Eur J Nucl Med Mol Imaging (2013) 40 (Suppl 1):S1–S4
DOI 10.1007/s00259-013-2444-5

EDITORIAL

Prostate cancer imaging

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Introduction

Prostate cancer is the most common cancer among men in the Western world, with the highest incidence and the second highest mortality rate among malignancies [1]. In recent years there has been rapid development in molecular imaging for visualizing the different phases of prostate cancer. In particular, integrated PET/CT and MRI are emerging as the primary tools in this clinical setting.

In the present supplement, leading experts were asked to present and discuss different aspects of imaging in prostate cancer, to specifically describe the state of the art and the most relevant improvements that have recently occurred in anatomical, molecular and functional imaging of prostate cancer. The main emphasis was placed on the current practice for diagnosing primary and recurrent prostate cancer using established and emerging PET radiopharmaceuticals. In this respect, the often overlooked problem of spatially matching imaging findings with pathology in primary prostate cancer was highlighted. A second focus was the growing role of MRI with related functional imaging components in prostate cancer. Lastly, the future role of PET/MR as a new multimodal imaging technique expected to improve diagnostic performance of prostate cancer imaging was addressed.

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Choline PET

Currently, choline PET/CT can be regarded as a well-investigated and established modality for restaging patients presenting with elevated prostate-specific antigen (PSA) levels following radical treatment of prostate cancer. However, certain factors may potentially influence the appropriateness and accuracy of choline PET/CT in a given clinical situation. As the detection rate of choline PET/CT rises together with the increase in PSA serum levels, the routine use of choline PET/CT has been recommended for PSA levels >1 ng/mL [2]. However, in addition to the PSA serum value at the time of PET/CT examination, attention should be paid to PSA kinetics to select the patient population benefiting most from this diagnostic procedure. Based on current literature, Castellucci and Picchio [3] recommend choline PET/CT as the first-line diagnostic procedure in patients with biochemical relapse showing fast PSA kinetics. In particular, they recommend performing choline PET/CT when the PSA doubling time is less than 6 months and/or the PSA velocity is higher than 1 ng/mL per year to allow a tailored treatment of prostate cancer recurrence.

At present, it remains unclear if androgen deprivation therapy negatively influences choline PET/CT detection rates in prostate cancer. The mechanisms of choline uptake and the role of the androgen receptor in prostate cancer treatment are most relevant when considering choline PET/CT under androgen deprivation. Dost et al. stated that the current working hypothesis suggesting that androgen deprivation therapy does not influence choline PET/CT has not been overruled [4]. However, one should keep in mind that related clinical studies are limited in number and were not primarily designed to prospectively assess the effect of androgen deprivation on choline uptake of prostate cancer.

As reviewed by Schwarzenbock et al. [5], there is now considerable literature about choline PET/CT for radiation treatment (RT) planning in prostate cancer. Due to a limited

sensitivity and specificity of choline PET/CT in the detection of primary prostate cancer, the use of choline for delineation of intraprostatic lesions for RT planning is of questionable utility. However, choline might have value in enabling boosting the dose of RT to the most aggressive features. Besides morphological imaging techniques and functional MRI, molecular imaging modalities such as PET/CT have been introduced and evaluated for RT planning in prostate cancer. Recent studies have shown that dose escalation based on biological target information might improve biochemical response and relapse-free survival in intermediate and high-risk prostate cancer. In particular, there are encouraging reports (with promising survival data) on the use of choline PET/CT for RT planning in recurrent prostate cancer [6]. Due to the limited sensitivity and specificity for detection of nodal disease, targeted lymphonodal RT in the primary and recurrent settings does not appear to have fulfilled initial hopes.

Other PET tracers

Despite different uptake mechanisms, both choline and acetate have a nearly identical biodistribution; thus, neither offers a substantial advantage over the other. The present issue includes a comparative analysis of choline and acetate tracers in prostate cancer patients from the literature of the last 10 years, reaching the conclusion that—although studies on choline tracers are much more abundant—available data on acetate do not discourage its use in clinical routine [7].

As one of the hallmarks of cancer is its elevated glucose metabolism and since the above-mentioned choline-based or acetate-based radiotracers are not generally available, the role PET imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in prostate cancer was investigated. ^{18}F-FDG PET/CT is limited in the detection of prostate cancer since many primary tumours are slow-growing and well differentiated, and because ^{18}F-FDG tumour uptake can overlap with that in normal tissue and benign prostatic hyperplasia (BPH). However, ^{18}F-FDG PET/CT may be useful in the detection of aggressive disease, in the evaluation of extent and treatment response in metastatic disease and in the prognostication of castrate-resistant clinical state [8].

Several promising alternative radiotracers are currently being investigated for the imaging evaluation of prostate cancer. In this issue, specific emphasis is placed on PET/CT with choline or acetate, whether ^{11}C-labelled or ^{18}F-labelled, as well as the investigational synthetic L-leucine analogue anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (anti-3-^{18}F-FACBC). While further studies are required to assess the efficacy of anti-3-^{18}F-FACBC in a larger series of prostate cancer patients, preliminary data reported by Nanni et al. in this issue indicate a superiority of anti-3-^{18}F-FACBC over choline PET/CT in the detection of prostate cancer recurrence [9]. Although not covered in this issue, other novel investigational radiotracers such as radiolabelled prostate-specific membrane antigen [10] and bombesin analogues [11], may also have potential for clinical applications in prostate cancer.

