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Molecular Imaging of Urogenital Diseases

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Abstract

There is an expanding and exciting repertoire of PET imaging radiotracers for urogenital diseases, particularly in prostate cancer, renal cell cancer, and renal function. Prostate cancer is the most commonly diagnosed cancer in men. With growing therapeutics options for the treatment of metastatic and advanced prostate cancer, improved functional imaging of prostate cancer beyond the limitations of conventional computed tomography (CT) and bone scan (BS) is becoming increasingly important for both clinical management and drug development. PET radiotracers beyond ^{18}F -Fluorodeoxyglucose (FDG) for prostate cancer include ^{18}F -Sodium Fluoride, ^{11}C -Choline and ^{18}F -Fluorocholine and ^{11}C -Acetate. Other emerging and promising PET radiotracers include a synthetic L-leucine amino acid analog (anti- ^{18}F -FACBC), dihydrotestosterone analog (^{18}F -FDHT) and prostate specific membrane antigen (PSMA) based PET radiotracers (ex. ^{18}F -DCFBC, ^{89}Zr -DFO-J591, ^{68}Ga (HBED-CC)). Larger prospective and comparison trials of these PET radiotracers are needed to establish the role of PET/CT in prostate cancer. Renal cell cancer imaging with FDG PET/CT although available can be limited, especially for detection of the primary tumor. Improved renal cell cancer detection with carbonic anhydrase IX (CAIX) based antibody (^{124}I -girentuximab) and radioimmunotherapy targeting with ^{177}Lu -cG250 appear promising. Evaluation of renal injury by imaging renal perfusion and function with novel PET radiotracers include p- ^{18}F -fluorohippurate (^{18}F -PFH) and hippurate m-cyano-p- ^{18}F -fluorohippurate (^{18}F -CNPFH) and Rubidium-82 chloride (typically used for myocardial perfusion imaging). Renal receptor imaging of the renal renin angiotensin system with a variety of selective PET radioligands are also becoming available for clinical translation.

PROSTATE CANCER

Prostate cancer is the mostly commonly diagnosed cancer and the second leading cause of cancer death among men in the United States.(1) The paradigm of cancer care in the future will be a risk adapted patient-specific therapy designed to maximize cancer control while minimizing the risk of complications and side effects. PET based molecular imaging techniques promises to play an important role in prostate cancer care in the future.

Most patients diagnosed with prostate cancer in the United States have clinically localized disease at diagnosis and despite definitive therapy of the primary disease by radical prostatectomy (RP) or external-beam radiation therapy. Many of these patients will eventually have biochemical recurrence and receive androgen-deprivation therapy (ADT). Subsequently, despite castrate levels of testosterone these patients will progress to develop

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castration-resistant prostate cancer (CRPC) usually with detectable metastatic disease, most commonly in bone then lymph nodes. (2)

In the past only docetaxel-based chemotherapy improved survival in patients with CRPC compared with mitoxantrone (3). Since 2010, the therapeutic options for the treatment of metastatic and advanced prostate cancer are now greatly improved especially for those patients with metastatic CRPC. There are now a myriad of novel anticancer drugs for CRPC including the novel taxane cabazitaxel, the immunotherapy sipuleucel-T, the anti-androgen CYP17 inhibitor abiraterone, the novel androgen-receptor antagonist enzalutamide and the alpha-emitting radioisotope radium-223. In addition to these newly approved therapies, there are a large number of targeted therapies that are being assessed at different phases of clinical trial development. (3, 4)

Issue that arise when evaluating these new therapeutic agents, and need for assessment of combinatorial studies of these agents, raises a need for robust biomarkers for optimization of therapy development and clinical management of this growing therapeutic armamentarium. Current strategies to evaluate disease response and progression employ a combination of parameters, including rising serum PSA levels, CT and bone scan criteria and worsening clinical symptoms which are limited in their sensitivity for monitoring disease progression. Current conventional imaging modalities for prostate cancer such as computed tomography (CT) and ^{99m}Tc -based bone scintigraphy have been limited by low accuracy, low specificity, and inability to detect nodal disease for bone scintigraphy. Newer imaging methodologies utilizing SPECT and PET based radiopharmaceuticals for prostate cancer detection promise improved detection of bone and lymph node metastases compared to current conventional imaging modalities. Despite advances in therapy options, the diagnostic landscape has remained relatively unchanged however. Newer imaging modalities may render a substantial proportion of patients with CRPC thought to be non-metastatic to be in fact metastatic based on the improved sensitivity of these imaging modalities. This raises the question whether earlier detection of metastatic disease in prostate cancer will ultimately result in any clinical benefit? An emerging variety of imaging techniques raise the need to reassess the optimal methodology and timing of metastasis detection of various imaging techniques.(2)

Functional imaging modalities such as PET with 3-dimensional spatial imaging and functional read out of a particular metabolic or molecular imaging signal are unique in their ability to assess tumor heterogeneity compared to other biomarkers. The main clinical indications for imaging can be broadly classified as: (1) diagnosis and initial staging, (2) detection of biochemical recurrent metastatic disease, (3) detection of advanced castrate resistant metastatic disease.(5) Currently available PET radiopharmaceuticals for prostate cancer imaging include glucose, choline, acetate and sodium fluoride based detection methodologies. Emerging radiopharmaceuticals include amino acid, androgen receptor, and prostate specific membrane antigen (PSMA) based radiotracers.

