Journal of Nuclear Medicine, published on July 16, 2021 as doi:10.2967/jnumed.121.262737

PSMA theranostics – is the time ripe to pave the way to further tumor entities?

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Running head: Editorial PSMA

Key words: PSMA, PET, therapy, glioblastoma multiforme

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Word count: 1855 words (including text and references, excluding title, authors name and affiliation)

Success of precision oncology is based on increasingly better and individualized tumor characterization. State of the art personalized treatment options are still primarily directed by site of tumor origin and tumor entity rather than by the tumor molecular signature as is the case with the novel treatment approach with neurotrophic tyrosine receptor kinase (NTRK) inhibitors in case of NTRK gene fusion positive tumors, irrespective of their origin. Molecular imaging using metabolic tracers and radiolabeled peptides and antibodies offer a unique possibility for non-invasive in-vivo tumor characterization, also based on molecular paradigms rather than tumor type. One such radiopharmaceutical, the prostate-specific membrane antigen (PSMA) is currently set to become a blockbuster for both PET diagnostics and radionuclide therapy in prostate cancer. Germany, specifically the University of Heidelberg team, has pioneered the rejuvenation of PSMA and its use in nuclear medicine. The evidence level from initial retrospective German studies was substantiated by subsequent prospective clinical trials in Australia.

The proPSMA diagnostic trial reported that “PSMA PET/CT is a suitable replacement for conventional imaging, providing superior accuracy to the combined findings of CT and bone scanning” in treatment-naïve patients with high-risk prostate cancer with respect to detection of both pelvic nodal and distant metastases (*1,2*). Similarly, PSMA PET/CT proved also superior in detecting local recurrences, lymph node and/or distant metastases in patients with early biochemical relapse and rising PSA levels as low as 0.2 ng/ml (*3*). These findings supported recent FDA approval of

two New Drug Applications for PSMA PET imaging at the Universities of California San Francisco and Los Angeles for both primary staging in high-risk prostate cancer patients and patients with biochemical recurrent disease, but also recommendation of PSMA PET imaging in the latter setting in the recently updated national German S3 guideline on prostate cancer (*4*), and reimbursement of this procedure within the framework of *Ambulante Spezialärtzliche Versorgung* in Germany. Most recently, the PSMA tracer ^{18}F-piflufolastat from Lantheus was approved by FDA (5).

There is also major progress in the realm of PSMA treatment in patients with prostate cancer. The results of the International, Prospective, Open Label, Multicenter, Randomized Phase 3 Study of ^{177}Lu-PSMA-617 in the Treatment of Patients With Progressive PSMA-positive Metastatic Castration-resistant Prostate Cancer (VISION trial) showed that ^{177}Lu-PSMA-617 significantly increased overall survival and radiographic progression-free survival in these patients (*6*). PSMA-based theranostics, therefore, very soon will increasingly become a clinical standard in prostate cancer patients – as long as these tumors express PSMA!

But PSMA is by far not as prostate-specific as suggested by its name! It is a type II transmembrane zinc metallopeptidase with enzymatic activity that hydrolyzes poly-γ-glutamated folates to folate which can be taken up by nearby tumor cells (*7*). The enzyme is also known as glutamate carboxypeptidase II, folate hydrolase 1, folypoly-gamma-glutamate carboxypeptidase, and N-acetylated-alpha-linked acidic dipeptidase I. PSMA is physiologically expressed in astrocytes and Schwann cells of the nervous

system, prostate, proximal renal tubule of the kidney, salivary glands, and the duodenal brush border (*8*) as can be seen and quantified on PET images of cancer patients (*9*).

In malignant tumors however, PSMA expression is not only documented for prostate cancer cells but also found in the tumor-associated neovasculature of almost all solid tumors though not in normal vasculature. Interestingly, PSMA expression often correlates with the aggressiveness of tumors, as has been shown for prostate cancer as well as other tumor entities, e.g. sarcomas in which PSMA expression was higher in more malignant tumors (*10*).

