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Proposal of Systemic Therapy Response Assessment Criteria in time of PSMA PET/CT imaging: PSMA PET Progression (PPP)

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Running head: PPP: defining PSMA PET Progression
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Abstract:

Around 20% of men with prostate cancer develop metastatic disease during the course of their disease. Accordingly, discovering and developing new potent treatment strategies for metastatic prostate cancer patients has been a major research focus of the last decades. Identifying disease progression, especially within clinical trials, is essential in determining drug effectiveness.
One major remaining question is how to best define disease progression. The Prostate Cancer Clinical Trials Working Group (PCWG) Criteria include clinical and laboratory parameters, as well as conventional imaging modalities such as MRI, CT and bone scan findings but advanced molecular imaging techniques, especially PSMA PET findings are not considered. This is a problem as PSMA PET is not only used for detecting biochemical recurrence but also for restaging at various disease stages and as intermediate endpoint biomarker in ongoing clinical trials. Therefore, response criteria and PSMA PET progression criteria need to be established with some urgency.
The intent of this manuscript is therefore to define prostate cancer progression by PSMA PET criteria. Our PPP (PSMA PET progression) proposal is based on the same principles that were applied for the PCGW2 criteria but adds value by including PSMA PET criteria.

PPP defines PSMA treatment response in 3 different criteria: 1) Appearance of 2 or more new PSMA positive distant lesions, 2) Appearance of 1 new PSMA positive lesion plus consistent clinical and/or laboratory data and recommended confirmation by biopsy or correlative imaging within 3 months of PSMA PET, and 3) Increase in size or PSMA uptake of 1 or more existing lesions by 30% plus consistent clinical and/or laboratory data and/or confirmation by biopsy or correlative imaging within 3 months of PSMA PET.

INTRODUCTION

Prostate cancer is the second most frequent cancer in men and approximately 20% of patients will eventually succumb to metastatic disease. Accordingly, discovering and developing new potent treatment strategies for metastatic prostate cancer patients has been a major research focus of the last decades. To differentiate between responding and non-responding patients, especially within clinical trials, is absolutely essential in determining drug effectiveness. The key challenge is to establish robust criteria for disease progression.

RECIST has long been the mainstay of assessing treatment response in clinical trials involving metastatic prostate cancer patients. This changed in 2008 when Scher et al. introduced the Prostate Cancer Clinical Trials Working Group (PCWG) Criteria (*1*) that additionally included bone scan findings into the response criteria. The most recent PCWG update, published in 2016, remained in essence unchanged (*2*). PSMA PET has still not been incorporated.

PET imaging targeting the prostate specific membrane antigen (PSMA) has a major impact on prostate cancer staging and management (*3,4*). It is now widely available in many countries, and has been incorporated into major clinical guidelines (EAU and NCCN since 2017), especially for the evaluation of biochemical recurrence. Criteria defining a positive PSMA PET (*5*-*8*) have been proposed. However, disease progression by PSMA PET has not been defined.

There is a need for well-defined progression criteria as patients, their families and physicians request unequivocal diagnostic information when undergoing PSMA PET studies. Moreover, drug companies are starting to integrate PSMA imaging into clinical trials and thus require firm definitions of progressive disease. The intent of this manuscript is therefore to define prostate cancer progression by PSMA PET. The PPP (PSMA PET progression) proposal defines treatment responses by PSMA PET criteria taking into account the same principles that were applied for the PCGW2 criteria. The authors propose a strategy to validate which is considered as a starting point for further discussion, and has to be updated along with future published data.

PROPOSAL

Progressive metastatic prostate cancer is usually defined by appearance of new lesions or growth of existing lesions. Location of new lesions, local vs distant, may add prognostic relevance. Whereas the appearance of new lesions is rather easy to assess, an increase in size or tracer uptake of existing lesions is more challenging. Regarding the definition of local and distant PPP focuses on its clinical impact aggregating progression within the prostate, prostate bed, local recurrence and pelvic lymph node progression as local.

