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PET/CT AND RADIOIMMUNOTHERAPY OF PROSTATE CANCER

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Abstract

Purpose of review—Traditional morphologically based imaging modalities are now being complemented by positron emission tomography (PET)/computerized tomography (CT) in prostate cancer. Metastatic prostate cancer is an attractive target for radioimmunotherapy (RIT) since no effective therapies are available. This review highlights the most important achievements within the last year in PET/CT and RIT of prostate cancer.

Recent findings—Conflicting results exist on the use of choline for detection of malignant disease in the prostate gland. The role of PET/CT in N-staging remains to be elucidated further. However, ¹⁸F-choline and ¹¹C-choline PET/CT have been demonstrated to be useful for detection of recurrence. ¹⁸F-choline and ¹⁸F-fluoride PET/CT are useful for detection of bone metastases. Prostate tumor antigens may be used as targets for RIT. Prostate specific membrane antigen (PSMA) is currently under focus of a number of diagnostic and therapeutic strategies. J591, a monoclonal antibody, that targets the extracellular domain of PSMA, shows promising results. HER2 receptors may also have a potential as target for PET/CT imaging and RIT of advanced prostate cancer.

Summary—PET/CT in prostate cancer has proven to play a significant role, in particular for detection of prostate cancer recurrence and bone metastases. Radioimmunotherapy of metastatic prostate cancer warrant further investigations.

Keywords

prostate cancer; positron-emission tomography; radioimmunotherapy; choline fluoride; PSMA; HER2 receptor

Introduction

Positron emission tomography (PET) provides unique insights into molecular pathways of diseases. PET, especially when combined with computed tomography (PET/CT), is the most advanced technique for metabolic imaging, and one of the most accurate tools for tumor staging in the pre-treatment, post-treatment, and follow-up phases of many malignant tumors. The most commonly used metabolic tracer for PET in oncology is ¹⁸F- fluorodeoxyglucose (FDG). FDG is an analogue of glucose that is taken up, phosphorylated, and trapped inside metabolically

active, proliferating cells. In prostate cancer, however, the use of ^{18}F -FDG PET has been limited mainly due to the low uptake of FDG and urinary excretion of the tracer. Recently, novel PET tracers with more favourable properties are being tested in clinical studies leading to increased application of PET/CT in prostate cancer [•1].

Advances in radiopharmaceuticals have resulted in the introduction of new useful therapeutic agents in the clinical management of cancer patients. In targeted therapy, selective molecules are used for tumor-specific delivery of the anti-cancer drugs and, thereby, limiting the damage to healthy tissues. The novel class of radiopharmaceuticals combined with molecular imaging of their targets offer the potential to develop patient-specific therapies. During the last decade, application of radiolabelled peptides and antibodies for endoradiotherapy have been extensively tested, and some of these drugs such as ^{90}Y -ibritumomab tiuxetan (Zevalin®), ^{131}I -tositumomab (Bexxar®), and the somatostatin receptor binding ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE are now successfully applied in cancer treatment [•2;•3]. Metastatic prostate cancer is an attractive target for radioimmunotherapy (RIT) since the current therapeutic approaches, based mainly on hormonal therapy, are not curative. The purpose of this review is to highlight the most important achievements of PET/CT and RIT published in the past year with respect to prostate cancer.

PET/CT

The most common PET tracers used for detection of prostate cancer are ^{11}C -acetate, ^{11}C -choline and ^{18}F -fluorocholine (FCH) [•1;4-6]. Recently, acetate has also been labelled with ^{18}F , i.e. ^{18}F -fluoroacetate [7]. Choline is a component of the phosphatidylcholines, a class of phospholipids and a major component of biologic membranes. Prostate cancer is characterized by upregulated choline kinase activity and increased choline uptake [8]. Therefore, malignant tumors of the prostate show increased metabolism of cell membrane components resulting in a relatively high uptake of choline as compared to less aggressive neoplasms. Acetate is a substrate for the tricarboxylic acid (TCA) cycle [•9;10]. Cellular uptake of ^{11}C -acetate is proportional to lipid synthesis, and increased fatty acid synthesis has been demonstrated in prostate cancer [8;10]. In a direct comparison of ^{11}C -choline and ^{11}C -acetate, Kotzerke *et al.* demonstrated that both tracers performed nearly identically in prostate cancer patients [11].

