone (92%, 95% CI 88–95% vs 65%, 95% CI 60–69%; $p < 0.0001$) [2]. The rate of pelvic nodal or distant metastatic disease reported was 30% (87/295).

Subgroup analyses revealed the superiority of PSMA PET/CT for patients with pelvic nodal metastases (91% vs 59%; absolute difference 32%, 95% CI 28–35%) and for patients with distant metastases (95% vs 74%; absolute difference 22%, 95% CI 18–26%). Of note, "hard criteria" (ie, histopathology) were available for only 20/87 men (23%) with nodal or distant metastases. This was because of numerous factors, including the use of radiotherapy, for which nodal biopsy is not clinically indicated, and lack of pelvic lymph node dissection (PLND) in 66% (83/126) at the time of radical prostatectomy.

Second, the prospective multicentre OSPREY study (NCT02981368) evaluated 252 men with high-risk prostate

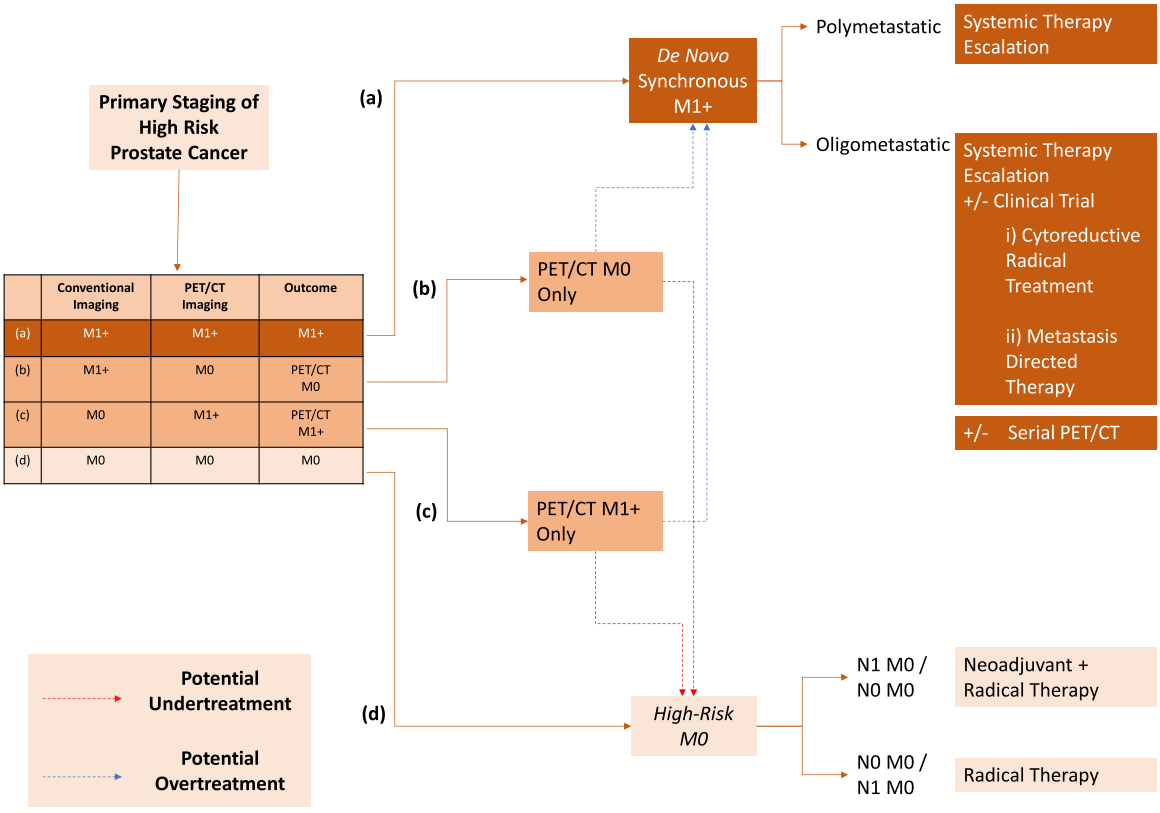

Fig. 1 – Impact of PET/CT imaging in the primary staging of high-risk prostate cancer. TMN prostate cancer staging according to the International Union Against Cancer 7th edition. Radical treatment refers to either radical prostatectomy or external beam radiotherapy. PET = positron emission tomography; CT = computed tomography.

