Title

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

Journal

European Urology, 83(6)

ISSN

0302-2838

Authors

Varatharajan, Abirramy
Olivier, Timothée
Prasad, Vinay

Publication Date

2023-06-01

DOI

10.1016/j.eururo.2023.01.024

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

European Association of Urology

Editorial

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

Abirramy Varatharajan [a,*], *Timothée Olivier* [b], *Vinay Prasad* [c]

[a] *Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;* [b] *Department of Oncology, Geneva University Hospital, Geneva, Switzerland;* [c] *Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, CA, USA*

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

* Corresponding author. Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland. Tel. +41 79 6144010.
E-mail address: abirramy12@gmail.com (A. Varatharajan).

https://doi.org/10.1016/j.eururo.2023.01.024

Please cite this article as: A. Varatharajan, Timothée Olivier and V. Prasad, Prostate-specific Membrane Antigen Positron Emission Tomography in the Staging of Newly Diagnosed Prostate Cancer: Is More Sensitivity Always Better?, Eur Urol (2023), https://doi.org/10.1016/j.eururo.2023.01.024

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-

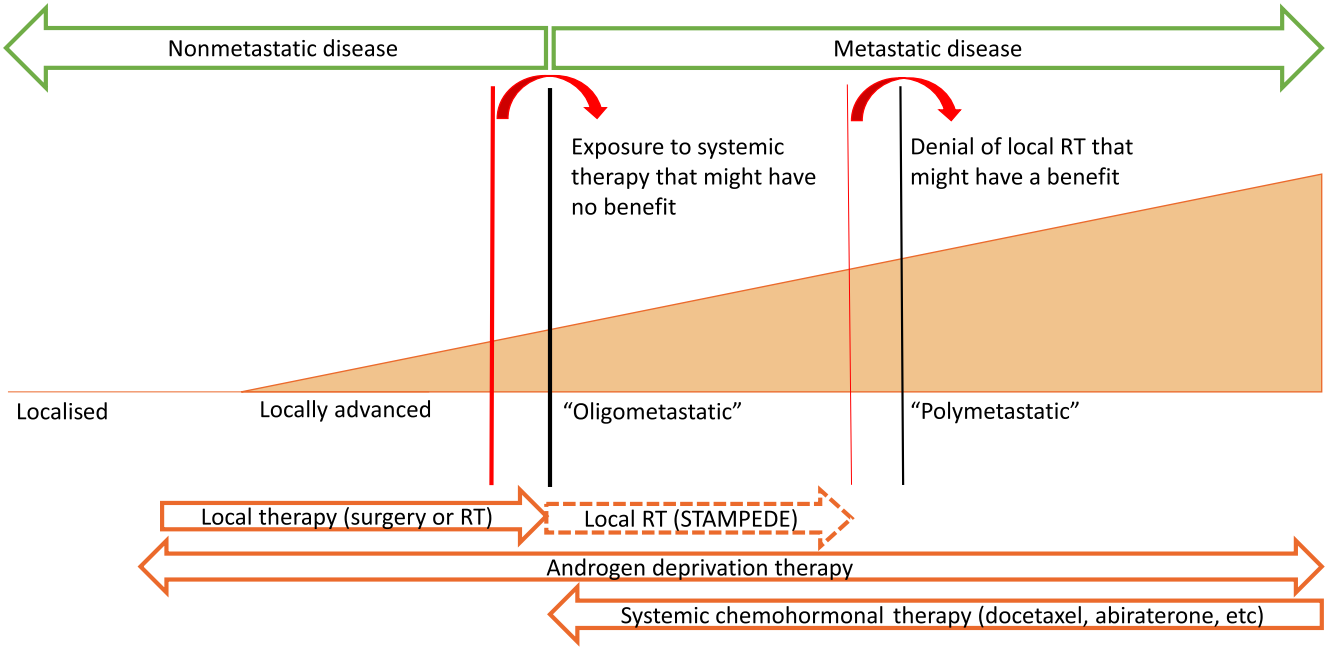

Fig. 1 – Potential impact of PSM PET as the initial staging modality for prostate cancer. Black lines denote the cutoffs for conventional imaging, which was used for all the benchmark trials in this field. Red lines denote the cutoffs with more sensitive PSMA PET staging. PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RT = radiation therapy.