Glucose Metabolism

Detection of prostate cancer by utilizing ^{18}F -FDG (FDG) for glucose metabolism is limited for detection of primary disease and local recurrence due to low sensitivity and overlap with prostatitis and benign prostatic hypertrophy (6, 7). FDG PET is not recommended for detection of metastatic disease, especially for soft-tissue metastases, in routine management of prostate cancer (8). However, the use of FDG PET for detection of metastatic disease in the clinical setting of PSA relapse after radical prostatectomy was optimized to 31% of patients with PSA by use of threshold PSA of 2.4 and PSA velocity of 1.3 ng/mL/year resulting in a sensitivity (80%; 71%) and specificity (73%; 77%), respectively for PSA parameters (9). As an outcome measure, >33% increase in the average maximal PET standardized-uptake value (SUV) of indicator lesions could potentially discriminate between

progressive or non-progressive disease on chemotherapy (10). FDG PET maximal SUV (SUV_{max}) in patients with progressive prostate cancer was also found to be an independent predictor of survival in the multivariate analysis (11).

Sodium Fluoride – Bone Remodeling

^{18}F -Sodium Fluoride (NaF) is gaining renewed interest and application for detection of osseous metastatic disease due to wider availability of PET/CT scanners, higher spatial resolution, and potential for PET quantitation of tumor burden (12), especially for prostate cancer in which metastases are bone predominant. NaF is a marker of bone perfusion and bone turnover, in which ^{18}F -Fluoride ions exchange with hydroxyl groups in the hydroxyapatite crystal of bone to form fluoroapatite with higher uptake in new bone (osteoid) because of higher availability of binding sites (12). Recent clinical practice guidelines for NaF PET/CT bone scans have been published by the Society of Nuclear Medicine and Molecular Imaging in 2010 (13). It is noted that NaF uptake post-treatment flare phenomenon, similar to that observed with ^{99m}Tc -MDP bone scans, has also been observed (14). NaF PET/CT has been reported to be a highly sensitive and specific modality for detection of bone metastases in prostate cancer compared to standard ^{99m}Tc -MDP (MDP) planar bone scans and MDP SPECT imaging (15). The anatomic CT portion of the PET/CT was able to differentiate between benign and malignant lesions improving the specificity of NaF PET/CT versus NaF PET alone. A recent systemic review of the literature provides evidence for superior detection of bone metastases by both NaF PET and a functional tumor based choline PET imaging agent (^{18}F -fluorocholine or ^{11}C -choline), with or without CT, compared with conventional planar MDP bone scan (16). This literature review found sensitivity and specificity for NaF PET or PET/CT of 88.6 and 90.7%, respectively, on per lesion basis, and 86.9 and 79.9% on a per patient basis. It is noted that NaF uptake post-treatment flare phenomenon, similar to that observed with MDP bone scans, has also been observed, which should be taken into consideration (14).

One of the benefits of NaF PET compared to ^{99m}Tc -MDP (MDP) bone scans is the potential for quantitation of tumor burden. A study of the kinetics and reproducibility of NaF PET/CT for oncology applications concluded an uptake period of 60 ± 30 minutes has limited temporal dependence with high tumor-to-normal tumor ratio (17). In terms of reproducibility, repeated baseline studies showed high intraclass correlations (> 0.9) and relatively low critical percentage change (the value above which a change can be considered real) for these parameters. An bone scan index using standard planar MDP bone scan has been proposed as an imaging biomarker to improve the reproducibility of treatment response assessment (18). This index aims to quantify tumor burden as a percentage of the total skeletal mass of a reference man. PET imaging with NaF for quantitative analysis for therapy response assessment would have benefits over MDP bone scan-based methods with one report in the literature. In this study, NaF PET when used for monitoring treatment response of bone metastases to radiotherapy ^{223}Ra -Chloride was found to be more accurate than the qualitative comparison of scans, correlating with the serum based PSA response and alkaline phosphatase activity (19).