MRI and PET/MR

In prostate cancer, PET/CT competes with MRI as the imaging modality for initial staging, identification of recurrent disease as well as in response evaluation of local and metastatic disease. As reviewed by Grant et al. in this supplement [12], anatomical, functional and multiparametric MRI has been shown to be effective for the detection and local staging of prostate cancer. For instance, anatomical T2-weighted MRI as part of multisequence endorectal coil MRI at 3 T showed a sensitivity and specificity of 73% and 89%, respectively. When combined with dynamic contrast-enhanced MRI and magnetic resonance spectroscopy (MRS), the predictive value further improved for peripheral zone tumours [13]. Studies directly comparing the performance of PET/CT and MRI in prostate cancer are however rare. Initial evidence in prostate cancer is inconclusive and may depend on the particular patient population or disease stage [14–16].

Currently, several profiling techniques are being evaluated. They provide comprehensive analyses of molecular alterations during prostate cancer development, its progression to clinically significant disease, and metastatic disease. While PET imaging with radiotracers targeting alterations of particular biochemical pathways have proven to be successful in many cancers, metabolic profiles may have even greater potential for diagnosis and disease monitoring. In this issue, Spur et al. review methods and results based on MRS and mass spectrometry (MS) in prostate cancer [17]. While MS requires sampling of tissue (or body fluids), it can assay large numbers of metabolites at low concentrations. High-throughput metabolite analysis (metabolomic profiling) has revealed that numerous metabolic processes are substantially different in prostate cancer compared to benign prostate tissues [18]. Similarly, metabolomic imaging is not limited to the assessment of individual metabolites or their isolated pathways, but evaluates specific conditions to profile a measurable metabolome. The discovery of specific metabolite profiles obtained from prostatectomy specimens (ex vivo) at high field strength (14.1 T) using high-resolution magic angle spinning (HRMAS) proton MRS has revealed the immense potential of MRS for diagnosis and assessment of aggressiveness in primary prostate cancer [19]. While initially described as a nondestructive ex vivo

method, HRMAS/MRS may ultimately have the ability to improve diagnostic imaging.

In this supplement, Souvatzoglou et al. review the technological advances that have been necessary to integrate PET and MRI, and present the initial results with PET/MRI in prostate cancer [20]. The article also features specific acquisition protocols for clinical hybrid PET/MRI. At present, clinical evaluation of PET/MRI in prostate cancer is in its infancy and its impact on prostate cancer detection, staging and disease monitoring has still to be established. A critical question is whether PET/MRI will be found to be advantageous over PET/CT, or whether PET/CT and MRI performed separately will be equal to (or even better than) PET/MRI in specific imaging situations. A good example is prostate cancer imaging, particularly when considering imaging of primary disease which often presents with multifocal disease of varying clinical significance. Hybrid PET/MRI opens the door to truly combining the advantages of both modalities. As reviewed in this issue, established radiotracers (choline/acetate) have specific weaknesses in areas where MRI shows relative strength. For instance, extracapsular spread of primary prostate cancer is identified earlier by high-resolution MRI than by PET. Also, lesion detection by anatomical MRI increases with Gleason grade, favouring detection of more aggressive disease stages even when lesion size is small [21]. On the other hand, the metabolic signature of lesions identified by ^{11}C-choline PET may also have prognostic value related to cancer aggressiveness [22]. Thus one would hope that the combination of both as a single examination (without the need for image fusion) may improve clinical staging by aiding in the identification of significant disease earlier than possible with MRI or PET/CT alone. Currently, no data are available to prove or disprove this hypothesis. Furthermore, the combination of metabolic PET and functional (or multiparametric) MRI as parametric crossmodality (PET/MRI) imaging performed on a hybrid PET/MRI scanner may further advance identification and localization of significant primary prostate cancer [23]. Thus far, evidence from related pilot studies is sparse and needs to be confirmed in larger prospective trials.

Prostate registration

Whether imaging is performed with PET or MRI, there is a growing need for accurate registration between imaging and pathology. This is especially true in primary prostate cancer in view of the existence of multifocal disease of varying relevance as well as the potential for additional benign features such as inflammation, BPH and prostatitis to interfere with lesion characterization. At the histological level, tumour tissue can also be heterogeneous and impure because adenocarcinoma are often mixed with varying amounts of normal or hyperplastic prostate glands, precursor lesions, and stroma. As highlighted by Meyer et al. [24], the scale of the registration problem and its relevance for research may have been underestimated in the past. Indeed, the lack of accurate registration may constitute a major obstacle in the validation of PET, PET/CT and MRI in primary prostate cancer. As reviewed, advances in registration techniques facilitating the mapping of pathology onto high-resolution imaging, preferably aided by the ex vivo imaging of the prostate specimen, are now available and should be considered for research applications.

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