PPP takes into account appearance of new lesions, their location, their size and intensity of tracer uptake to arrive at simple, robust and reproducible criteria for disease progression in metastatic prostate cancer patients. PPP builds on criteria established by PCWG2 that defined bone progression as appearance of at least 2 new lesions on radionuclide bone scan. However, it also required 2 or more additional new lesions identified on a confirmatory scan within at least 6-9 weeks resulting in the term “2+2 rule.” This delay in time to differentiate between flare and true progression may not be needed with PET imaging.

Two new distant lesions are required for definition of disease progression (Fig. 1). This approach was chosen to reduce the risk of false positives including flare phenomena. However, as flare phenomena are comparatively uncommon for PSMA PET and false positive findings rarely occur in pairs, the proposed PPP concept does not require a confirmatory scan (*9*). In case of multiple lesions with discordant behaviour, i.e. in a patient with some lesions responding by size or uptake or even disappearing while others are newly appearing, the same criteria apply. Therefore emergence of 2 new distant lesions independent of discordant treatment response behaviour of existing lesions meets the criteria of progression (Figs. 2 and 3).

Appearance of only 1 new lesion is not sufficient for progression according to PCGW2, which is justified by the poor specificity of bone scanning (Fig. 4). In contrast, because of its high specificity, 1 new distant lesion by PSMA PET is considered progressive disease by PPP (Fig. 3), if the following criteria are met: consistent clincial and/or laboratory data including PSA and other parameters such as pain assessments, LDH, anemia among others. Lesion validation by either biopsy or correlative imaging within 3 months of PSMA PET (by BS, MRI or CT) is recommended but not required. In fact, false positives are highly unlikely, as the known causes are usually easily identified by cross-sectional imaging.

Defining progression in absence of new lesions by mere growth of an existing lesion remains challenging. Despite their limitations morphologic RECIST criteria (*10*) are quite reliable for response assessments. Similary, PERCIST (*6*) and EORTC (*11*) for FDG PET imaging are robust response criteria using defined changes in lesion SUV. However, as semi-quantitative values are not established for PSMA PET these response approaches cannot be directly translated into PSMA PET imaging (*12*). PPP aims to reliably identify disease progression while avoiding false positives. Therefore, progression without new lesions is defined by increases in size or tracer uptake by ≥ 30%. Findings should be confirmed by either biopsy or correlative imaging within 3 months of PSMA PET. The cut-off of 30% is arbitrarily used and requires confirmation or adaptation in future prospective studies.

In summary, PPP defines PSMA PET derived progression definition in 3 particular constellations:

- Appearance of 2 or more new PSMA positive distant lesions
- Appearance of 1 new PSMA positive lesion plus consistent clinical and/or laboratory data and recommended confirmation by biopsy or correlative imaging within 3 months of PSMA PET
- Increase ≥30% in size or uptake plus consistent clinical and/or laboratory data and confirmation by biopsy or correlative imaging within 3 months of PSMA PET

DISTANT VS LOCAL PROGRESSION

For the purpose of clinical trials, but also for the management of patients, it is important to distinguish between distant versus local progression. Metastasis free survival has been demonstrated to correlate with survival in men with localized disease(*13*). While the appearance of at least 1 new distant lesion is indicative of distant progression, the definition and clinical impact of local progression is less straight forward and requires additional considerations.

Isolated local progression is quite uncommon, as most PSMA scans after treatment are carried out in patients already submitted to local treatment such as radical prostatectomy, definite or salvage

radiation therapy or non-conventional primary therapies. However the event may occur, and it could include progression in the prostate, prostate bed/local recurrence (therefore growth of existing lesion) or in local (pelvic) lymph nodes alone without any distant progression (therefore a new local lesion). Both situations are rare in our experience, but nonetheless it could occur and can be encomprised in the previously detailed definition. However it would be important to specify that the progression is only local: whether local progression might be locally treated without requiring discontinuation of an otherwise successful therapy is a matter of debate.

SPECIAL CONSIDERATIONS ABOUT DIFFERENT THERAPIES

The proposed criteria can be applied for response assessments after any therapy including loco-regional and systemic treatments. Appropriate timing could be relevant, as is the case for FDG PET based treatment response assessments. For instance, intervals of 4 weeks and 8 weeks are recommended for response assessments after chemotherapy and radiation therapy, respectively. Even longer intervals may be required after surgery. The proposed time intervals are frequently applied in the clinical routine despite the lack of prospective data; indeed intervals required for reliable response monitoring using PSMA PET imaging are unknown.

