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Prostate-specific Membrane Antigen Positron Emission Tomography in the Staging of Newly Diagnosed Prostate Cancer: Is More Sensitivity Always Better?

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1. Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) is a novel imaging modality with higher sensitivity and greater specificity for detection of prostate cancer than conventional imaging, such as bone scintigraphy or computed tomography (CT) [1]. Moreover, PSMA PET imaging can identify small bone lesions that might be missed by bone scintigraphy alone [2]. For this reason, some suggest that PSMA PET should be used as the primary staging modality for newly diagnosed prostate cancer [3].

However, there is disagreement between major oncological societies. The National Comprehensive Cancer Network guidelines recommend staging with PSMA PET, stating that the higher sensitivity and specificity of PSMA PET tracers for detection of micrometastatic disease in comparison to conventional imaging mean that PSMA PET/CT or PSMA PET/magnetic resonance imaging “can serve as an equally effective, if not more effective front-line imaging tool for these patients” [4]. Conversely, the European Society for Medical Oncology guidelines do not have a recommendation in favour of PSMA PET scans as yet, citing a lack of data on the clinical benefit [5]. Although it is plausible that more accurate identification of lesions would lead to more accurate staging and better treatment outcomes, there are several reasons why this may not be the case. Here we explore three reasons why staging with PSMA PET may not enhance outcomes, but could, at times, worsen them.

2. Exposing patients to systemic therapy that may not benefit them

The mainstay of therapy for newly diagnosed metastatic prostate cancer is systemic chemohormonal therapy. Abiraterone, apalutamide, docetaxel, and enzalutamide, all in combination with androgen deprivation therapy (ADT), have shown an overall survival benefit in hormone-sensitive metastatic prostate cancer. For localised disease, systemic therapy plays only a minor role, in the form of adjuvant ADT or docetaxel in high-risk cases [5].

Owing to its higher sensitivity, PSMA PET staging is more likely to detect extraprostatic lesions not visible on conventional imaging. This can lead to upstaging in patients who were previously considered to have nonmetastatic disease, changing their overall treatment plan. Staging with PSMA PET can change management from local to systemic therapy in as many as 11.5% of patients with newly diagnosed prostate cancer [6].

All the benchmark trials evaluating the efficacy of the most widely used systemic agents (listed above) were conducted in an era in which PSMA PET scans were not widely available, and relied on conventional imaging [7–13]. Patients staged as having metastatic disease solely on the basis of PSMA PET imaging were not included in these trials. Therefore, it remains unclear whether and how much this group of patients benefits from these systemic agents.

Emerging evidence suggests that patients with a low number of metastases benefit from local therapy [14]. This...
fact changes the paradigm whereby metastatic disease can only be treated with systemic therapy. Some studies, such as CHAARTED, suggest that such “oligometastatic” disease does not benefit from systemic chemotherapy [8]. However, a later meta-analysis could find no such distinction and found survival benefits for all patients with metastatic cancer, regardless of disease volume [5]. It is not clear how this situation will change if the effect of the more sensitive PSMA PET staging is taken into account. It is possible that some of the patients staged as having metastatic disease solely on the basis of PSMA PET will derive no benefit from systemic therapy.

As long as PSMA PET is not the staging modality used in trials evaluating the efficacy of systemic agents in metastatic prostate cancer, it is not possible to draw any reliable conclusions. Before such trials are conducted, PSMA PET staging could lead to some patients being exposed to systemic therapy and its associated toxicities without proper evidence that they derive any benefit from it.

3. Depriving patients of local therapy that would benefit them

One arm of the STAMPEDE multiarm trial demonstrated that radiotherapy to the primary site can improve overall survival in oligometastatic prostate cancer, defined as fewer than five bone metastases and no visceral involvement visible on conventional imaging [15].

Since PSMA PET staging is able to detect small bone lesions not visible on conventional imaging, it may influence the classification of oligometastatic status in prostate cancer. Primary staging with PSMA PET leads to a significant increase in detection of polymetastatic disease (2% to 11%) at the expense of disease confined to the prostate bed (85% to 74%). An increase in detection of oligometastatic disease (8% to 15%) was also observed, but the difference did not reach statistical significance [16].

