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# The VISION Forward: Recognition and Implication of PSMA-/FDG+ mCRPC

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## ABSTRACT

Metastatic castration resistant prostate cancer (mCRPC) is incurable. The expression of the transmembrane protein prostate specific membrane antigen (PSMA) is markedly increased in most mCRPC lesions. PSMA has been recognized as a viable biological target for imaging and radionuclide therapy (theranostics) in mCRPC. The positron emission tomography (PET) agents 68Ga-PSMA-11 and 18F-DCFPyL have recently been approved for imaging evaluation of patients with suspected metastasis who are candidates for initial definitive therapy and patients with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. Radioligand therapy (RLT) with 177Lu-PSMA-617 is anticipated to be approved relatively soon based on the favorable results of the VISION trial. It has been recognized that PET imaging of PSMA expression and glucose metabolism (with 18F-fluorodeoxyglucose) provides a more comprehensive assessment of the tumor burden and heterogeneity. However, there are many unresolved issues that surround whether or not imaging with $^{18}$F-fluoroodexyglucose PET is advantageous in the clinical setting of PSMA RLT in mCRPR.

## INTRODUCTION

The recently published VISION trial grounded on targeting the prostate specific membrane antigen (PSMA) is a momentous milestone for nuclear medicine adding to the drive that has been generated over the past decade in the growth of theranostics and radiopharmaceutical therapy in cancer management. While metastatic castration-resistant prostate cancer (mCRPC) remains incurable despite significant strides in the development of various drug regimens, PSMA-based radioligand therapy (RLT) provides an additional viable option for prolonging life. According to the definition and spirit of theranostics, it is self-evident that the imaging component is an essential partner for assessing the presence, extent, and intensity of the target expression prior to commencing the therapy companion in the anticipation of favorable response and acceptable biological and financial toxicities. It is therefore curious to note that the essential step of PSMA imaging in the theranostics process has been a topic of debate (1, 2). However, in this discussion, my focus is on whether or not imaging with $^{18}$F-fluoroodexyglucose (FDG) is needed or desired in the clinical setting of PSMA radioligand therapy (RLT).

## PIVOTAL RELEVANCE OF TUMOR HETEROGENEITY

It is recognized that there is remarkable molecular heterogeneity between neoplastic cells in an individual tumor mass, between primary tumor and its metastases, and among the metastases, although it appears that intra-individual genomic diversity is more limited than inter-individual genomic diversity (3). The multi-feature heterogeneity of mCRPC renders its potential cure exceptionally challenging. It is posited that only when the reality of biological heterogeneity is taken into full consideration, then there may be opportunities for early suitable therapeutic maneuverers to prolong life substantially, preferably with the least compromise on life quality. We have already encountered the heterogeneity concept in nuclear medicine. An example clinical setting includes patients with metastatic thyroid cancer and negative radioiodine scan but positive FDG PET/CT scan. Another similar setting involves patients with neuroendocrine tumors who harbor metastases with discordant somatostatin expression and glucose metabolism. Accordingly, discordance of PSMA expression and FDG uptake is not unanticipated in mCRPC.

In a recent prospective investigation of a cohort of men with metastatic prostate cancer, there was only 22% concordance between $^{18}$F-DCFPyL and FDG revealing substantial tumor heterogeneity (4). In another study of men with mCRPC undergoing $^{177}$Lu-PSMA-617 RLT, at least one mismatch PSMA-/FDG+ metastasis was noted in 59% of patients and this mismatch was associated with significantly shorter overall survival compared to those patients without mismatch lesions (3.3 mo. vs. 6 mo., p=0.008) (5). Similar finding was reported in an investigation of 54 men with mCRPC who underwent PSMA PET/CT and FDG PET/CT at baseline before $^{177}$Lu-PSMA-617 RLT. Patients with at least one PSMA-/FDG+ metastasis at baseline had significantly lower median overall survival compared to those without mismatch lesions (6.0 mo. vs. 16.0 mo., p<0.001) (6). The Australian investigators noted that in patients who were