Lipid Metabolism

Radiolabeled choline derivatives, ^{11}C -Choline and ^{18}F -Fluorocholine, are taken up in prostate cancer cells through choline transporters and phosphorylated intracellularly by choline kinase, associated with phospholipid metabolism (20-23). ^{11}C -Choline demonstrates rapid prostate cancer, rapid blood pool clearance (within minutes), relatively small excretion in urine and relatively high diffuse liver uptake (24). ^{11}C -Choline has been recently approved by the U.S. Food and Drug Administration in 2012 by the Mayo Clinic in Rochester, Minnesota, for production and PET imaging of patients with suspected recurrent

prostate cancer after initial therapy based on elevated serum prostate specific membrane antigen (PSA) levels and noninformative bone scintigraphy, CT, or MRI imaging to help localize potential sites of tumor for subsequent histologic confirmation (25). ^{18}F -Fluorocholine demonstrates higher urinary excreted radiotracer compared to ^{11}C -Choline but has the advantage of longer half-life allowing for wider distribution through regional radiosynthesis distribution networks without a need for an on-site cyclotron and radiochemistry facility (26).

Both ^{11}C -Choline and ^{18}F -Fluorocholine have been used widely for a variety of prostate cancer imaging applications, mostly in Europe and Japan, in a large number of publications. There have been several recent systematic reviews which help to compile and summarize potential clinical applications. Overall, ^{11}C -Choline PET/CT was also reported to affected therapy management in 24% (11/45) of patients with advanced prostate cancer (27).

A systematic literature review and meta-analysis by Evangelista et al. in 2013 for diagnosis performance of ^{18}F -Fluorocholine and ^{11}C -Choline PET or PET/CT for staging at initial diagnosis for prostate cancer reported low sensitivity but high overall specificity for detection of lymph node metastases prior to prostatectomy. They analyzed 10 selected studies with a total of 441 patients from 2000 to January with pooled sensitivity of 49.2% (95% confidence interval [CI], 39.9–58.4) and pooled specificity of 95% (95% CI, 92–97.1). The area under the curve was 0.9446 ($p < 0.05$) (28). They note that a major issue for the low sensitivity is due to the limitation of PET imaging to detect small metastatic lymph nodes less than 0.4 cm in diameter.

For detection of prostate cancer recurrence after definitive radical prostatectomy or external-beam radiation therapy, another systematic literature review and meta-analysis by Evangelista et al. in 2013 found ^{18}F -Fluorocholine and ^{11}C -Choline PET or PET/CT to have a high sensitivity and specificity for detection of locoregional and distant metastases (29). They selected 19 selected studies with combined total of 1555 patients from 2000 to 2012 with pooled data demonstrating sensitivity of 85.6% (95% CI: 82.9%-88.1%) and specificity of 92.6% (95% CI: 90.1%-94.6%) for all sites of disease (prostatic fossa, lymph nodes, and bone), sensitivity of 75.4% (95% CI: 66.9%-82.6%) and specificity of 82% (95% CI: 68.6%-91.4%) for prostatic fossa recurrence, and sensitivity of 100% (95% CI: 90.5%-100%) and specificity of 81.8% (95% CI: 48.2%-97.7%) for lymph node metastases. They conclude that choline PET/CT can be used for the identification of lymph node recurrence, but raise concerns that due to the loss in specificity it could determine unnecessary surgical treatments. The authors recommend identification of relapse in prostate cancer patients with the strongest predictor of PET positivity based on threshold PSA-based parameters (PSA > 1 ng/mL, PSA velocity (vel) > 1 ng/mL/year, and a PSA_{dt} < 3 months. Ongoing hormonal therapy did not limit the diagnostic accuracy for detection of metastatic disease. However, they do not recommend choline PET/CT for detection of local recurrence.

Umbehr et al. performed another systematic review and meta-analysis of ^{18}F -Fluorocholine and ^{11}C -Choline PET or PET/CT for staging and restaging of prostate cancer (30). They reviewed the literature from up to July 2012 and selected 44 studies. They concluded that due to the limited number of studies per clinical scenarios, meta-analysis was not possible in patients with suspected prostate cancer on a per-lesion level for patients with biochemical failure after local treatment with curative intent, or in patients with advanced-stage disease. The authors cannot be recommend Choline PET or PET/CT imaging without reservation for routine clinical use for prostate cancer imaging based on current evidence, although the diagnostic evidence was found to be higher in restaging than in staging settings. They also recommend careful selection of eligible patients seems to avoid false negative imaging results up front in staging as well as restaging clinical scenarios. In staging settings, mainly

high-risk Gleason scores (8–10) and high PSA levels (≥ 20 ng/mL) were thought to be predictive. In restaging settings, minimal recurrent PSA levels (> 1 ng/mL), short PSAdt (< 3 mo to a maximum of 6 months) and initial tumor stage ($> pT3b$ or $pN1$) were found to improve imaging detection.

