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EDITORIAL COMMENT

Editorial Comment: Advances in MRI and PET of the prostate: concurrence or complementarity?

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Abstract

This Editorial Comment refers to the articles "Diagnostic evaluation of magnetization transfer and diffusion kurtosis imaging for prostate cancer detection in a re-biopsy population" by Barrett T et al., Eur Radiol. 2017 Dec 8 and "18F-Fluciclovine PET/MRI for preoperative lymph node staging in high-risk prostate cancer patients" by Selnæs KM et al., Eur Radiol. 2018 Jan 2.

Abbreviations

DKI	Diffusion kurtosis imaging
GRPR	Gastrin-releasing peptide receptor
MTI	Magnetisation transfer imaging
PCa	Prostate cancer
PSMA	Prostate-specific membrane antigen

Prostate cancer (PCa) is the most common cancer in men. Although many of these tumours may be indolent and do not require treatment, prostate cancer is the third cause of mortality in Europe and the USA. Recent advances in management of PCa have become possible with improved staging and restaging, with multimodality imaging being instrumental. A rapid survey of recent issues of European Radiology confirms the vitality of the clinical research in modern non-invasive imaging of prostate cancer.

Advances in MRI

MRI plays an important role in the clinical imaging evaluation of the prostate gland. Prostate MRI is recommended for the local staging by EAU guidelines for intermediate- and high-risk prostate cancer [1]. The diagnosis of prostate cancer differs from that in other solid organs where imaging is used to identify those patients who require biopsy. Many men without prostate cancer undergo unnecessary biopsies, clinically insignificant cancers are often detected and clinically significant cancers are missed. The introduction of pre-biopsy MRI as a triage test could potentially minimise unnecessary detection of clinically insignificant disease while improving the identification of clinically relevant disease. With a very high negative predictive value [2], approaching 90%, MRI combining T2, perfusion (DCE) and diffusion-weighted (DW) imaging is now discussed before the first biopsy and validated before a re-biopsy [1]. MRI-targeted biopsy, using cognitive or software-based fusion of prostate MRI and real-time ultrasound (US) images, increases the detection of clinically significant PCa using fewer cores than standard biopsy [3].

MRI provides information, beyond anatomy (T2W), on tissue characteristics such as prostate volume, cellularity and vascularity with DCE and DW. It is now appreciated that most clinically relevant solid tumours are highly heterogeneous at the phenotypic, physiological and genomic levels and that they continue to evolve over time. This highlights the need for improvement of existing acquisition sequences, or development of additional functional sequences in order to find new biomarkers. In their study, Barrett et al. [4] evaluate two additional functional sequences, diffusion kurtosis imaging (DKI) and magnetisation transfer imaging (MTI) for prostate cancer detection. These techniques evaluate the heterogeneity of water diffusion and the structural integrity of tissues and

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microstructural changes induced by pathological processes. The authors found that those techniques were able to differentiate benign tissue from tumour, which is the first triage step to decide whether the patient should or should not undergo a re-biopsy. However, none of the measured parameters reliably differentiated low-grade from high-grade disease, whereas the prognosis is completely different. Accurate classification of the different Gleason score patterns on MRI is still a challenge and requires objective, reproducible, quantitative analysis methods. Texture analysis, which is a promising technique, could potentially distinguish between these different PCa patterns [5].

Advances in PET

Positron emission tomography (PET) has become the leading modality of nuclear medicine functional and molecular imaging compared to scintigraphy, due to superior image resolution, shorter waiting and image acquisition times, for a similar radiation exposure and a major player for PCa. A PubMed search for 'prostate PET' retrieved two articles on this topic in 1997, 62 in 2007 and 510 in 2017.