Please cite this article as: A. Varatharajan, Timothée Olivier and V. Prasad, Prostate-specific Membrane Antigen Positron Emission Tomography in the Staging of Newly Diagnosed Prostate Cancer: Is More Sensitivity Always Better?, Eur Urol (2023), https://doi.org/10.1016/j.eururo.2023.01.024

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 casual 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 SABR.

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.

Acknowledgments: This project was funded by Arnold Ventures, LLC, through a grant paid to the University of California, San Francisco.

References

[1] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16. https://doi.org/10.1016/S0140-6736(20)30314-7.

[2] Lengana T, Lawal IO, Boshomane TG, et al. ^{68}Ga-PSMA PET/CT replacing bone scan in the initial staging of skeletal metastasis in prostate cancer: a fait accompli? Clin Genitourin Cancer 2018;16:392–401. https://doi.org/10.1016/j.clgc.2018.07.009.

[3] Killock D. PSMA PET-CT improves staging. Nat Rev Clin Oncol 2020;17:337. https://doi.org/10.1038/s41571-020-0364-4.

[4] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®). Prostate cancer version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

[5] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1119–34. https://doi.org/10.1016/j.annonc.2020.06.011.

[6] Grubmüller B, Baltzer P, Hartenbach S, et al. PSMA ligand PET/MRI for primary prostate cancer: staging performance and clinical impact. Clin Cancer Res 2018;24:6300–7. https://doi.org/10.1158/1078-0432.CCR-18-0768.

[7] James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol 2015;67:1028–38. https://doi.org/10.1016/j.eururo.2014.09.032.

[8] Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080–7. https://doi.org/10.1200/JCO.2017.75.3657.

[9] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149–58. https://doi.org/10.1016/S1470-2045(12)70560-0.

[10] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60. https://doi.org/10.1056/NEJMoa1704174.

[11] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24. https://doi.org/10.1056/NEJMoa1903307.

[12] Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37:2974–86. https://doi.org/10.1200/JCO.19.00799.

[13] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121–31. https://doi.org/10.1056/NEJMoa1903835.

[14] Galgano SJ, McDonald AM, West JT, Rais-Bahrami S. Defining oligometastatic disease in the new era of PSMA-PET imaging for primary staging of prostate cancer. Cancers 2022;14:3302. https://doi.org/10.3390/cancers14143302.

[15] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66. https://doi.org/10.1016/S0140-6736(18)32486-3.

[16] Roach PJ, Francis R, Emmett L, et al. The impact of ^{68}Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. J Nucl Med 2018;59:82–8. https://doi.org/10.2967/jnumed.117.197160.

[17] Lecouvet FE, Oprea-Lager DE, Liu Y, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. Lancet Oncol 2018;19:e534–45. https://doi.org/10.1016/S1470-2045(18)30571-0.

[18] Connor MJ, Smith A, Miah S, et al. Targeting oligometastasis with stereotactic ablative radiation therapy or surgery in metastatic hormone-sensitive prostate cancer: a systematic review of prospective clinical trials. Eur Urol Oncol 2020;3:582–93. https://doi.org/10.1016/j.euo.2020.07.004.

[19] O'Shaughnessy MJ, McBride SM, Vargas HA, et al. A pilot study of a multimodal treatment paradigm to accelerate drug evaluations in early-stage metastatic prostate cancer. Urology 2017;102:164–72. https://doi.org/10.1016/j.urology.2016.10.044.

[20] Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol 2020;6:650–9. https://doi.org/10.1001/jamaoncol.2020.0147.

Please cite this article as: A. Varatharajan, Timothée Olivier and V. Prasad, Prostate-specific Membrane Antigen Positron Emission Tomography in the Staging of Newly Diagnosed Prostate Cancer: Is More Sensitivity Always Better?, Eur Urol (2023), https://doi.org/10.1016/j.eururo.2023.01.024