As shown in animal experimental and human studies ADT can result in PSMA overexpression which may lead to false positive findings (*14*). Alternatively, it may increase the number of true positive findings (*15*). In most studies, the impact of ADT and AR-targeted therapies on PSMA expression is more relevant early after start of treatment (*16*). Therefore, PSMA-PET ADT response assessments should probably be done earliest at 4-8 weeks after start of treatment. Limited reports are available regarding the use of PSMA PET to evaluate RLT responses (for instance with 177Lu-PSMA-617). Preliminary data suggests that PPP could be applicable also in this setting (*17*).

CONFIRMATORY TRIAL

The PPP proposal is not evidence based but rather an initial motivational push to arrive at a structured response assessment. Thus, the current proposal can only be a starting point for a validation study that will hopefully arrive at robust response and progression criteria. We therefore propose an international data repository that includes all prospective treatment trials in metastatic prostate cancer that use PSMA-PET assessments. These data can then be used to determine the PPP performance validated against histopathology or correlative imaging within 3 months of PSMA PET. A correlation between PPP assessments and survival is of interest but might be of limited value due to the bias of many consecutive treatments.

DISCUSSION

Morphological response criteria such as RECIST have been the backbone of treatment response assessment in metastatic prostate cancer. This changed with the introduction of PCWG2, which based progression mainly on bone scan findings. The appearance of two or more new lesions which in case of ambiguity had to be confirmed by other imaging modalities or additional two new lesions were required for progression. PCWG 2 recommended bone scans and conventional imaging (CT or MRI)

in addition to blood work and symptom assessment (both every cycle) in 12 week intervals. The PCWG update, published in 2016, did not significantly change the image-based definition of disease progression (*2*). PCWG criteria proved to be reliable endpoints and prognostic and for OS and rPFS within clinical drug development trials (*18,19*).

With the introduction of ligands targeting the PSMA (*20*) PET has changed prostate cancer imaging. Within only five years PSMA imaging is now ubiquitously available and under consideration for FDA approval. It also has been incorporated into major clinical guidelines for detection of biochemical recurrence at very low serum PSA levels (EAU guidelines). The confirmed high positive predictive value (*21*) and higher sensitivity for disease detection (*4*) also suggest superiority for assessing disease progression. However, the available data preclude the establishment of evidence-based PSMA PET progression criteria. There is a need for well-defined progression criteria as patients, their families and physicians request unequivocal diagnostic information when undergoing PSMA PET studies. Moreover, drug-companies are integrating PSMA imaging into clinical trials and thus require firm definitions of progressive disease.

Here we propose a pathway to addressing this need by developing PSMA PET Progression (PPP) criteria based on PCWG2 criteria (Table 1). We also propose a strategy to validate or adjust the criteria by creating a repository that would include data from any prospective clinical trials that use PSMA imaging for response assessments. Finally, PPP will also attempt to derive prognostic information in patients with progressive disease as it distinguishes between distant and local progression.

Identification of disease progression is essential in clinical practice and trials to determine the effectiveness of an established or new therapy. The overarching goal of therapies is improved patient outcome. PPP focuses on distant disease, which may add granularity to prognostication. PSMA PET progression criteria may be more sensitive than the established PCWG criteria as progression is assessed earlier. The authors are aware that high specificity is equally important as false positives may result in overtreatment. We attempted to address this issue by requiring histopathology and image verification in patients with only one new distant lesion or growing lesions on PSMA scans.

As PSMA PET is signficantly more sensitive but also more specific than bone scan the single presentation of two new lesions is sufficient for progression. False positive PSMA findings are much less frequent that false positive bone scan findings (*9*). Moreover, they rarely appear in two locations at the same time. PPP also considers a single new distant lesion as progression, if the finding is consistent with the clinical presentation. This is justified as PSMA imaging is highly sensitive and specific and lesion verification by biopsy or conventional imaging or laboratory findings is required. According to PPP an increase in size and PSMA uptake greater 30% is also coupled with disease progresion. Reproducibility studies for PSMA PET have suggested that such changes are beyond the expected reproducibility/repeatability variance.

