

Re: ⁶⁸Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis

von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G

Eur Urol Focus 2018;4:686–93

Experts' summary:

The authors present a meta-analysis of the utility of positron emission tomography (PET)/computed tomography (CT) with Ga-labelled prostate-specific membrane antigen (PSMA) ligand in the initial staging and restaging of prostate cancer. In the staging studies, PET/CT detected PSMA-avid sites in 74% of patients, including 60% within the prostate, 4% in regional nodes, and 10% in multiple sites. Pooled sensitivity (based on histopathology) was 70% and pooled specificity was 84%. Pooled sensitivity for lymph node metastases was 61% and specificity was 97%. In the restaging studies, PET-avid sites were identified in 81% of patients; 10% in prostate bed, 22% in pelvic lymph nodes, 13% in distant organs, and 36% in multiple sites. 50% of patients with prostate-specific antigen (PSA) of 0.2–0.5 ng/ml, had a positive scan and 53% with a PSA of 0.5–1.0 ng/ml.

Experts' comments:

PSMA PET/CT can help in identification and localisation of the primary tumour and of early metastatic spread. As Ga-PSMA PET/CT surpasses all other imaging modalities to date, it will continue to challenge the way we currently approach management decisions. It has stimulated trials on the role of primary local therapy (either radiation or radical prostatectomy) for low-volume oligometastatic disease that can be excised or treated within a radiation field. In the restaging setting, Ga-PSMA PET/CT challenges the role of early salvage radiotherapy to the prostate bed, as it has now been proven that many recurrences lie outside the prostate bed field, and has already led to several trials examining the utility of metastasis-directed therapy. A recent study demonstrated that stereotactic radiotherapy to regional nodes and/or bony sites detected on PSMA PET/CT revealed no in-field recurrences, with minimal toxicity. However, only 31.9% of patients had durable PSA responses, suggesting that micrometastases smaller than the minimal resolution of PET/CT were present [1]. This was previously highlighted in a study by van Leeuwen et al. [2] in which PSMA PET/CT failed to detect any node <2 mm. Similar results have been

seen for salvage pelvic node dissection, with early recurrence noted in 25% of patients within 1 yr after surgery [3]. Prostate bed detection is problematic owing to the inability of PET/CT alone to detect small recurrences, compounded by overlying tracer activity in the bladder. It is therefore important to look at the role of magnetic resonance imaging to potentially supplement PSMA PET/CT in this setting. Lastly, ⁶⁸Ga-PSMA PET/CT continues to open promising avenues for therapeutics in end-stage castration-resistant prostate cancer using ¹⁷⁷Lu-PSMA radioligand therapy [4]. We are entering a new era of diagnostics that will only improve the precision of the treatment we deliver to our patients but we do need to recognise the limitations, namely that PET PSMA will not detect all lesions especially those of small size.

Conflicts of interest: The author has nothing to disclose.

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Re: Effect of Adding Docetaxel to Androgen-Deprivation Therapy in Patients with High-risk Prostate Cancer with Rising Prostate-specific Antigen Levels After Primary Local Therapy A Randomized Clinical Trial

Oudard S, Latorzeff I, Caty A, et al

JAMA Oncol. In press. <https://doi.org/10.1001/jamaoncol.2018.6607>

Experts' summary:

Oudard et al. conducted an open-label, multicentre, phase 3 trial comparing the effect of adding docetaxel to standard

androgen deprivation therapy (ADT) for patients with prostate-specific antigen (PSA) recurrence after primary local therapy and no radiographic sign of distant metastases who were considered to be at high risk of developing metastatic disease on the basis of Gleason score and PSA velocity. The primary endpoint was PSA progression-free survival (PFS). In total, 254 patients were enrolled between June 2003 and September 2007. After median follow-up of 30.0 mo, the authors found a median PSA-PFS of 19.3 mo for the ADT arm compared to 20.3 mo in the chemohormonal combination therapy arm (hazard ratio [HR] 0.85, 95%

confidence interval [CI] 0.62–1.16; $p=0.31$). For the secondary endpoints of radiographic PFS and overall survival (OS), median follow-up was 10.5 yr. Radiographic PFS was 9.0 yr for the ADT group versus 8.9 yr for the combination therapy arm (HR 1.03, 95% CI 0.74–1.43; $p=0.88$). Median OS was not reached in either arm. Consequently, the authors concluded that addition of docetaxel had no beneficial effect in this patient cohort and seems unwarranted in this population.

Experts' comments:

Do the results for this trial justify burying the idea of chemohormonal combination therapy for patients with nonmetastatic prostate cancer who experience PSA recurrence after primary therapy and are at high risk of developing metastases? The answer might be “Not quite yet”.

There has recently been a paradigm shift towards earlier administration of chemohormonal therapy, supported by results of several phase 3 trials, and secondary ADT using abiraterone acetate has seen a corresponding stage evolution [1]. In this setting, though, the notion that patients with low-volume disease might benefit to a lesser extent has been challenged by recently published data from the STAMPEDE trial [2]. To further complicate the matter, the recently published SPARTAN, PROSPER, and ARAMIS trials showed significant metastasis-free survival benefits for patients with nonmetastatic castration-resistant prostate cancer receiving secondary ADT [3–5].

Why do these results differ in patients with apparent low-volume disease? It has been postulated that the answer might be the androgen environment rather than the disease volume [6]. This notion is based on the hypothesis that castration resistance driven by molecular androgen receptor modifications increases the net survival benefit of addition of docetaxel. In patients with hormone-sensitive disease, by contrast, this beneficial effect might be less prevalent. Furthermore, some methodological limitations of the trial have to be addressed. First, it is a relatively small study with only 79 versus 81 events for the primary PSA-PFS endpoint in the two arms, despite median follow-up of more than 10 yr. The authors acknowledge that the OS data are still immature. Patients had to fulfill only one of the predefined risk factors to be eligible for enrollment, resulting in a more favorable risk distribution compared to PROSPER, SPARTAN, and ARAMIS. Since enrolment was performed between 2003 and 2007, the results must be extrapolated with caution in the contemporary era, in particular because of the increasing use of more sensitive imaging. However, it still has to be shown how greater imaging sensitivity (and hence greater diagnosis of occult metastases) translates into better survival for patients with advanced prostate cancer. Lastly, the issue of biochemical recurrence following local treatment has to

be addressed. It has been shown that a minority of patients with biochemical recurrence progress towards systemic disease; consequently, only adequately powered large studies will be able to shed light in this challenging field of advanced prostate cancer [7].

Despite the issues addressed, the results presented by Oudard et al. provide important insights into the therapeutic approach for high-risk hormone-sensitive disease in patients with no evidence of distant metastases. Although it seems that there is no survival benefit for the general population, improvements in risk stratification and biomarker development are needed to identify the subgroups with aggressive disease that might benefit from early systemic therapy.

Conflicts of interest: The authors have nothing to disclose.

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