Primary diagnosis

Li *et al.* investigated 49 patients for the potential of ^{11}C -choline PET/CT imaging for differentiating prostate cancer from benign prostatic hyperplasia (BPH) [•12]. PET data were analyzed visually and semiquantitatively by measuring maximum standardized uptake value (SUVmax) in the prostate lesions (target) and in the muscles (non target), and calculating their ratios (P/M). Using 2.3 (P/M) as the criterion, ^{11}C -choline PET/CT imaging showed a sensitivity of 90.48%, a specificity of 85.71%, and a negative predictive value of 92.31%. These results suggest that the parameter P/M could differentiate prostate cancer from benign lesions better than SUV. Kwee *et al.* investigated the value of ^{18}F -FCH PET for sextant localization of malignant prostate tumors in 15 patients prior to radical prostatectomy [•13]. The SUVmax corresponding to prostate sextants on PET was compared with histopathologic results. Histopathology demonstrated malignant involvement in 61 of 90 prostate sextants. Mean SUVmax was 6.0 in malignant sextants and 3.8 in benign sextants. The area under the receiver operating characteristic curve was 0.82 for ^{18}F -FCH PET detection of malignant sextants. The sensitivity was lower for sextants with small tumors.

Conflicting conclusions regarding application of PET for the detection of malignant lesions in the prostate gland have been reported in other studies [•1]. A previous study by Schmidt *et al.* [14] reported no significant difference in ^{18}F -FCH uptake between malignant and benign

prostate lesions. Recently, *Igerc et al.* presented a study of ^{18}F -FCH PET/CT in men ($n=20$) who had not yet been diagnosed with prostate cancer, but were at increased risk of having the disease in view of persistently elevated levels of PSA and repeated negative prostate biopsies [•15]. ^{18}F -FCH PET/CT was used to delineate prostate cancer and guide repeat prostate biopsy. Focal ^{18}F -FCH uptake was detected in 13 out of 20 patients. In five patients, prostate cancer was revealed by repeat biopsy. The authors concluded that the use of ^{18}F -FCH cannot be generally recommended for localizing prostate cancer. In this study, dual-phase protocol (images after 2-3 min and 30 min) provided no clear benefit in discriminating malignancy from benign alterations. However, other ^{18}F -FCH PET studies have reported that late imaging is superior to early imaging [•1].

Staging

Schiavina et al. investigated prostate cancer patients at intermediate risk ($n=27$) or high risk ($n=30$) for preoperative lymph node (LN) staging [•16]. All patients underwent preoperative ^{11}C -choline PET/CT and radical prostatectomy with extended pelvic LN dissection. Risk of LN metastasis was assessed using available nomograms. The authors found that the sensitivity and specificity of correctly recognized cases with ^{11}C -choline PET/CT were 60.0 % and 97.6 %, respectively, whereas on a lesional based (lymph node) analysis, these numbers were 41.4 % and 99.8 %. ^{11}C -choline PET/CT for LN metastases detection performed better than clinical nomograms, with equal sensitivity and better specificity. *Husarik et al.* used ^{18}F -FCH PET/CT for correlation with lymphadenectomy for initial N-staging. Histopathological work-up was performed on 115 LN sampled from 25 patients. Only one of these LN showed pathological ^{18}F -FCH accumulation and was proven to be a metastasis measuring more than 1 cm. Four lymph nodes that did not show ^{18}F -FCH accumulation turned out to contain metastatic cells, with an overall tumor load measuring less than 0.5 cm. The results obtained using ^{18}F -FCH PET/CT for initial N-staging were discouraging, especially in terms of its inability to detect small metastases (micrometastases) [17]. The role of PET/CT in N-staging remains to be evaluated in larger clinical trials.

Recurrence

Rinnab et al. investigated the diagnostic value of ^{11}C -choline PET/CT in patients with suspected LN metastases before salvage LN dissection in 15 consecutive patients with rising PSA [18]. In this study ^{11}C -choline was found useful for targeted salvage LN dissection. However, the presented cohort was limited in size. In another small study by *Shilling et al.* ^{11}C -choline PET/CT was found useful for detection of recurrence of prostate cancer [19]. However, a limited PPV for locating pelvic LN metastases in recurrent prostate cancer was found. *Reske et al.* assessed the value of ^{11}C -choline PET/CT for localizing occult relapse after radical prostatectomy in 49 patients [•20]; 13 patients served as controls (mean PSA 0.10 ng/mL, clinically unremarkable follow-up after ≥ 1 year). PET/CT was judged negative for local remission in 12/13 of the controls. The other group consisted of 36 men who were suspected to have occult relapse of prostate cancer (mean PSA 2.0 ng/mL). In this group, PET/CT showed true positive focal lesions with increased ^{11}C -choline uptake in 70 % (23/33) of the patients with histological verification of local recurrence.

