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EDITORIAL COMMENTARY

A new perspective for nuclear medicine: expanding the indications for PSMA targeted imaging and therapy

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The erroneously named prostate specific membrane antigen (PSMA), also known by the functional description of glutamatedecarboxypeptidase 2, has in recent years seen a massive upsurge in interest in nuclear medicine due to the newly available specific functional substrate tracers for both positron emission tomography (PET) imaging and radionuclide therapy [1–12]. Because of its superior characteristics [13–15] PSMA targeted imaging and therapy has become part of routine clinical care in an almost unprecedented rapid adoption process and has replaced the previous clinical standard wherever the necessary facilities are available and regulations allow the use of PSMA targeted tracers before completion of the formal trials on efficacy and pharmaceutical registration procedures.

Initially, PSMA targeted imaging and radionuclide therapy were developed for prostate cancer. Prostate cells show an elevated expression of PSMA [16, 17], and prostate cancer cells show an even higher expression [18, 19] of this structure, which increases with the aggressiveness of the tumour (although 10–15% of prostate cancers will be PSMA negative).

However, it has been known for a long time that PSMA is also expressed in a variety of benign tissues such as the gut and the pancreas, as well as nervous structures [20, 21], leading to potential pitfalls in the interpretation of PSMA targeted imaging. PSMA-PET/CT then also showed a strong uptake in salivary glands [20], occasionally resulting in side-effects of therapy such as sialadenitis and even xerostomia [9]. Furthermore, even well before the introduction of PSMA targeted imaging and therapy it was already shown in immunohistochemical studies that PSMA is also expressed in a variety of solid malignancies including e.g. breast cancer and gliomas [22]. Incidental findings on PSMA PET/CT performed for prostate cancer have already expanded this list of PSMA expressing tumours by e.g. renal cell carcinoma and thyroid cancer [23–31].

However, in most non-prostate neoplasms PSMA is not expressed by the tumour cells itself, but rather on the membrane of the endothelial cells in the tumour neovascularization [22]. While this may suffice for a sufficient degree of uptake to enable localization of malignant lesions in PSMA targeted PET/CT, it may not suffice for therapy, as radionuclide therapy will be most effective when the radionuclide is internalized in the malignant cells themselves, especially when alpha-emitters are used [11].

In this edition of the EJNMMI Klein Nulent et al. [32] followed the logical train of thought to investigate the use of PSMA in a specific malignancy of the salivary glands, in this case the adenoid cystic carcinoma. It was hoped that this rare malignancy would, like the benign salivary gland cells, show a sufficient expression of PSMA to allow for both PSMA targeted imaging and, if strong enough, for radionuclide therapy. They were not disappointed: both in immunohistochemical studies and in PET/CT imaging adenocystic carcinoma showed a clear expression of PSMA with a strong tracer accumulation not just in the endothelial cells of the neovascularization, but also on the surface of the tumour cells themselves.

There are a number of implications of these findings. Firstly, for patients with an adenocystic carcinoma of the salivary glands these findings open up a new avenue for potential treatments. As Klein Nulent et al. [32] point out, adenoid cystic carcinoma is a rare malignancy for which no further established medical treatment is available after surgery and external beam radiation therapy. Hence PSMA targeted

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therapy might fulfil un an unmet need for a rare cancer and as such should certainly be tested further for this indication.

Secondly, even though the data are of a preliminary nature, the study by Klein Nulent et al. [32] also shows that PSMA PET/CT in patients with adenoid cystic carcinoma may be as good for staging of disease as PET/CT with 2-fluoro-2-desoxyglucose (FDG). In fact, considering the perineural growth and spread often seen in these tumours, PSMA PET/CT migh even prove superior considering the difference in physiological distribution: whereas PSMA is not taken up in the brain and surrounding structures and thus a high tumour to background contrast will exist for lesions in the head/neck area in PSMA PET/CT, most cranial tumour lesions will be masked by glucose uptake in the brain on FDG PET/CT.

Although the results by Klein Nulent et al. are encouraging and again indicate that PSMA is anything, but prostate specific, they need to be considered as preliminary. If PSMA is really to remain in clinical practice, or for that matter even enter clinical practice in many countries, nuclear medicine as a whole will need to step up its act, bridge differences, and carry out the tedious work of performing proper, outcome based, radomized, double blind trials showing that for each potential indication, PET/CT will provide an advantage in terms of patient outcome, either directly through better patient outcome or at least indirectly by guidance of therapy and reduction of useless therapeutic interventions. The same goes of course for PSMA targeted radionuclide therapy. Where perhaps PET/CT or even radionuclide therapy trials with PSMA targeted radionuclide pharmaceuticals can still be handled by a handful of institutions, this of course is not the case for such much rarer indications, where many centres will need to be involved. However, considering that such rare disease often see authorities lowering the acceptance threshold, it may still be worthwhile setting up and performing such trials, given adequate funding and of course support by professional organizations such as the EANM. These authors would gladly contribute to such trials where possible.

Compliance with ethical standards

Disclosure of potential conflicts of interests Frederik A. Verburg was a consultant to Bayer Healthcare and Sanofi-Genzyme and has received speaker honoraria from Diasorin and SanofiGenzyme. Markus Lustre was a consultant for AstraZeneca, Bayer Healthcare, SanofiGenzyme, and Sobi and has received speaker honoraria and research support from SanofiGenzyme, Henning, and Merck.

Ethical approval This Editorial does not contain any studies with human participants or animals performed by any of the authors.

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