A comprehensive review on PSMA PET imaging of non-prostatic diseases has been recently compiled by Galiza Barbosa et al., in which a variety of different tumors including almost all relevant carcinomas as well as brain and nerve-derived tumors, lymphomas, and soft and bone tissue sarcomas were shown PSMA-positive, usually related to endothelial expression in the associated neovasculature. The authors therefore concluded that “these unintentional findings have paved the way for the application of PSMA PET imaging as an additional diagnostic tool” (*11*).

These “unintentional” findings of PET-detectable PSMA expression in many different malignant tumors do not only imply potential use for imaging but also for therapy: it may open up a universal theranostic approach of tumor treatment in many tumors, and, thus, should be followed in more detail for different tumor entities, especially in tumors with a high medical need for therapy improvement.

Amongst all the non-prostatic PSMA expressing tumors, aggressive brain tumor, glioblastoma multiforme (GBM) holds special mention as treatment results in this tumor type, despite extensive research, are still very poor with no curative options so far. Initial results in 16 patients with histopathologically documented GBM showed PSMA expression, albeit highly heterogeneous, on both tumor associated vessels and in non-endothelial cells (12). Similarly, further case reports and case series have also demonstrated mild to intense PSMA expression on PET/CT in GBM patients (*13*–*18*).

At first instance, these results appear promising but using a PSMA-based theranostic concept in gliomablastoma may face several challenges based on these first reports: First of all, PSMA as the binding target is primarily expressed on neovascular rather than tumor cells in GBM, thus, irradiating tumor cells only in immediate vicinity to vascular cells, depending on the range of the respective radionuclide. The often low and diffusely distributed tumor volume in GBM recurrences with their infiltrating tumor cell clusters in comparison to e.g. solid metastatic prostate cancer lesions may further reduce the therapeutic index because in this setting the beta emitting radionuclide ^{177}Lutetium with a maximum path length of approx. 2 mm may release significant amounts of radiation to peritumoral brain parenchyma and nerves rather than to the infiltrating tumor cells, which in turn results in higher treatment toxicity. Finally, low to moderate PSMA expression in GBM may not allow sufficient tumor radiation doses if PSMA endoradiotherapy is used as stand-alone treatment.

However, these limitations may be overcome: We first should perform clinical studies on PSMA PET/CT in correlation to conventional imaging, contrast-enhanced MRI, and ^{18}F-fluoroethyltyrosine or ^{11}C-methionine PET, as well as tumor panel analysis for characterizing GBM lesions in terms of PSMA expression and the respective genotype, and then use PSMA therapy with ^{177}Lu in case of “sufficient” PSMA tumor uptake. Thorough state-of-the-art dosimetry in these patients in combination with meticulous tumor response assessment will allow to evaluate the clinical value of this treatment option as stand-alone therapy and help defining “sufficient” tumor uptake. Based on our above-mentioned caveats, combination treatments with stereotactic radiation therapy, sequentially or alternatively, or tyrosine kinase inhibitors should be evaluated very early on in these highly treatment-resistant tumors. Furthermore, more effective therapeutic radionuclides, e.g. ^{161}Terbium or the alpha emitter ^{225}Actinium (cave: very short path length), have to be tested in comparison to ^{177}Lu for assessing both treatment efficacy and toxicity, and thus, their therapeutic index. Experience from radiation therapy suggests that apart from inherent radiation sensitivity of GBM cells, several other factors like immune cell infiltration, radiation dose, duration of radiation therapy, etc. play a role in determining the treatment outcome. Radiolabeled PSMA binding to the neovasculature of GBM is expected to deliver relatively moderate radiation doses for inducing double strand breaks in tumor cell DNA but at the same time modulate the tumor microenvironment to enhance tumor immunity as well as induce apoptosis through metabolic pathways.

The radiobiology of PSMA endoradiotherapy of GBM needs to be properly investigated in appropriate preclinical and mathematical models.

It is most evident but imperative to state that such studies in GBM patients, either as prospective studies or under compassionate use programs, have to be performed in interdisciplinary settings and close collaboration with neurosurgeons and radiation oncologists. Considering the extremely poor outcome of GBM patients, both in terms of survival and quality of life, the potential of PSMA radionuclide therapy should be explored for the benefit of these patients. Let us pave the way for PSMA theranostics to GBM and further tumor entities!

Disclosure

No potential conflict of interest relevant to this article was reported.

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