A review of the literature of ^{11}C -Choline by Fuccio et al. (31) reported the use of ^{11}C -Choline for initial diagnosis and local staging of prostate cancer was not recommended due to low sensitivity and specificity, and reserved for individual cases to help direct transrectal ultrasound (TRUS) guided biopsy in which patients with at least two inconclusive previous TRUS biopsies. Preoperative lymph node staging studies showed a wide range of sensitivities but good specificity and positive-predictive value (PPV), with potential application for use for patients selected for high risk for lymph node metastases by nomograms in order to reduce negative or inconclusive PET findings. Further studies incorporating cost-effective analyses in large prospective studies are recommended to fully assess this application of ^{11}C -Choline. Studies for ^{11}C -Choline for restaging to detect of metastatic disease in the setting of PSA recurrence demonstrated high detection rates compared to conventional imaging modalities with a direct correlation of PET metastatic detection rates to serum based PSA parameters (trigger threshold PSA values, PSA kinetics). They similarly recommend a clinical algorithm in which patients with proposed trigger serum PSA of > 1.5 - 2 ng/mL and fast PSA doubling time (PSAdt) of < 7 - 8 months would warrant an ^{11}C -Choline PET as a first imaging procedure for restaging.

In a systematic review of ^{18}F -Fluorocholine for prostate cancer imaging in 37 studies including 1244 patients ranging from 2001 to August 2011 was performed by Bauman et al. for a variety of clinical indications (32). On basis of these studies, the authors make similar recommendations as on other systematic reviews for the following clinical scenarios where ^{18}F -Fluorocholine PET can be considered for further evaluation in clinical trials: (1) Target biopsy in high-risk men with persistently elevated PSA and repeated negative biopsy, (2) Initial staging in intermediate-to high-risk population (PSA > 10 ng/mL or GS ≥ 7), (3) Restaging in recurrent and castrate-resistant disease (> 2 ng/mL, shorter PSA doubling times, or initially higher GS ≥ 7), (4) Definition of dominant intra-prostatic foci or limited LN recurrence for focal therapy escalation or focal salvage therapy, and (5) Treatment Monitoring of hormone therapy or radiation therapy.

Acetate is incorporated into prostate cancer cells due to over-expression of fatty acid synthase, a key enzyme in fatty acid synthesis from acetyl CoA (33). ^{11}C -Acetate was first demonstrated to detect primary prostate cancer and metastatic disease at initial staging (34) patients with rising PSA after radical prostatectomy or external-beam radiation therapy (35).

A recent systematic review of the literature with meta-analysis of ^{11}C -Acetate PET imaging in prostate cancer was published by Beheshti et al. in 2013 (36). They reviewed all published studies up to March 2013 and selected 24 studies for meta-analysis. For primary tumor detection, pooled sensitivity 75.1% (95% CI: 69.8–79.8) and specificity was 75.8% (95% CI: 72.4–78.9). For detection of recurrence tumor, pooled sensitivity was 64% (95% CI: 59–69) and specificity was 93% (95% CI: 83–98), with higher sensitivity in patients with PSA > 1 ng/mL and in post prostatectomy compared to external-beam radiation therapy patients. Studies comparing ^{11}C -acetate and Choline based PET imaging were reported to be comparable in their analyses with low sensitivity and relatively high specificity for detection of tumor recurrence and limited value for detection of primary tumor.

When ^{11}C -Acetate was compared with MRI and prostatectomy histopathological correlation, ^{11}C -acetate PET/CT demonstrated higher uptake in tumor foci than in normal prostate tissue but PET uptake was not able to distinguish tumor from benign prostate

hyperplasia nodules. In a sector-based comparison with histopathology, all tumors greater than 0.5 cm by histopathology revealed sensitivity of 61.6% and specificity of 80.0% for ^{11}C -acetate PET/CT, versus sensitivity of 82.3% and specificity of 95.1% for multi-parametric MRI (T1, T2, DWI, MRS), with the accuracy of ^{11}C -acetate comparable to that of MRI when only tumors greater than 0.9 cm were assessed (37).

A recent large trial evaluated ^{11}C -Acetate PET/CT prior to prostatectomy for nodal staging compared with pathologic nodal status and clinical follow-up for treatment failure in 107 men with intermediate- or high-risk localized prostate cancer (38). ^{11}C -Acetate was positive for local pelvic nodal or distant metastatic disease in 33.6% of patients, with lymph node metastasis present histopathologically in 23.4% of these PET positive metastatic patients. The overall performance of ^{11}C -Acetate for detection of lymph node metastasis prior to prostatectomy revealed a sensitivity of 68.0%, specificity 78.1%, positive-predictive value of 48.6%, and negative predictive value of 88.9%. ^{11}C -acetate PET positivity for any metastasis in this clinical study also independently predicted treatment-failure-free survival in a multivariate analysis.