Thus far, PSMA PET has been validated in patients with biochemical recurrence and in the setting of restaging (*21*). In contrast, its role for disease staging and therapy response monitoring is unknown. It may be argued that using PET for evaluating clinical outcomes in advanced prostate cancer may not be cost-effective. However effective patient care and efficient drug development require accurate tools to assess treatment effects. For metastatic prostate cancer, response biomarkers have historically been poorly reproducible, inaccurate, inconsistently applied, or only loosely associated with tangible clinical benefits such as survival (*22*). Furthermore, available treatments are

quite expensive and reliable intermediate endpoint biomarkers are needed to identify non-responders early after start of therapy. Also in patients undergoing ADT PSMA PET imaging might be helpful.

Studies assessing the role of different PSMA PET response criteria are lacking. A recent paper by Gupta (*12*) compared several criteria (RECIST, PERCIST, EORTC, and MDA) for assessing treatment response with ^{68}Ga-PSMA PET-CT in metastatic prostate cancer patients with biochemical progression, and concluded that molecular criteria performed better than morphological parameters. This is expected as functional approaches provide earlier response information than anatomical imaging methods. The PPP criteria we are proposing are exquisitely functional, and may provide early information on therapy response, which is clinically highly relevant.

The authors are aware that PPP is only the beginning of standardized PSMA driven response assessment in metastatic prostate cancer patients. For the future evolution of PPP a number of determinants have to be closely monitored including the variety and combination of therapies and consecutively different impact on the PSMA signal (*23-25*), the so far arbitrarily chosen discriminator of 30% SUV reduction disregarding volume-parameters, the still not fully understood influence of androgen-receptor targeting therapies on the PSMA expression (*26*), as well as the possibility that another complementary metabolic tracer such as FDG will be needed. However, we believe this is an excellent starting point and warrants further evaluation, testing and discussion.

Disclosure Statement

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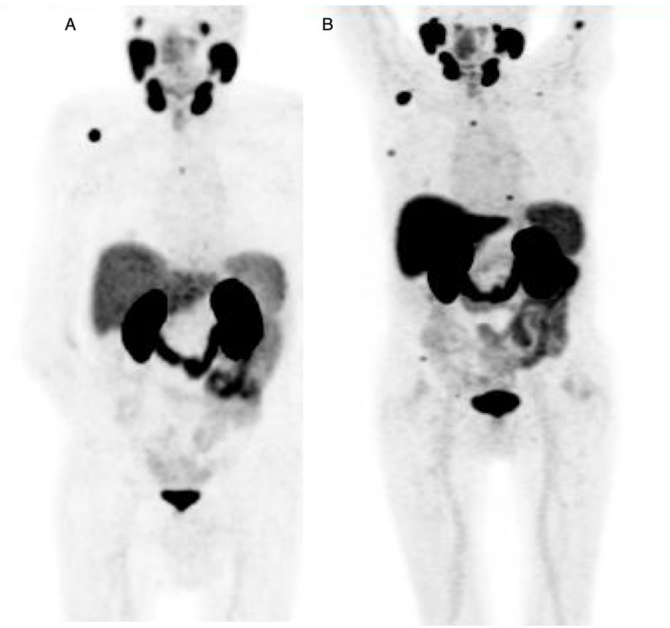

Figure 1 – PPP for appearance of more than 2 new distant lesions. 77 years old patient, s/p radical prostatectomy (pT3bpN0 Mx, Gleason Score 4+4, iPSA=11 ng/mL). Consecutive treatment with ADT. At presentation of BCR baseline PSMA PET (A) showing some PSMA avid lesions. After additional treatment (B) the scan reveals several new lesions (arrows). According to PPP more than two new PSMA avid lesions and accordingly progression.

