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New aspects of molecular imaging in prostate cancer

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ABSTRACT

Nowadays several new imaging modalities are available for investigating prostate cancer (PCa) such as magnet resonance imaging (MRI) in the form of whole body MRI and pelvic multiparametric MRI and positron emission tomography (PET) using choline as radiotracers. Nevertheless, these modalities proved sub-optimal accuracy for detecting PCa metastases, particularly in the recurrence setting.

A new molecular probe targeting the prostate specific membrane antigen (PSMA) has been recently developed for PET imaging. PSMA, the glutamate carboxypeptidase II, is a membrane bound metallopeptidase over-expressed in PCa cells. It has been shown that PSMA based imaging offers higher tumor detection rate compared to choline PET/CT and radiological conventional imaging, especially at very low PSA levels during biochemical recurrence. In addition PSMA, as theranostics agent, allows both radiolabeling with diagnostic (e.g. 68 Ga, 18 F) or therapeutic nuclides (e.g. 177Lu, 225Ac). Initial results show that PSMA-targeted radioligand therapy can potentially delay disease progression in metastatic castrate-resistant PCa.

Despite still investigational, the bombesin-based radiotracers and antagonist of gastrin releasing-peptide receptor (GRP) (RM2) and anti1-amino-3-18 Ffluorocyclobutane-1-carboxylic acid (18 F-FACBC) are emerging as possible alternatives for investigating PCa.

Considering the wide diffusion of PCa in the Europe and the United States, the presence of these new diagnostic techniques able to detect the disease with high sensitivity and specificity might have a clinical impact on the management of patients. PET/CT imaging with new radiopharmaceuticals can implement the patient management identifying lesion(s) not detectable with conventional imaging procedures. In this review article will be discussed the most promising new PET radiopharmaceuticals (68 Ga-PSMA-11, 18 F-FACBC, 68 Ga-RM2) available at the moment, focusing the attention on their accuracy and their impact on treatment strategy.

1. Introduction

Prostate cancer (PCa) is the most common cancer and the third most common cause of cancer death in men [1]. At present, depending on the clinical stage, imaging of PCa can be indicated for primarydiagnosis, staging and detection of biochemical recurrent (BCR) disease as well as therapy response. Conventional imaging modalities, including ultrasound (US), bone scintigraphy (BS) and computed tomography (CT) are used to detect primary and metastatic PCa for staging and risk stratification. Despite significant efforts, these modalities do not contribute essentially to patient management as much as imaging performed in patients with other common cancers [2]. Magnetic resonance imaging (MRI), especially innovative methods such as diffusion-weighted MRI (DWI-MRI) or dynamic contrast-enhanced MRI (DCE-MRI) allowing functional assessment of the disease, are growingly important for imaging of PCa [3]. Nevertheless, these techniques do not allow tumor-specific imaging and cannot be applied throughout the whole body. Functional imaging with positron emission tomography (PET) shows molecular function and metabolic activity information in a single-step whole body examination [4]. Over the last decade, PET/CT (with 11 C-choline or 18 F-choline) proved its role for investigating PCa [5]. Particularly, choline PET/CT proved to be a better diagnostic tool for restaging PCa patients presenting BCR, as compared with radiological imaging [6]. Furthermore, choline PET/CT demonstrated its usefulness for

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staging high-risk PCa, with high PSA levels and Gleason Scores (GS), before the primary treatment [7]. However, choline based PET imaging presents several limitations both for staging the disease (lack of accuracy for detecting lymph-node involvement) and for restaging in case of BCR (lack of accuracy in case of PSA < 2 ng/mL). As a consequence functional metabolic imaging still holds a sub-optimal performance for investigating PCa [6].

Several efforts have been made over the last years to develop new probes able to provide better performances when compared with the choline-PET/CT [8]. A new molecular probe targeting the prostate specific membrane antigen (PSMA) has been developed recently for PET imaging [9]. PSMA, the glutamate carboxypeptidase II, is a membrane bound metallo-peptidase physiologically expressed in several tissues. Although the function of GCPII in prostate remains unclear, it is well-known that this protein is over expressed in PCa [10]. The first investigations reported a higher tumor to background ratio for 68 Ga-PSMA PET/CT for the detection of suspected PCa metastases when compared with choline PET/CT [11] and very promising performances also at very low PSA levels. In addition, other recently developed PSMA-inhibitors (PSMA I&T, PSMA-617, PSMA-1007) can be used as theranostics agents allowing radio-labeling with diagnostic (e.g. 68 Ga, 18 F) or therapeutic nuclides (e.g. 177Lu, 225Ac). In recent years an investigational amino acidic PET compound, anti1-amino-3-18 Ffluorocyclobutane-1-carboxylic acid (18 F-FACBC), a synthetic L-leucine analogue, was developed and tested in PCa patients with BCR after radical treatment. This radiotracer that actually falls within the category of metabolic radiotracers has been recently approved in the US, by the Food and Drug Association (FDA), as alternative metabolic radiopharmaceuticals for investigating PCa patients with biochemical recurrence [12]. Finally, Bombesin-based radiotracers and antagonists of gastrin-releasing peptide (GRPr) receptor, labeled with 68 Ga (68 Ga-RM2), are also of interest [13,14] and a recently PSMA-GRPr PET hybrid tracer developed (tested on murine samples) [15] suggests that this field is ever evolving towards new and hopefully more accurate diagnostic tools.