Radiolabeled ^{11}C-choline or its fluorinated analogues have for over a decade been the reference PET radiotracers for PCa detection, especially in case of occult recurrence [6]. They are effective in detecting metastases in the skeleton, in distant lymph nodes and in the viscera [7]. Conversely, these tracers lack sensitivity in detecting small locoregional lymph node metastases and specificity in characterising lesions in the prostate bed. The radioligands of prostate-specific membrane antigen (PSMA) or of gastrin-releasing peptide receptor (GRPR) and ^{18}F-fluciclovine, an amino-acid analogue, are currently in the forefront of innovative radiopharmaceuticals for PET. They are meant to not only detect metastatic PCa but also delineate PCa inside the prostate bed and in locoregional lymph nodes.

PSMA is a transmembrane type II glycoprotein, which is expressed by almost all PAs, either in primary tumours or metastases [8]. The diagnostic performance of PET imaging, using ligands of PSMA labelled with gallium-68 or more recently fluorine-18 in a PCa workup (initial staging and recurrence) has been reported in several concordant studies to be superior to that of radiolabeled ^{11}C-choline or its fluorinated analogues [9, 10]. Compared with the radioligands of PSMA, the regulatory status of the amino-acid analogue ^{18}F-fluciclovine, which has been developed in the USA, is quite different [11]. It is currently registered in the USA and EU, even though the published data about comparison with PET choline are currently limited to one study with ^{11}C-choline [12] but none with ^{18}F-fluorocholine. Only one short series of ten patients comparing ^{18}F-fluciclovine and the ligand ^{68}Ga-PSMA-11 has been published to date, suggesting a superior detection rate of ^{68}Ga-PSMA-11 PET/CT compared to ^{18}F-fluciclovine PET/CT in recurrent PCa [13]. Bombesin analogue antagonists of the GRPR labelled with radionuclides for PET are also entering evaluation in humans, showing favourable results compared to a choline analogue in preliminary studies [14]. A preliminary clinical series in PCa of PET/CT with radiotracer combining ligands of integrin $\alpha_v\beta_3$ and gastrin-releasing peptide receptor reported better results than with a radioligand binding to GRPR alone [15]. One major goal of this blossoming clinical research on PET radiotracers is the theranostic approach to select, based on PET, those patients who will be eligible for targeted radiotherapy using the same tracer labelled with a radionuclide designed for the destruction of tumours and of invisible spread [16, 17].

Evidence concerning all those flourishing tracers and imaging procedures is pending the results of ongoing prospective trials.

PET/MRI and complementarity

Combining the unique functional and/or biological information provided by PET with the performance of morphological imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), is currently evidence for optimising the detection and identification of lesions and impact on patient care, especially in oncology.

PET/MRI, the most recent hybrid-imaging technology, appears to be particularly suited for the analysis of the prostate gland. Some authors have found that simultaneous PET/MRI using a radiolabelled PSMA ligand improved the diagnostic accuracy for PCa localisation compared to PET and multiparametric MRI considered separately [18].

Indeed, PET/MRI combines a multiparametric MRI with the molecular approach of PET imaging, which can pinpoint and characterise subcentimetre lesions. It has been recently demonstrated that textural analysis may assist in PCa detection in the transition zone on multiparametric MRI [19] and on PET/MRI using a PSMA ligand radiolabelled with gallium-68 [20].

Nevertheless, considering on the one hand the very high number of patients with PCa, and on the other the foreseeable limited availability of these machines, it is likely that MRI and PET will in most cases be performed separately. This stresses the importance of comparing the relative input of each examination for specific clinical questions like early detection of significant PCa, selection of cases for biopsy or re-biopsy, initial staging and detection of recurrences.

In addition, the development of radiomics is finding a fertile ground in the field of PCa. The disease is common, and most patients undergo iterative MRI, and PET examinations for detection, staging, surveillance, restaging and assessment of treatment efficacy, building an unprecedented large source of data for the elaboration of radiomics. Image interpretation

for all these studies will potentially benefit from radiomics, as will the definition of imaging strategies. Although we learn a lot each day from MRI and PET, even more remains to be discovered.

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