FACBC

Anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC) is a synthetic L-leucine amino acid analog which is taken up in prostate cancer cells by amino acid transporters system ASC transporter 2 (ASCT2) and to a lesser sodium-coupled neutral amino acid transporters but not incorporated into proteins intracellularly (39). The initial clinical study of anti- ^{18}F -FACBC demonstrated uptake in primary prostate and metastatic disease (40). Subsequent clinical study comparing anti- ^{18}F -FACBC with ^{111}In -capromab pendetide for detection of recurrent disease in fifty men after prostatectomy or external-beam radiation therapy for prostate carcinoma revealed anti- ^{18}F -FACBC PET/CT was more sensitive than anti- ^{18}F -FACBC SPECT/CT for detection of recurrent disease, especially for detection of extraprostatic recurrence. For disease detection in the prostate bed, anti- ^{18}F -FACBC had a sensitivity of 89 % (95% CI: 74%- 97%), specificity of 67% (95% CI: 35%-90%), and accuracy of 83% (95% CI: 70%-93%). For the detection of extraprostatic recurrence, anti- ^{18}F -FACBC had a sensitivity of 100% (95% CI: 69%-100%), specificity of 100% (95% CI: 59%-100%), and accuracy of 100% (95% CI: 80%-100%). A recent small study compared anti- ^{18}F -FACBC with ^{11}C -Choline PET/CT imaging for detection of recurrent disease in 15 men after definitive therapy with prostatectomy or external-beam radiation therapy. Anti- ^{18}F -FACBC was found to have a higher detection rate compared to ^{11}C -Choline on a per patient (detection rate of 40% versus 20%, respectively) and per lesion basis (6 versus 11 lesions, respectively), with all ^{11}C -Choline positive lesions also identified by anti- ^{18}F -FACBC (41). These promising initial studies will need further validation anti- ^{18}F -FACBC in larger multi-center clinical trials.

FDHT

16 β - ^{18}F -fluoro-5 α -dihydrotestosterone (^{18}F -FDHT) is an analog of dihydrotestosterone, the primary ligand for the androgen-receptor (AR) which can non-invasively image AR expression (42). An initial study of seven patient with progressive metastatic castrate-resistant prostate cancer demonstrated ^{18}F -FDHT detection of 78% of the lesions compared to conventional imaging in patients with progressive castrate-resistant prostate cancer with average lesion SUV_{max} value of 5.28 (43). Another early study also demonstrated ^{18}F -FDHT uptake at sites of metastatic disease, which after competition of the AR with flutamide, demonstrated interval decreased ^{18}F -FDHT uptake from baseline (SUV_{max} decreased 9% to 70%) suggesting tumor uptake is an AR-mediated process (44).

^{18}F -FDHT and FDG PET/CT imaging of a subset of 22 patients enrolled on a phase 1-2 study of MDV3100 (Enzalutamide) demonstrated a reduction in ^{18}F -FDHT tumor uptake from baseline (range of percent SUV_{max} change 20-100%) after starting treatment consistent with competition and displacement of MDV3100 with the AR binding site (45). However, only 45% of these patients receiving ^{18}F -FDHT PET/CT scans had 25% or greater decrease in the SUV_{max} after 12 weeks of therapy, which would be compatible with ^{18}F -FDHT as a pharmacodynamic marker of AR binding rather than a therapy response biomarker. A more recent study also utilized ^{18}F -FDHT-PET/CT imaging to measure pharmacodynamic response in a phase I clinical trial of a novel anti-androgen ARN-509 to incorporate imaging to visualize and quantitatively assess by SUV analysis the heterogeneity of AR-binding sites of metastatic disease and determine maximal AR inhibition by the study drug (46). A clinically applicable method using ^{18}F -FDHT PET quantitative marker as a surrogate of pharmacokinetic parameter to non-invasively assess free AR concentration has been proposed for validation studies in clinical trials (47).

PSMA

Prostate-specific membrane antigen (PSMA) is a type II integral membrane protein expressed on the surface of prostate cancer cells, also called glutamate carboxypeptidase II (GCPII) and folate hydrolase (48). PSMA is a promising and a biologically established biomarker specifically associated with prostate cancer aggressiveness. Histological studies have associated high PSMA expression with metastatic spread (49-51), androgen-independence (52), and expression levels have been found to be predictive of prostate cancer progression (53, 54). The first clinical imaging agent for prostate cancer imaging with PSMA was ^{111}In -capromab pendetide demonstrated limited performance for tumor detection which may be explained by binding to the intracellular epitope of PSMA (55). A humanized intact antibody that binds to the extracellular epitope of PSMA, J591, has been used labeled to Indium-111 and Lutetium-177 for gamma planar and SPECT/CT imaging of metastatic prostate cancer as part of a number of radioimmunotherapy trials (56-60). A recent retrospective review of these trials presented as a research abstract ranging over a decade demonstrated J591 planar imaging reported a detection rate of 86.4% of known lesions (57). Next generation imaging trials are incorporating PET/CT imaging of prostate cancer with ^{89}Zr -DFO-J591 which demonstrated high prostate tumor uptake in preclinical models (61).