Tuncel et al. reported that ^{11}C -choline PET/CT (low-dose CT) results in improved lesion localization and changed disease management in 11 (24%) of 45 patients with advanced prostate cancer [21]. *Krause et al.* assessed the relationship between the detection rate of ^{11}C -choline PET/CT and PSA level in 63 patients with biochemical recurrence after primary therapy [•22]. The detection rate was 36% for a PSA-value <1 ng/mL, 43% for a PSA-value $1-2$ ng/mL, 62% for a PSA-value $2-3$ ng/mL, and 73% for a PSA-value ≥ 3 ng/mL. Thus, the detection rate depended on serum PSA level.

Husarik et al. used ^{18}F -FCH for restaging of prostate cancer in 68 patients with mean PSA 10.81 $\mu\text{g/l}$ [17]. In this study, ^{18}F -FCH PET/CT correctly revealed local recurrence in 36 patients. No pathological ^{18}F -FCH uptake was observed in 11 patients with biochemical recurrence. Twenty-three patients showed ^{18}F -FCH positive lymph nodes (LN). Twenty LN were surgically removed in seven patients. Histopathology verified metastases in all LN, but revealed two additional metastatic, ^{18}F -FCH-negative LN. Overall sensitivity to detect recurrent disease was 86%.

Bone metastases

Conventional bone scan with $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) is still used as the most common imaging technique to detect bone metastases in prostate cancer patients. However, this technique does not differentiate between the metastatic and benign processes in the bones. PET/CT with ^{18}F -fluoride seem to be superior to MDP bone scan for detection of bone metastases [23;24]. Fluoride uptake depends on regional blood flow, and in particular on local osteoblastic activity [8;25]. In a prospective study *Beheshti et al.* compared the value of ^{18}F -FCH and ^{18}F -fluoride PET/CT for the detection of bone metastases in 38 men with prostate cancer [•25]. Overall, 321 lesions were evaluated in the study. The sensitivity, specificity and accuracy of PET/CT were 81%, 93%, and 86% for ^{18}F -fluoride and 74%, 99%, and 85% for ^{18}F -FCH, respectively. ^{18}F -fluoride suggested higher sensitivity than ^{18}F -FCH for detection of bone metastases; however, this difference was not statistically significant. In a small pilot study conducted by *Luboldt et al.*, ^{11}C -choline PET/CT seemed to be equally effective as diffusion weighted MRI in detection of bone metastases [26]. However, this finding needs to be confirmed in larger trials.

Radioimmunotherapy

Endoradiotherapy using peptides or antibodies combines the favourable targeting properties with the effect of radiation-induced cell death. In endoradiotherapy, smaller amounts of drug can be applied as compared to other forms of cancer therapy. Furthermore, these drugs can not only be labelled with therapeutics nuclides but also with diagnostic ones. Thus, it is possible to perform imaging and dose estimation of the compound prior to the treatment. As the radiation is not restricted to the targeted cell, it may also affect all tumor cells in its range; for electrons, typically a few millimetres from the directly targeted cell. This effect, called “bystander” or “crossfire effect”, is particularly important for treatment of tumors with a heterogeneous antigen or receptor expression or insufficient vascularization [•2]. The most common nuclides that are currently used for endoradiotherapy are β -emitters such as ^{131}I , ^{177}Lu , and ^{90}Y . Several studies have shown that medium-energy β -emitters, ^{131}I and ^{177}Lu , are more effective for the treatment of small tumors [•2;•3]. In larger tumors, isotopes emitting high-energy β -radiation might present a better alternative [•2;•3]. For example, β -radiation of ^{90}Y has a much longer range in tissue (12 mm) than ^{131}I (3 mm) and ^{177}Lu (2.5 mm) [•3] and would be more effective for treatment of larger tumors.