cancer who underwent [^{18}F]-DCFPyL PSMA PET/CT in addition to conventional imaging before planned radical prostatectomy with PLND [2]. Pelvic nodal disease was identified in 37 men (14.7%) and metastatic disease in 27 (10.7%). In the metastatic cohort, staging was one (0.4%) with M1a, 23 (9.1%) with M1b, and three (1.2%) with M1c. For histology-proven nodal disease, [^{18}F]-DCFPyL PSMA PET/CT has positive predictive value of 86.7% (95% CI 70–95%), sensitivity of 41.9% (95% CI 30–54%), and specificity of 97.9% (95% CI 95–99%). Overall, 56 men (22%) were upstaged with regional nodal or distant metastatic lesions because of findings reported exclusively on [^{18}F]-DCFPyL PSMA PET/CT [2].

Routine integration of PSMA PET/CT in the primary staging of high-risk prostate cancer will lead to significant changes in the current treatment pathway. This has the potential to create two further uncertain subgroups of conventional metastatic lesions found "positive" or "negative" on PSMA PET/CT imaging. The downstream uncertainty has the potential to lead to both undertreatment and overtreatment effects (Fig. 1). Furthermore, this creates difficulties in interpreting stage-specific survival outcomes for men who may move between disease risk groups and undergo interventions at an earlier stage (the Will Rogers phenomenon) [5].

Interestingly, 2.7% (8/300) of men in the proPSMA study underwent radical treatment despite the presence of [Ga^{68}]-PSMA PET/CT–detected oligometastases and the treatment being outside normal clinical practice [2].

3. PSMA PET/CT and MDT

Studies are incorporating MDT for de novo synchronous disease without a uniform requirement for conventional imaging. This is despite significant uncertainty regarding the value of targeting distant PSMA PET/CT–positive oligometastasis [4,5].

In the metachronous disease setting, the ORIOLE study (NCT02680587) reported on 54 men randomised to stereotactic ablative radiation to oligo-macrometastasis (n = 36) compared to observation alone (n = 18), with double-blind [Ga^{68}]-PSMA PET/CT at baseline and after treatment [6]. An additional 49 lesions that were only positive on [Ga^{68}]-PSMA PET/CT were identified at baseline. Thus, a proportion of men had a higher disease burden when defined according to PSMA PET/CT alone, yet they still derived an oncological benefit from MDT directed to oligo-macrometastasis identified on conventional imaging [6]. It could be hypothesised that the same uncertainty might apply to de novo synchronous disease (Fig. 2).

4. PSMA PET/CT as an imaging biomarker for assessment and tumour response

Molecular assessment provides granular anatomical detail regarding active disease sites not available from either PSA trend analysis or conventional morphological assessment [7,8]. PSMA PET/CT imaging may offer utility in identifying men who have had the greatest response to upfront systemic therapy, and thus might benefit from added cytoreductive interventions and defer the toxicity of further systemic agents. However, the overall evidence for use in assessment and tumour response is highly limited [9,10].

Seitz and colleagues [9] evaluated [Ga^{68}]-PSMA PET/CT in predicting radiological response (RR) in six men receiving upfront docetaxel for newly diagnosed hormone-sensitive metastatic prostate cancer. Concordance between the