Smaller low molecular weight imaging agents for PSMA would have inherent advantages over intact antibodies such as rapid tumor uptake and clearance from nontarget sites (48). N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4- ^{18}F -fluorobenzyl-L-cysteine (^{18}F -DCFBC) is a clinically practical low-molecular weight inhibitor of PSMA which in preclinical studies demonstrated high specific localization to PSMA-expressing prostate cancer xenografts (62). An initial first-in-man study of ^{18}F -DCFBC PET/CT was able to demonstrate uptake at sites of bone and lymph node metastatic disease detected at two hours after injection, with ^{18}F -DCFBC PET detecting more lesions than corresponding conventional imaging modalities (CT, bone scan) (63). These findings are undergoing further validation in ongoing clinical trials evaluating ^{18}F -DCFBC PET/CT in primary and metastatic prostate cancer. Another fluorine-18 labeled low molecular weight PSMA targeted PET radiopharmaceutical, BAY 1075553, has been published recently with preclinical validation (64).

Gallium-68 labeled PSMA-based low molecular weight radiopharmaceuticals also have been radiosynthesized (65). Afshar-Oromieh et al. reported their initial experience with PET/CT using Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBED-CC)] (^{68}Ga -PSMA) which also was able to detect prostate carcinoma relapses and metastases at high signal-to-background

at one hour after radiopharmaceutical administration (66). Another recent study comparing ^{68}Ga -PSMA with ^{18}F -Fluorocholine with biochemical relapse of prostate cancer in the same patients within a 10 day time window in 37 patients was able to detect more lesions and higher signal-to-background by ^{68}Ga -PSMA compared to ^{18}F -Fluorocholine (78 versus 56, respectively; $P=0.04$) (67).

First-in-man study of two Iodine-123 labeled small molecule SPECT agents for PSMA, ^{123}I -MIP-1072 and ^{123}I -MIP-1095, also demonstrated uptake and detection of prostate cancer in soft tissue, bone, and the prostate gland as early as one to four hours after injection (68). Cell culture studies with prostate cancer cells showed high-affinity binding of ^{123}I -MIP-1072 and ^{123}I -MIP-1095 to PSMA on these cells and indicated internalization into the cell after PSMA binding by endocytosis (69), which is the proposed mechanism of internalization of other small molecule and antibodies binding to PSMA. Other SPECT agents for PSMA have been radiosynthesized with technetium-99m demonstrating high specific PSMA targeted tumor uptake in preclinical models (70-72).

Evans et al reported in preclinical studies that PSMA can be repressed by androgen treatment in multiple animal models of AR-positive prostate cancer in an AR-dependent manner, whereas anti-androgens can up-regulate PSMA expression (73). When treated with an anti-androgen, MDV3100, increased PSMA expression in response to treatment was able to be quantitatively measured non-invasively human prostate cancer xenograft models by ^{64}Cu -J591 PET imaging. Assessment of androgen receptor signaling in circulating tumor cells was able to utilize PSMA and prostate-specific antigen (PSA) expression as a marker of hormonally responsive prostate cancer to androgen deprivation therapy (74). In their model, cells initially have increased PSMA but decreased PSA expression in an androgen-starved/androgen-inhibited “AR-off” environment compared to “AR-on” environment when exposed to androgen with a change in phenotype to decreased PSMA expression and increased PSA expression. With the emergence of these PSMA radiopharmaceuticals the possibility of utilizing non-invasive PSMA imaging by PET/CT or SPECT/CT as a downstream biomarker of androgen-receptor signaling is a possibility.

RENAL CELL CANCER

Glucose metabolism

Clear cell renal cell carcinoma (RCC) is the most frequent malignant tumor of the kidneys (RCC) while papillary (chromophil) RCC, chromophobe RCC and collecting duct type RCCs are less common. Malignant tumors in the kidneys of nonrenal epithelial origin include lymphomas, malignant fibrous histiocytomas and angioliopomas. Best treatment of RCC is surgery in early stages but due to its high metastatic potential the overall prognosis of RCC is poor (75). Novel medical therapies which are based on molecular targeting prolong patient life by metabolically silencing the tumor (76) and molecular imaging aids detection of targetable tissue (77) and evaluation of treatment response.

Detection of renal cell carcinoma has been hampered by the background activity caused by excretion and accumulation of FDG in the renal parenchyma. A meta-analysis of multiple publications revealed a pooled sensitivity and specificity of FDG PET/CT of 62 % and 88% for renal lesions. For extrarenal lesions the pooled sensitivity and specificity was 84% and 91 % on a per lesion basis (78).

Clear cell RCC is characterized by increased glucose uptake, increased lactate production and a switch from oxidative to glycolytic metabolism (79). The glucose transporter subtype 1 (GLUT1) is strongly expressed in clear cell RCC (80) and the reason for the limited accuracy of detection is the accumulation of FDG in the normal renal parenchyma.