Advanced prostate cancer is attractive for RIT since metastases from prostate cancer are almost exclusively located in bone marrow and lymph nodes (good access to antibodies) and the metastases are often small enough to ensure good antibody penetration [27;28]. *Goldenberg et al.* were the first to demonstrate that a prostate-associated marker could be targeted and imaged by antibodies labelled with radionuclides [29]. Later *Meredith et al.* treated prostate cancer patients with ^{131}I -labelled CC49 monoclonal antibodies to TAG 72 [30]. Six of 10 symptomatic patients had bone pain relief, but no patients met the radiographic or PSA criteria for objective response. Positive imaging of bone and/or soft-tissue lesions was noted for 13 of the 15 patients.

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein which is expressed by nearly all prostate cancers and their metastases [27]. PSMA is upregulated in poorly differentiated and advanced prostate cancer. PSMA is not secreted like PSA which makes PSMA an excellent target in prostate cancer. The first commercial antibody against PSMA was 7E11, which is used in ^{111}In -CYT-356 (ProstaScint) - a FDA-approved imaging agent for evaluation of metastatic prostate cancer [27]. In two trials CYT-356, labelled with ^{90}Y , had no therapeutic effects in prostate cancer patients [31;32]. This lack of therapeutic efficacy is due to the fact that 7E11 antibody targets an intracellular epitope of PSMA and therefore binds only to permeabilized, necrotic cells. This observation led to the development of the monoclonal antibody J591, which specifically targets epitopes located on the external domain of PSMA [33]. Thus, J591 binds to both intact and permeabilized cells. J591 labelled with radionuclides has been tested in in-vitro, in vivo, and recently in clinical trials [34-42].

In radioimmunotherapy, myelotoxicity due to bone marrow radiation-absorbed doses (BMrad) is frequently the dose-limiting factor that determines the maximum tolerated dose (MTD). In a dose-escalation study by *Vallabhajosula et al.* 28 patients with prostate cancer received either ^{90}Y - or ^{177}Lu -labelled J591 antibodies for radioimmunotherapy [39]. It was demonstrated that myelotoxicity after treatment with ^{177}Lu -J591 could be predicted on the basis of the amount of radioactive dose administered or the BMrad. However, there was no correlation between myelotoxicity and ^{90}Y -J591 dose. This may be explained by the fact that the cross-fire effect of high energy beta particles within the bone and the marrow may deliver radiation doses nonuniformly within the bone marrow. Alternatively, ^{90}Y -J591 may be less stable than ^{177}Lu -J591 in vivo and, as a result, higher amounts of free ^{90}Y may be localized in the bone. In a phase I trial, *Bander et al.* found the MTD of ^{177}Lu -J591 to be 70mCi/m² in a study including 35 patients with progressing androgen-independent prostate cancer [42]. Multiple doses of 30 mCi/m² were well tolerated, and excellent targeting of known sites of prostate cancer metastases was shown in the study. In a recent study by *Pandit-Tascar et al.*, 14 patients with metastatic prostate cancer received escalating doses of ^{111}In -J591 in a series of administrations each separated by 3 weeks [•41]. In these 14 patients, a total of 80 lesions were detected. Both skeletal and soft-tissue metastases were targeted by the antibody as seen on ^{111}In -J591 scans. The antibody localized 93.7% of bone lesions detected by conventional imaging. The results from this study indicate that the optimal antibody mass for RIT may be greater than or equal to 50 mg. Recently, *Tagawa et al.* found in a phase II trial that a single dose of ^{177}Lu -J591 was well tolerated, with reversible myelosuppression, and demonstrated anti-tumor activity in patients with progressive metastatic castrate-resistant prostate cancer [43]. Excellent targeting of known sites of metastases was seen in 31 of 32 (97%) patients, with trend for better response with more intense imaging.

Other tumor antigens, such as HER2, CA 170, L6, and E4 antigen may also serve as targets for RIT in prostate cancer [27]. Overexpression of the HER2 receptor protein and amplification of the HER2 gene have been implicated in tumor development and progression, and associated with a poor prognosis in several types of cancers [•44]. In prostate cancer patients, HER2 expression is associated with disease progression and androgen independence [45;46]. Furthermore, preoperative plasma HER2 levels are associated with prostate cancer progression after radical prostatectomy and predict for aggressive outcome after chemotherapy [45;•47]. Therefore, HER2 imaging and treatment with HER2-specific antibodies, un-conjugated or labelled with radionuclides for RIT, has become an attractive therapeutic option for castration resistant prostate cancer patients. *De Bono et al.* found the HER2 inhibitor pertuzumab ineffective in an open phase II study including patients with castration resistant prostate cancer [48]. There may be several explanations why pertuzumab was ineffective in this study, including insufficient target inhibition at the dose levels used, limited dependence of the treated tumours on HER2 signalling, differences in drug penetration to various HER2-expressing

tumors, and the unknown HER2 status of the patients (immunohistochemistry, serum level etc.) prior to treatment.