excluded from the $^{177}$Lu-PSMA-617 RLT clinical trial based on metastases with low PSMA expression and high FDG uptake, the outcome was poor with short median survival of only 2.5 mo. even if the patients received additional systemic treatments (7). New discordant PSMA-/FDG+ lesions can also develop during $^{177}$Lu-PSMA-617. Hartrampf et al noted that after only 2 cycles of PSMA RLT, new PSMA-/FDG+ metastases developed in 13% of their patients (8). The authors paid particular attention to the newly appearing liver metastases. Liver metastases from prostate cancer are not uncommon, being the second most common site (along with lung) after bone with clinically evident macro-metastatic incidence of up to 25% and association with worst prognosis despite therapy (9, 10). Most liver metastases (~80%) are PSMA-avid and amenable to PSMA RLT (11). The lack of sufficient PSMA uptake may be either due to low PSMA expression (e.g., genomic dedifferentiation) or reduced target to background ratio in relation to high physiological hepatic of the radiotracer (e.g., $^{18}$F-PSMA-1007). In the Hartrampf et al's investigation, the few PSMA- liver metastases were all FDG+. Except one case, these lesions were also identified on contrast-enhanced CT. These observations imply that aside from effects of the type of PSMA radiotracer that is employed and the available ancillary anatomic imaging information in identifying metastatic lesions, the change in tumor biology early in the PSMA RLT, probably through clonal selection with transdifferentiation from an epithelial phenotype to the more aggressive neuroendocrine phenotype, may affect efficacy of the subsequent RLT cycles and the overall impact on patient outcome (12).

## WHAT PREDICTS DISCORDANT PSMA-/FDG+ METASTATIC DISEASE?

Chen et al noted at least one PSMA-/FDG+ lesion in 23.2% of their patients with mCRPC who underwent both $^{68}$Ga-PSMA-11 PET/CT and FDG PET/CT. Multivariate regression analysis revealed that dichotomized thresholding of Gleason score (GS) at 8 and serum prostate specific antigen (PSA) level at 7.9 ng/mL could predict PSMA-/FDG+ mismatch lesions with no mismatch lesions at GS and PSA levels below the threshold levels, 21.7% mismatch with GS<8 but PSA$\geq$7.9 ng/mL and as high as 61.5% mismatch metastases when both GS and serum PSA level were above the threshold values (13). Interestingly, in the M0 CRPC clinical setting, Wang and colleagues reported that a high Gleason grade group was associated significantly with PSMA-/FDG+ disease. Moreover, they noted that castrate-sensitive metastatic disease (mCSPC) was rarely associated with PSMA-/FDG+ lesions (14).

Blood parameters (liquid biopsy) may also be helpful as simple predictors of mismatch lesions. Rosar and colleagues observed that serum neuron-specific enolase (a cytoplasmic enzyme and a marker for tumors of neuroendocrine origin) concentration was significantly and positively associated with FDG-avid and low PSMA expressing metastases in patients with mCRPC (15). A recent systematic review reported that serum NSE correlates with prognosis in patients with progressive mCRPC (16). The LuPSMA trial investigators assessed for prognostic biomarkers that included blood parameters (ALP, LDH), and imaging (whole-body segmented and quantified tumor volume on PET and EXINI index for bone scan). For FDG PET/CT, lesions were considered if they displayed standardized uptake values greater than mean hepatic

parenchyma uptake plus 2 standard deviations. For PSMA PET/CT, any lesion with standardized uptake value above 3 was considered. The hazard ratios of prognostic biomarkers for overall survival were 2.6, 2.3, 1.2, 1.1, and 0.89 for FDG+ tumor volume, bone scan index, LDH, ALP, and mean intensity of PSMA-avid tumor uptake, respectively (17). The FDG+ tumor volume was the most informative prognostic biomarker.