Considering the wide diffusion of PCa in the Europe and the United States, the presence of these new diagnostic techniques able to detect the disease with high sensitivity and specificity might have a clinical impact on the management of patients. PET/CT imaging with new radiopharmaceuticals can implement the patient management identifying lesion(s) not detectable with conventional imaging procedures. In this review article will be discussed the most promising new PET radiopharmaceuticals (68 Ga-PSMA-11, 18 F-FACBC, 68 Ga-RM2) available at the moment, focusing the attention on their accuracy and their impact on treatment strategy.

2. New molecular probes in prostate cacncer: PSMA PET/CT imaging

The prostate-specific membrane antigen (PSMA) is a type II transmembrane protein that was first detected on the human PCa cell line LNCaP [16]. Its expression and localization in the normal human prostate is associated with the cytoplasm and apical side of the epithelium surrounding prostatic ducts but not basal epithelium, neuroendocrine or stromal cells [17]. In malignant tissue, PSMA is involved in angiogenesis, as increased PSMA expression was found in the stroma adjacent to neovasculature of solid tumors [18]. Due to its selective overexpression in 90–100% of PCa lesions [19], PSMA is a reliable tissue marker for PCa and is considered an ideal target for tumor specific imaging and therapy [20]. Several studies showed that PSMA expression levels increase according to the stage and grade of the tumor as well as aneuploidy and biochemical recurrence thus potentially allowing PSMA-imaging to account for prognosis [21]. Recently, a large number of urea-based PSMA ligands labeled with 68 Ga have been presented, including PSMA HBED-CC (PSMA-11), PSMA I&T [22] and PSMA-617. More recently, 18 F-labeled compound with hepatobiliar excretion (PSMA-1007) attracted the most attention [23]. According to preliminary data, PSMA-1007 seems to be the most promising tracer showing a comparable accuracy to 68 Ga-PSMA-11, but its longer half-life combined with its superior energy characteristics and non-urinary excretion overcomes some practical limitations of 68 Ga-labeled PSMA tracers. Furthermore, 18 F-PSMA-1007 can be produced in large amounts per batch in PET radiopharmacies with an onsite cyclotron, reducing the demand for multiple tracer syntheses per day and enabling transfer to satellite centers. Preliminary data suggest reduced urinary excretion and high tumor to background ratios contribute to exceptional sensitivities including for tiny tumor deposits in the body.

2.1. Staging

In patients eligible to curative primary therapy, the decision to proceed with a further staging work-up is guided by which treatment options are available, taking into account the patient's preference and co-morbidity. Several imaging modalities have been proposed to assess the extension of the intraprostatic lesion before radical prostatectomy (RP). In predominantly Gleason pattern 4, multiparametric MRI (mp-MRI) provided the most valuable performance with best values both for sensitivity and specificity. Thus, the use of mp-MRI is recommended by the European Association of Urology (EAU) guidelines in intermediate and high-risk PCa before primary treatment [3,24]. The use of choline PET/CT in the pre-operative setting has not been recommended by the EAU, both for intermediate and high-risk patients. Despite EAU guidelines still consider PSMA based PET imaging an investigational procedure, very promising results have been recently presented, both for detecting the intraprostatic lesion and for the assessment of lymph-node metastases (LNM).

Fendler et al. [25] evaluated the accuracy of PET/CT with 68 Ga-PSMA-11 to localize cancer in the prostate and surrounding tissue at initial diagnosis in cohort of 21 patients. It was assessed a sensitivity of 67%, a specificity of 92%, an accuracy of 72%, a PPV of 97% and a NPV of 42%. Histopathology positive segments (100/126; 79%) demonstrated a significantly higher mean SUVmax than histopathology-negative segments. However, despite better values for specificity and PPV if compared to choline PET/CT, the sensitivity still remain sub-optimal. Thus, it was recently proposed the combination of PSMA based PET with MRI to improve the performance of both methodologies. Zamboglou et al. [26] demonstrated that the hybridization of the two techniques performed even better in terms of sensitivity (82%) and specificity (89%). Eiber et al. confirmed these results [27]: authors compared the diagnostic performance of simultaneous 68 Ga-PSMA PET/MRI for the localization of primary PCa with mpMRI and PET alone in a cohort of 53 patients. Simultaneous PET/MRI statistically outperformed mpMRI and PET imaging alone for a precise localization of PCa. The hybrid diagnostic procedure detected correctly the lesion in the 98% of cases with a sensitivity of 76% and a specificity of 98% (MRI alone 43%, 98%; PET alone 58%, 82%). Moreover, according to the data available in literature so far, it seems reasonable to assume that PSMA PET/MRI is able to distinguish with good accuracy between intraprostatic PCa lesion and BPH [25,27].

The individual risk of finding LNM can be estimated using externally validated with preoperative nomograms according to D'Amico criteria [28]. A risk of nodal metastases > 5% is an indication to perform an extended nodal dissection (ePLND). As a consequence, the role of imaging is crucial in the work-up of high-risk