Glucose undergoes glomerular filtration and is reabsorbed from the tubular lumen mostly in segment S1 by means of the type 2 sodium glucose transporter (SGLT2). FDG also undergoes glomerular filtration but its affinity for the SGLT2 is low. Approximately 56 % of filtered glucose but only 16 % of filtered FDG is reabsorbed in the proximal tubule. Net effect is accumulation of the radiopharmaceutical in the renal tubules, collecting system and urinary bladder. Urinary dilution can reduce the intensity of tracer accumulation (81) in the urinary system which increases detectability of tumor. Detection of renal cancer enhanced in renal insufficiency (82).

FDG PET can be used for characterization of indeterminate renal masses. Renal cysts are very common in the adult kidney. They are divided into 4 categories Bosniak I-IV. FDG PET is best for characterization of indeterminate cysts of categories IIF and III (83). During the diagnostic workup for RCC, FDG PET can help detect vascular invasion as well as local (lymph nodes, adrenals) and distant metastatic foci. Of particular importance is metabolic characterization of thrombi in the vicinity of RCC (84). FDG uptake indicates intravascular invasion (85, 86) and has important implications for the planning of surgical intervention (84). PET/CT is also helpful for planning tumor ablation with radiotherapy or radiofrequency therapy (87).

Distant metastatic disease detected by FDG PET/CT may represent contraindication for surgery while detection of localized disease may help choose between total or partial nephrectomy (88). During restaging after partial or radical nephrectomy FDG PET/CT has a high positive (100%) but limited negative predictive value (67%) (89).

Bony metastases of RCC can be detected by X ray radiography and elevated alkaline phosphatase levels and localization can be supported by bone scintigraphy or FDG PET/CT imaging (90). Sensitivity of both bone scintigraphy and FDG PET/CT may be limited. Promising new technique for detection of bone metastases is PET/CT with the radiopharmaceutical Na¹⁸F (91).

FDG PET/CT is an important tool for non-invasive evaluation of the spread and localization of lymphomas. Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL) can arise from extranodal sites which include the gastrointestinal tract, nervous tissue, bone, skin and the genitourinary tract. Primary renal lymphoma is rare but secondary renal involvement is frequent (92, 93). PET/CT can detect multifocal renal involvement or involvement of adjacent abdominal lymph nodes. Detection of metabolically active lymph nodes increases diagnostic certainty since interpretation of renal lymphoma can be hampered by physiologic renal uptake of FDG (94). Diffuse renal lymphoma results in diffusely increased FDG uptake (95). Renal tissue can be involved in Burkitt's lymphoma (96). Renal malignant fibrous histiocytoma is a primary renal tumor with intense FDG uptake on PET/CT (97).

When a fat-containing mass is found on a CT scan in the kidney one has to differentiate benign angiomyolipoma from a malignant tumor such as RCC, liposarcoma or Wilms tumor. FDG PET/CT imaging is useful for differentiating a renal angiomyolipoma with low uptake from a fat-containing malignant tumor with high uptake (98). Renal angiomyolipoma with a low fat content and extrarenal involvement is hard to be differentiated from RCC with lymph node metastases. However, angiomyolipoma biochemically uses a very high level of 11C-acetate, a substrate for acetyl coenzyme A synthetase in free fatty synthesis. Uptake of C-11 acetate in angiomyolipomas is also high (99). C-11 acetate is of particular for detection of multicentric angiomyolipoma (99). The epithelioid variant of renal angiomyolipoma is more malignant and shows increased FDG uptake (100). The uptake of FDG in oncocytomas may also be variable and of limited value for differentiation from renal cell carcinoma (83).

Urothelial carcinoma is a malignant epithelial tumor of the renal collecting system, renal pelvis, ureter or bladder. Most common histological type is transitional cell cancer. In the kidneys it occurs in the pelvis and represents 5-10 % of the renal carcinomas (101). Detection is hampered by the presence of urinary FDG but it can be enhanced by urine dilution, administration of Lasix, delayed imaging and with the help of coregistered CT images (102). Correlation with the registered CT images will help detection of extravascular extension, involvement of adjacent pelvic organs and evaluation of regional or distant nodal disease (102). All these findings are important for treatment planning.

Molecular markers and therapeutic targets

Molecular markers are being developed as diagnostic agents complementary agents to imaging in RCC (103). Both molecular markers and therapeutic targets share underlying genetic alterations. Genes that have been linked to RCC include von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé (BHD) syndrome, hereditary leiomyomatosis and renal cell carcinoma (HLRCC), succinate dehydrogenase (SDH)-associated familial kidney cancer, and tuberous sclerosis complex. VHL subtype 2B has particularly high risk for clear cell kidney cancer (76) and can also lead to multiple other tumors. When any of the masses reaches 3 cm in size it gets resected, otherwise treatment involves targeting the VEGF and mTOR pathways (104, 105).