## HOW IS A LESION CHARACTERIZED AS PSMA- AND FDG+?

The definition of PSMA positivity and FDG negativity is not standardized. The phase 2 LuPSMA trial defined PSMA positivity when the lesion uptake level as measured by maximum standardized uptake value (SUVmax) was at least 1.5 times greater than liver SUV. Patients with any FDG+ disease and corresponding PSMA uptake lower than the selected positivity definition were excluded (18). With these dual imaging criteria, 16% of the patients were excluded. In phase 2 TheraP trial, PSMA positivity was defined as SUVmax of at least 20 at a disease site and greater than 10 at all other measurable sites of metastatic disease. Patients were excluded if there were any PSMA-/FDG+ metastases (10% for PSMA- metastases, 18% for FDG+ metastases) (19). Despite differing PSMA positivity definitions in the 2 trials, these maneuvers preselected patients with relatively high PSMA expressing metastases which enriched the potential for favorable outcome in patients undergoing $^{177}$Lu-PSMA-617 RLT in these 2 clinical trials (PSA reduction of 50% or more from baseline or PSA50 in 57% and 66% of patients for LuPSMA and TheraP, respectively). The strategy was successful and supported additional clinical trials including the recently published pivotal randomized open-label phase 3 VISION trial comparing standard care plus $^{177}$Lu-PSMA-617 to standard care alone (20).

In the VISION trial, only $^{68}$Ga-PSMA-11 PET/CT was performed with the eligibility criteria that the patients harbor at least one PSMA+ metastatic lesion (defined as uptake greater than that of liver parenchyma in lesion of any size in any organ system) and no PSMA- lesions (defined as uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any solid organ lesion with a short axis of at least 1.0 cm, or in any bone lesion with a soft-tissue component of at least 1.0 cm in the short axis). With these imaging selection criteria, 12.6% of patients were excluded after PSMA PET/CT imaging. FDG PET/CT was not performed. Outcome of PSA50 was noted in 46% of patients. The lower PSA50 in VISION trial in comparison to those reported in the LuPSMA and TheraP trials may be in part due to the differing imaging-based patient eligibility criteria among the trials. It is probable that at least some patients who were eligible for VISION trial would have been excluded from LuPSMA and TheraP trials. It is interesting to concoct how the results of the VISION trial would have been impacted if the patient eligibility criteria included FDG PET/CT similar to LuPSMA and TheraP trials. However, in broader term, it remains to be determined if patients with low PSMA expression and discordant FDG+ lesions should be excluded from PSMA RLT (6).

## PROS AND CONS OF FDG PET/CT INCLUSION IN PSMA RLT

Imaging evaluation of mCRPC with both FDG and a PSMA radiotracer will provide a more comprehensive assessment of the tumor burden. However, how the levels of PSMA expression and FDG discordance should impact PSMA RLT management decisions remain an open debate and will need further investigation. It is reasonable to anticipate that patients with tumors that display moderate PSMA expression, but with FDG discordance may be candidates for combination therapy (PSMA RLT plus chemotherapy, immunotherapy, and/or ADT in patients with polymetastatic disease or PSMA RLT plus stereotactic body radiation therapy with or without ADT in patients with oligometastatic disease). Interim FDG PET/CT scanning during a course of PSMA RLT may also provide important information on any evolutionary biological changes of the tumor sites which may facilitate the tailoring of the subsequent RLT cycles (in terms of timing and dosage) with or without inclusion of other therapies. Clinical trials may be envisioned to address these matters. In this regard, a standardized method to quantify PSMA PET/CT and FDG PET/CT scans would be helpful to simplify image analysis and interpretation. A six-tier image scoring system referred to as Pro-PET score has been proposed, although there has been no external validation (21). There are also proposed semi-automated algorithms that can facilitate quantification of total tumor burden on either PSMA PET/CT or FDG PET/CT (22-24).

While there are rational motives to include FDG PET/CT in PSMA RLT, it renders the entire process more complex from multiple points of view. The scans will likely be performed on 2 separate days which may be inconvenient to patients. The imaging components of the theranostics will need to be interpreted in combination and results provided in a simple standardized format that can inform clinical decision-making. While FDG PET/CT is covered by the Center for Medicare and Medicaid Services (CMS) under “subsequent treatment strategy” category for prostate cancer, the coverage for PSMA PET/CT has yet to be instituted. It is also unclear if CMS or insurance agencies would be amenable to pay for 2 PET/CT scans in close temporal proximity to each other for the same indication if the outcome benefit for such diagnostic imaging strategy is unestablished. Notwithstanding, the overall cost of imaging will increase, and cost-utility studies will be needed to decipher whether higher cost and incorporation of combined FDG PET/CT and PSMA PET/CT results improve patient management and outcome. Aside from the important issues of cost and logistics, and as alluded to above, many questions arise that remain unanswered at this time. It is unclear what treatment strategy may be best to treat patients with PSMA-/FDG+ disease (however this condition ends up being defined) and if these patients should be excluded from PSMA RLT or if some patients may be included as potential candidates for the therapy if PSMA expression can be primed with intervention (e.g., properly timed and dosed ADT) (Fig. 1).