There is increasing evidence that small non-immunoglobulin based tracers have the best potential for the development of high-contrast imaging agents for visualization of HER2 in vivo as compared to whole full-length monoclonal antibodies. Affibody molecules are a new class of relatively small proteins based on a 58-amino-acid scaffold, derived from the B domain of *Staphylococcus aureus* protein A. Combinatorial randomization of 13 amino acid in the binding site of that scaffold lead to creation of Affibody library containing 3 billions members, each characterized by a unique amino acid composition determining binding to the unique target structures. The specific binders can be identified by the phage display selection method. Their small size (Affibody molecules are 20 x smaller than antibodies) and high specificity makes them ideal candidates for imaging purposes allowing for rapid blood clearance and good tumor penetration. Furthermore, the lack of sulfite bridges and high stability facilitate the conjugation chemistry [44]. Recently, *Kramer-Marek et al.* have radiolabeled a HER2-binding Affibody molecule with ^{18}F for in vivo monitoring of HER2 expression by PET [••49]. The same tracer was then used to assess the changes of HER2 expression following therapeutic intervention [••50]. PET imaging of HER2 has also been found promising by *Cheng et al.* in a xenograft tumor model [•51]. *Baum et al.* recently presented pilot clinical data on HER2 imaging using HER2-specific Affibody molecules labelled with ^{111}In or ^{68}Ga [52]. The results suggested that the use of HER2-specific Affibody molecules facilitate high quality SPECT and PET/CT imaging. It was possible to detect even very small malignant lesions. *Tolmachev et al.* labelled a HER2-specific Affibody molecule with ^{177}Lu for radionuclide therapy of HER2-positive microxenografts, a promising approach for treatment of micrometastases by HER2-expressing malignant tumors [••53]. *Puri et al.* have recently used nanoparticles, i.e., thermosensitive liposomes conjugated with Affibody molecules (Affisomes) as vehicles for HER2-specific delivery of therapeutic agents. [54]. Affisomes present a promising, novel strategy for HER2-specific drug-delivery that could be used to improve the treatment of HER2-positive tumors. Although major challenges must be addressed (further clinical development of Affibody molecule-based imaging agents, optimization of clinical protocols regarding amount of tracer injected, radioactivity, imaging time, etc.), HER2 represents an attractive target for PET/CT and RIT of HER2-expressing tumors. At present, the main role of HER2 imaging is to select patients that would benefit from anti-HER2 therapy with trastuzumab [44]. HER2 imaging may also have the potential to predict for response to therapy, to evaluate the effect of a given therapy, and to detect recurrence of disease.

CONCLUSION

Today's molecular imaging technologies aim to provide early and accurate detection of cancers at initial presentation, and following therapeutic interventions. Advances in imaging techniques may lead to early prostate cancer detection, more accurate tumor staging, better monitoring of the disease, and early and accurate detection of recurrence. The role of PET/CT in prostate cancer is still being established, especially in the detection of recurrences and bone metastases. As no effective therapies are available for advanced metastatic disease, there is a need for new treatment modalities. Prostate cancer is well-suited for molecular imaging and radioimmunotherapy, leading to the development and clinical evaluation of therapeutic monoclonal antibodies and engineered affinity proteins directed to targets in prostate cancer.

Abbreviations

BMrad, bone marrow radiation-absorbed doses
BPH, benign prostatic hyperplasia
CT, computerized tomography

FCH, fluorocholine
 FDG, fluorodeoxyglucose
 LN, lymph nodes
 MDP, methylene diphosphonate
 MTD, maximum tolerated dose
 MRI, magnetic resonance imaging
 PET, positron emission tomography
 PSA, prostate specific antigen
 PSMA, prostate specific membrane antigen
 RIT, radioimmunotherapy

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