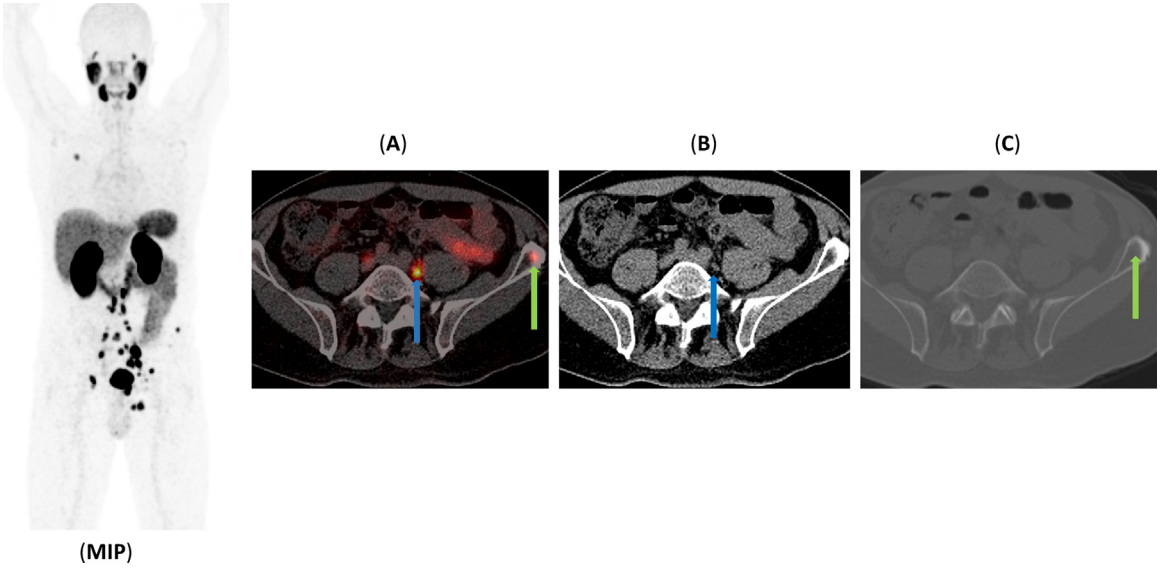

Fig. 2 – Addition of [Ga^{68}]-PSMA PET/CT compared to conventional imaging at baseline diagnosis. In a 58-yr-old male with Gleason 3 + 4 (grade group 2), and prostate-specific antigen 4.2 ng/mL, conventional imaging work-up (multiparametric magnetic resonance imaging of the prostate, CT of the thorax, abdomen, and pelvis, bone scintigraphy) demonstrated de novo synchronous oligometastatic disease (T3b N1 M1b) with two discrete metastases (left inferior pubic ramus and right medial acetabulum). This was upstaged on [Ga^{68}]-PSMA PET/CT to widespread bony polymetastatic disease, occult on CT (including the iliac crest, sacrum, ischium, lumbar spine, sternum, and a rib lesion). (MIP) Focal disease in the left hemi-prostate, multiple tiny [Ga^{68}]-PSMA–positive pelvic and para-aortic nodes, and several bone metastases including the right rib. (A) Fused [Ga^{68}]-PSMA PET/CT, (B) axial CT, and (C) axial CT (bone window) images. A PSMA-positive left common iliac node (3 mm blue arrow) and a left iliac bone metastasis, occult on CT (green arrow), are evident. PSMA = prostate-specific membrane antigen; PET = positron emission tomography; CT = computed tomography.

biochemical response (BR) and PET/CT-RR was superior to that between BR and CT-RR (86% vs 50%). However, the sample size and risk of selection bias prevent definitive conclusions [9].

A retrospective series of 25 men with hormone-sensitive metastatic prostate cancer (7 de novo synchronous; 18 metachronous) underwent [Ga^{68}]-PSMA PET/CT at baseline and after chemotherapy [10]. Patients achieving a complete response on visual analysis of [Ga^{68}]-PSMA PET/CT images were significantly less likely to progress to castrate-resistant disease (22% vs 69%; p = 0.04; median follow-up 37.7 mo) [10].

Detection of tumour harbouring clinically significant prostate cancer that might benefit from local treatment after systemic therapy is another possible use in this cohort. The ATLANTA (NCT03763253) randomised substudy is recruiting 25 men to undergo [Ga^{68}]-PSMA PET/CT, blinded to investigators, at baseline and post-systemic therapy to help answer this research question.

5. Conclusions

Routine integration of PSMA PET/CT imaging into the diagnostic pathway for men with high-risk prostate cancer is likely to lead to a rise in the diagnosis of de novo synchronous oligometastatic prostate cancer. This has key implications for the current treatment pathways and may impact on interpretation of future stage-specific survival data.

Conflicts of interest: Martin J. Connor receives funding from the Wellcome Trust and University College London Hospitals (UCLH) Charity. Tara Barwick and Suraiya Dubash are supported by the National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Edward Bass receives funding from the Wellcome Trust. Hashim U. Ahmed is supported by core funding from the NIHR Imperial Biomedical Research Centre, the Wellcome Trust, the Medical Research Council (UK), Prostate Cancer UK, Cancer Research UK, The BMA Foundation, The Urology Foundation, The Imperial Health Charity, Sonacare, Trod Medical, and Sophiris Biocorp; is a paid medical consultant for Sophiris Biocorp, Sonacare, and BTG/Galil; and is a paid proctor for HIFU, cryotherapy, and Rezum water vapour therapy. The remaining authors have nothing to disclose.

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