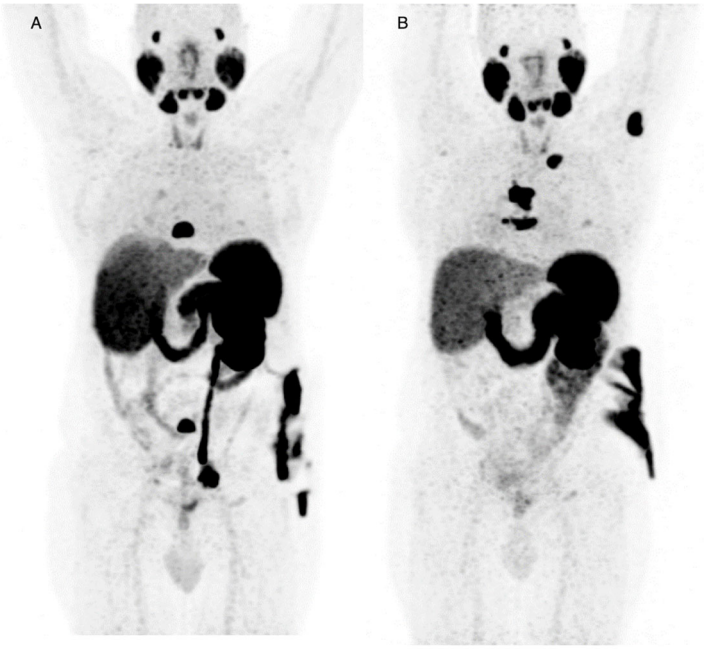

Figure 2 – PPP for appearance of more than 2 new distant lesions, with other lesion disappearing. 63 years old male with history of previous nephrectomy due to clear cell renal cell carcinoma; in 2011 radical prostatectomy (pT3bpN0 Mx, Gleason Score 4+5, iPSA=11 ng/mL), plus adjuvant EBRT; in 2016 biochemical recurrence, treated with ADT, castration resistance in 2018, with evidence of PSMA positive bone lesions at dorsal and lumbar spine (A). After EBRT to these lesions, almost complete disappearance of the previously evident lesions, but appearance of other new lesions (B). As more than 2 new PSMA positive lesions progression according to PPP.