## POTENTIAL STRATEGY FOR FUTURE

The current evidence suggests that at least in the clinical trial settings, incorporation of both PSMA PET/CT and FDG PET/CT can be informative and potentially impactful. Post-hoc analysis of the pertinent data collected from completed clinical trials can also be contributory. Inclusion of various clinical features such as GS, PSA and its kinetics, prior therapies, and relevant blood indicators may also provide the important stratification parameters for justifying the inclusion or exclusion of FDG PET/CT imaging in the clinical setting of PSMA RLT.

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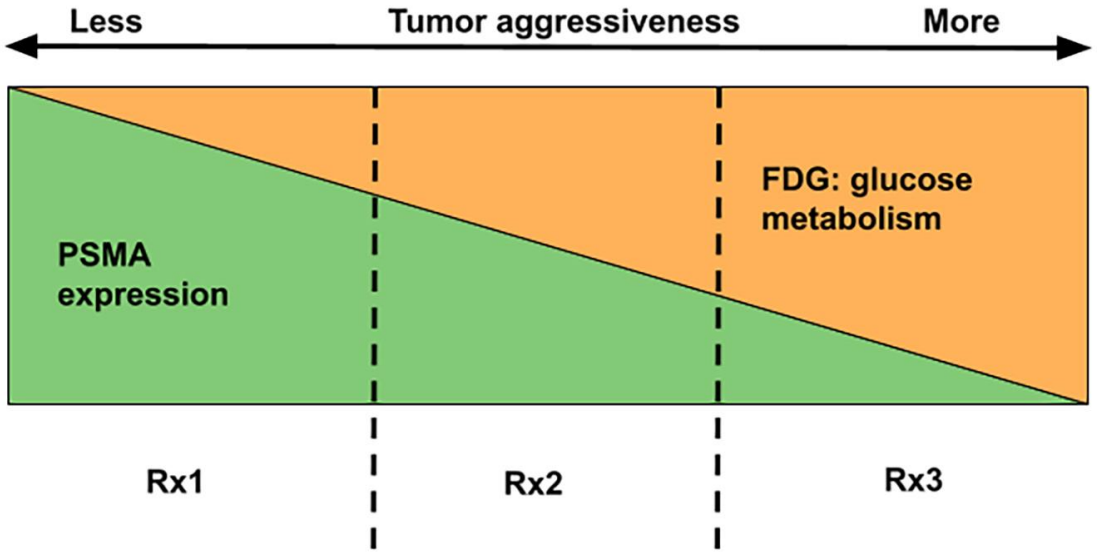


**Fig. 1.** Simplified schematic of the spectrum of PSMA and FDG uptake in mCRPC lesions. Tumor aggressiveness generally increases from left to right, although there can be aggressive tumors without marked hypermetabolism (e.g., neuroendocrine phenotype). The prognosis is also poorer as tumor aggressiveness increases. The vertical dashed lines designate yet to be defined borders of PSMA and FDG avidity of the total tumor burden which may lead to different therapy strategies, RX1: in tumors with mainly PSMA+ disease, PSMA RLT may be the primary choice of therapy, RX2: in tumors with mixed PSMA and FDG avidity, combination therapy (PSMA RLT, chemotherapy, immunotherapy, ADT) may be considered, RX3: in tumors with low or no PSMA expression and discordant FDG+ disease, non-RLT therapy may be the mainstay strategy, although interventions may be instituted to shift the tumor phenotype to the left for enabling additional therapeutic approaches that may include PSMA RLT.