Patients who are staged as having polymetastatic disease on the basis of PSMA PET alone who would have been staged as having oligometastatic disease on conventional imaging belong to the group for which STAMPEDE demonstrated a survival benefit. It would be wrong to deny these patients local radiotherapy solely on the basis of PSMA PET findings. If PSMA PET is the only staging modality used, it is impossible to discern the patients who would have benefited from those who would not. Therefore, replacing conventional imaging with PSMA PET in prostate cancer staging might lead to some patients being denied local radiotherapy, which they would have benefited from.

4. Encouraging experimental therapies without strong supporting evidence

Metastasis-directed therapies (MDTs) such as stereotactic ablative radiotherapy (SABR) and surgical metastasectomy are novel approaches in the treatment of oligometastatic prostate cancer and are becoming increasingly popular with the rise of highly sensitive imaging techniques such as PSMA PET. Some preliminary evidence suggests that the use of PSMA PET to identify targetable lesions for MDT may improve outcomes [17]. However, there are several reasons why this evidence is weak and should not inform practice.

Prospective data on MDT use in de novo oligometastatic prostate cancer are scarce [18]. There is only one prospective pilot study without randomisation and with a weak primary endpoint (complete prostate-specific antigen response) in this setting [19], while four prospective trials (mostly phase 2 trials) are still ongoing or have not yet published data [18]. The strongest evidence in favour of PSMA-

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**Fig. 1 – Potential impact of PSM PET as the initial staging modality for prostate cancer. Black lines denote the cutoffs for conventional imaging, which was used for all the benchmark trials in this field. Red lines denote the cutoffs with more sensitive PSMA PET staging.**

- **Nonmetastatic disease**
- **Metastatic disease**
  - Exposure to systemic therapy that might have no benefit
  - Denial of local RT that might have a benefit
- **Localised**
- **Locally advanced**
- **“Oligometastatic”**
- **“Polymetastatic”**
- **Local therapy (surgery or RT)**
- **Local RT (STAMPEDE)**
- **Androgen deprivation therapy**
- **Systemic chemohormonal therapy (docetaxel, abiraterone, etc)**

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guided MDT comes from the recurrent setting. A post hoc analysis for ORIOLE, a randomised phase 2 trial, demonstrated that patients in whom all PSMA-avid lesions were ablated (with SABR) had better outcomes than patients in whom some lesions were missed [20]. However, there are several issues with extrapolating from these data to de novo oligometastatic disease. ORIOLE was conducted in the oligorecurrent setting with the aim of prolonging the treatment-free interval by increasing the time to progression. The results are therefore not directly applicable to de novo oligometastatic disease, for which the aim should be an overall survival benefit. Moreover, PSMA PET was not the imaging modality used to determine targetable lesions in ORIOLE and was only performed in addition to conventional imaging in the experimental arm and analysed post hoc after completion of the intervention. Thus, it is not possible to deduce any causal effect from this analysis. It is possible that patients with PSMA-avid lesions that were not visible on conventional imaging had more aggressive tumour biology overall and therefore would not have derived a benefit from SABL.

5. Conclusions

While PSMA PET has superior sensitivity and specificity to conventional imaging, there are potential risks with its use for initial staging of prostate cancer (Fig. 1). First, if the results from all of the benchmark trials evaluating interventions in metastatic prostate cancer are not validated with PSMA PET staging, there is a risk of patients being harmed in two ways: (1) exposure to therapy (systemic therapy) from which they might not benefit and (2) denial of therapy (local radiotherapy) from which they might benefit. Moreover, use of PSMA PET motivates providers to perform experimental procedures with therapy directed to metastases (MDT), for which robust evidence is still lacking.

Conflicts of interest: Vinay Prasad has received research funding from Arnold Ventures; has received royalties from Johns Hopkins Press, Medscape, and MedPage; has received honoraria for grand rounds/lectures from universities, medical centres, nonprofit organisations, and professional societies; is a consultant for United Healthcare and OptumRX; and has Patreon backers for the Plenary Session podcast and YouTube and Substack content. Abirramy Varatharajan and Timothée Olivier have nothing to disclose.

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References