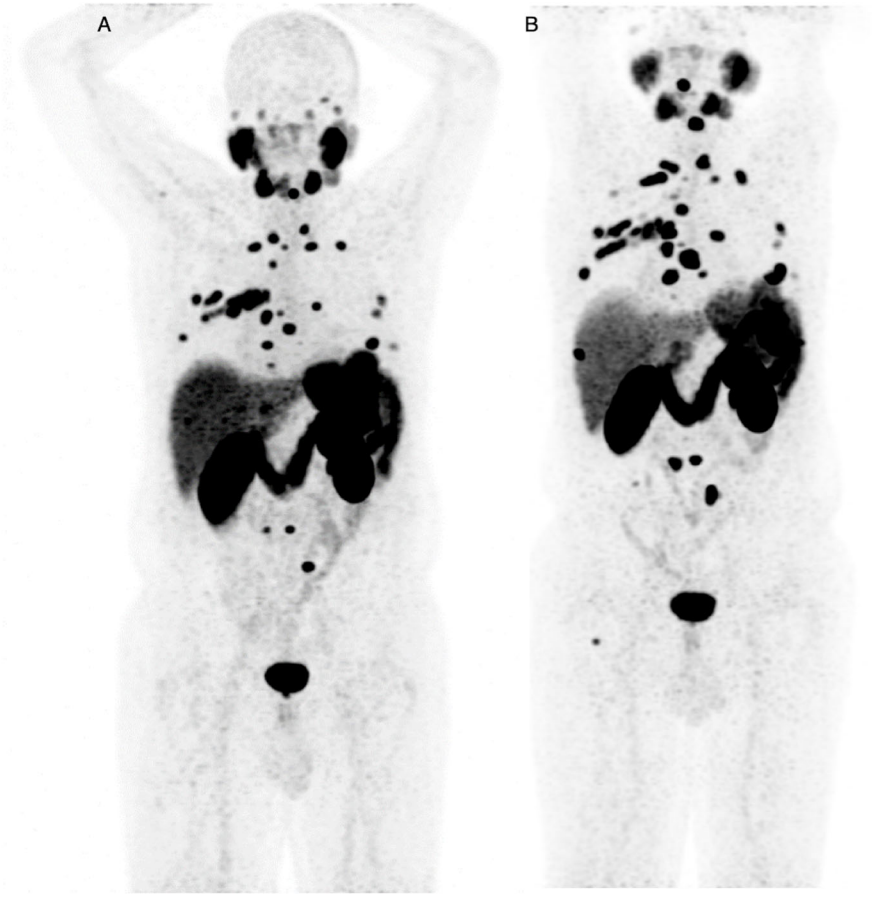

Figure 3 – PPP for appearance of more than 2 new distant lesions. 70 years old patient who had a radical prostatectomy (Gleason Score 5+4, iPSA=7 ng/mL) plus adjuvant EBRT in 2009. In 2013 biochemical recurrence, treated with lymphadenectomy + ADT, castration resistance in 2017, with evidence of multiple bone lesions at PSMA PET (A). After enzalutamide, persistence of the previously evident lesions, with appearance of few new lesions (B) fulfilling the criteria of progression according to PPP.

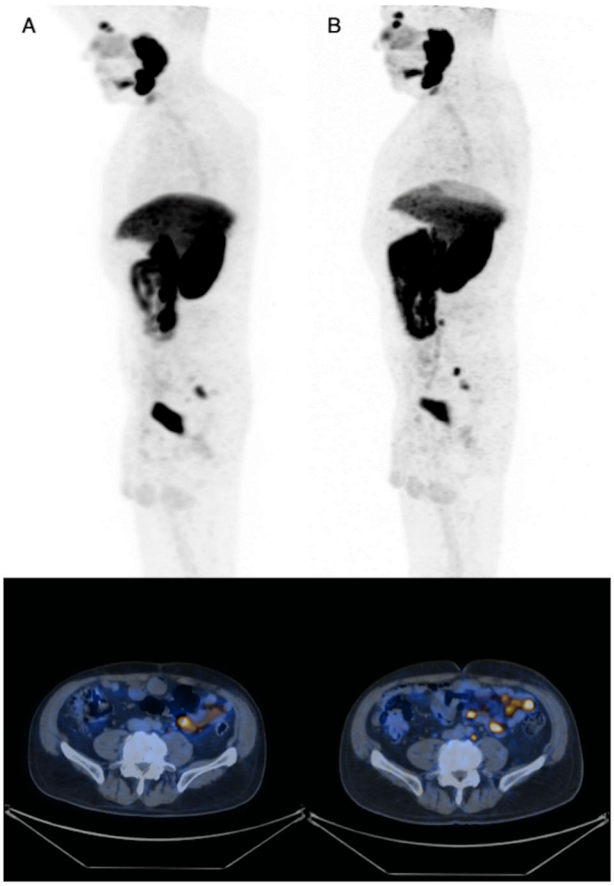

Figure 4 – PPP for appearance of only 1 new distant lesion. 67 years old male with history of prostate cancer. S/p radical prostatectomy and adjuvant EBRT in 2003. In 2015 biochemical recurrence, treated with salvage lymphadenectomy and ADT, further increase of PSA with evidence of one nodal lesion at PSMA PET (A). At follow up appearance of a only one new nodal lesion (B). According to PPP in case of only 1 new lesion progression is only confirmed if there is consistent clinical and/or laboratory data and confirmation by biopsy or correlative imaging within 3 months of PSMA PET.

Table 1 – Summary of PSMA PET Progression (PPP) Criteria

Progression Criteria	Explanation
2 or more new PSMA positive lesions	**Appearance of 2 or more new PSMA positive distant lesions**
1 new PSMA positive lesion	**Appearance of 1 new PSMA positive lesion plus consistent clinical and/or laboratory data and recommended confirmation by biopsy or correlative imaging within 3 months of PSMA PET**
No new lesions but size increase	**Increase ≥30% in size or uptake plus consistent clinical and/or laboratory data and confirmation by biopsy or correlative imaging within 3 months of PSMA PET**