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EDITORIAL COMMENTARY

Molecular imaging using PSMA PET/CT versus multiparametric MRI for initial staging of prostate cancer: comparing apples with oranges?

Felix M. Mottaghy[1,2] · **Alexander Heinzel**[1] · **Frederik A. Verburg**[1,2]

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Molecular imaging of glutamate carboxypeptidase II, also called prostate-specific membrane antigen (PSMA) [1], has seen an unprecedentedly rapid adoption in prostate cancer (PCA) imaging in the last few years. Wherever local laws and regulations allow and a sufficiently equipped radiochemical laboratory is available, this tracer has now completely replaced radiolabelled choline PET/CT in the imaging of recurrent PCA. Indeed, even though the first results from larger retrospective series have only been published in the last 18 months [2–5], PSMA PET/CT is already considered the standard of reference wherever it is available. It is important to mention that the different available probes ([^{68}Ga]PSMA HBED CC, [^{68}Ga]PSMA I&T, [^{18}F]DCFPyL) appear to show equivalent effectiveness in this application, although no direct comparisons have been performed.

This molecular imaging approach certainly represents a major advance over previous PET/CT tracers. It has a much better signal-to-background ratio and its very strong uptake in target lesions allows lesions as small as 2.4 mm in short-axis diameter to be detected [6]. As these probes are still very new, we as nuclear medicine physicians are still on the ascending slope of a steep learning curve. For instance, it has become clear that while the very high sensitivity of this tracer has often been confirmed [2, 7], it is not as specific as we would wish: a considerable degree of tracer uptake is seen both in other malignancies [8, 9] and in normal anatomical structures such as the coeliac ganglia which can easily be mistaken for malignant lesions [10].

Whereas the clinical value of PSMA PET/CT in the imaging of (suspected) recurrent PCA is largely uncontested, this is not the case in the setting of primary staging. In the determination of lymph node status, the results published so far have been rather mixed – although it is remarkable that a study in which a nuclear medicine physician was not involved had rather poorer results [11] than studies in which nuclear medicine physicians were involved [7]. The intraprostatic delineation of tumour manifestations has been the focus of several recent studies [12–14]. In one study only the volumes on MRI and PSMA PET were compared [12]. The most accurate approach seems to be the integration of information obtained from PSMA PET/MRI imaging and from histopathology [13]. In another study an assessment of a small patient collective comparing multisegmental analysis of the prostate on PET/CT with the same segmental analysis on postprostatectomy histology showed a very high positive and negative predictive value for the presence of PCA for each segment [14]. The initial results also showed that the intensity of PSMA uptake on PET correlates positively with the Gleason score [15].

For the assessment of the local tumour status, multiparameter MRI is already a well-established, highly accurate imaging modality. The study presented by Giesel et al. [16] in this issue of the *European Journal of Nuclear Medicine and Molecular Imaging* compared local staging using this well-established standard imaging modality and [^{68}Ga]PSMA-HBED-CC PET/CT in ten patients who underwent imaging with both modalities prior to curative radiation therapy. Using a multisegment model in which each segment was analysed for PCA involvement by two independent reviewers, most

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✉ Felix M. Mottaghy
fmottaghy@yahoo.de

[1] Department of Nuclear Medicine, RWTH Aachen University Hospital, Pauwelsstrasse 30, 52074 Aachen, Germany

[2] Department of Nuclear Medicine, Maastricht UMC, Maastricht, The Netherlands

MRI-positive segments were positive on [^{68}Ga]PSMA-HBED-CC PET/CT and nearly all [^{68}Ga]PSMA-HBED-CC PET/CT-positive segments were MRI-positive. In five of the ten patients there was perfect concordance between the two modalities. Furthermore, both modalities were concordant in the identification of seminal vessel involvement. The drawback of this study was the lack of a direct correlation with a thorough histopathological analysis, since none of the patients underwent surgery. Thus the authors were only able to confirm that in all patients both MRI and [^{68}Ga]PSMA-HBED-CC PET/CT correctly identified the general area of tumour involvement. Therefore it could not be determined which of these two modalities was "better" or "more accurate" at a detailed level in terms of the few and minor differences, leaving room for future research. However, the minor differences that were found were unlikely to have affected any decision on radiation therapy of PCA and would only marginally have affected any integrated radiation boost given to the tumour as the differences in tumour extent were minor even in the worst case.

Therefore, the question still remains as to which modality should be used for imaging before curative radiation therapy. Certainly each modality has its advantages. MRI provides a sharper, higher spatial resolution image and therefore a higher accuracy for the assessment of the delineation between the tumour and surrounding anatomical structures [17]. PSMA PET/CT detects the same if gross invasion is present, as was the case in the example given by Giesel et al. [16]. However, PET/CT, with either a PSMA ligand or radiocholine, cannot detect marginal invasion of other surrounding structures, such as the rectum, as the dividing plane between these structure can simply be too thin to be assessed with PET/CT. On the other hand, especially when curative local radiation therapy of the prostate is concerned, the accurate assessment of locoregional lymph nodes, as well as the various possible locations of distant metastases (i.e. extrapelvic lymph nodes, bones, visceral organs), is very much more sensitive with PSMA PET/CT than with MRI. Whereas PSMA PET/CT can detect lymph node (and other) metastases of diameter 2 – 3 mm, MRI can generally only identify pathological lymph nodes when they show aberrant anatomical characteristics (e.g. non-oval shape, short axis diameter >1 cm). Thus extraprostatic whole-body staging with MRI is much less sensitive (and therefore less accurate) than imaging with PSMA ligands [7].

Considering the advantages and disadvantages of each method, it is clear that the information delivered by each may have a large degree of overlap, but in part is also of a complementary rather than a competing nature. Therefore, it seems we are in a position to serve a well-balanced and perfectly fitting mix of apples and oranges if we will implement PSMA PET/MRI in this setting. Some studies [13, 18–20] support this notion, and we can consider this the ideal method to provide all of this complementary information in a "one stop shop" solution.

Compliance with ethical standards

Conflicts of interest F.M.M. has received grant support and speaker's fees from, and is a consultant to, Bayer Healthcare. F.A.V. is a consultant to Bayer Healthcare and Sanofi Genzyme.

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