In addition to mTOR (mammalian target of rapamycin), the second important molecular pathway essential to the pathophysiology of clear cell RCC is the hypoxia-inducible factor (HIF) pathway which is often associated with mutations of the VHL suppressor gene (106). Hence, therapeutic molecular targets of renal cancer include the HIF and mTOR. Other potential targets are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiopoietin receptor 2 (TIE2), hepatocyte growth factor (HGF), proto-oncogene that encodes a protein known as hepatocyte growth factor receptor (c-MET), transforming growth factor alpha (TGF- α), Epidermal growth factor receptor (EGFR), cyclin D1, Cell division protein kinase 6 (Cdk6), interleukin-6 (IL-6), lactate dehydrogenase A and monocarboxylate transporters (107).

In healthy tissues hypoxia stabilizes HIF which triggers angiogenesis, glycolysis, cell migration, cell survival and stem cell recruitment, mechanisms aiming at improvement of the effects of reduced oxygenation. In RCC and many other cancer types loss of VHL constitutively activates HIF inspite of adequate oxygen supply. Stabilization of HIF factors in the presence of sufficient oxygen has been called pseudohypoxia (108). True hypoxia may also be present when tumor outgrows its vascular supply and results in radioresistance and chemoresistance of the tumor. This increases the importance of hypoxia PET/CT imaging with radiopharmaceuticals such as ^{18}F -fluoromisonidazole CT (109).

Metabolism measured by deoxyglucose uptake is not uniform among renal tumors which is related to the heterogeneous profile of HIF expression (83, 110). FDG PET with SUV measurement may provide a biomarker opportunity, as high-SUV patients demonstrate poorer survival than those with reduced deoxyglucose uptake (111).

Overexpression of HIF-responsive growth factor TGF- α and its receptor EGFR is frequent in RCC yet the treatment efficacy of EGFR inhibitors is limited. This is explained by upregulation of other hypoxia inducible genes such as vascular endothelial growth factor (VEGF), erythropoietin (EPO) and glucose transporter GLUT1 (112). 70 % of renal cancer respond to angiogenesis inhibiting VEGF inhibitors such as bevacizumab, sunitinib, sorafenib, or pazopanib. VEGF inhibitors inhibit tyrosine kinase receptors simultaneously acting as VEGF-R and PDGFR (112). Using ^{18}F -fluoromisonidazole PET/CT one has shown that sunitinib reduced hypoxia in hypoxic but not in non-hypoxic metastatic tumor

masses (109). Cardiovascular toxicities and tumor resistance to VEGF inhibitors can occur and have been linked to interleukin-8 polymorphisms (107). Bevacizumab (Avastin®) is a monoclonal humanized recombinant antibody against VEGF that neutralizes circulating isoforms of VEGF (112).

Carbonic anhydrase IX (CAIX) is a transmembrane glycoprotein which catalyzes hydration of CO₂ to HCO₃⁻ and H⁺. CAIX is involved in the regulation of proton flux into cells and consequently in the regulation of intracellular pH. These effects are of particular importance in cancer cells. Immunohistochemistry with the monoclonal antibody mAbG250 has revealed that CAIX is strongly expressed in clear cell RCC and moderately expressed in papillary and other forms of RCC (113). CAIX is absent in normal renal cells. In RCC, synthesis of CAIX is promoted by loss VHL and by activity of the hypoxia-inducible factor 1α (HIF-1α). This mechanism is uncoupled from hypoxia despite of the fact that hypoxia is a prominent feature of RCC (114).

In tumor tissue CAIX reduces cell adhesion, increases tumor cell motility and migration, induces neo-vascularization and enhances other hypoxia-inducible processes. Net effect is a more invasive tumor grade with increased metastatic potential and increased resistance to radiotherapy and chemotherapy (115).

CAIX has multiple potential clinical applications in RCC: as a survival/prognosis factor, as a circulating biomarker, as a diagnostic imaging target, and as a therapeutic target. Low CAIX expression correlates with increased death rate while high CAIX expression correlates with longer survival. There is also a positive correlation between CAIX expression and response of RCC to angiogenesis inhibitors (113). The imaging potential of CAIX is explained by dimerization of the protein which doubles the antibody binding epitopes in close proximity and results in enhanced binding and slow dissociation of the monoclonal antibody mAbG250. To utilize these molecular interactions for imaging and therapy, a chimeric variant (cG250) has been labeled with various radioactive isotopes such as I-131, I-124 and Zr-89 (116).

Radioimmunotherapy of RCC has been first carried out using I-131 labeled cG250. Subsequently followed by radiolabeling with metallic radionuclides was introduced based on the rationale that I-131 can be released from tumor cells in form of ¹³¹I-tyrosine while metallic label with In-111 results in prolonged cellular trapping and higher tumor-non-tumor ratios (117). For imaging clear cell RCC radiolabeled I-124-cG250 is very promising (83). Due to high countrate sensitivity and spatial resolution of PET, the positron emitting iodine isotope I-124 is particularly suited for imaging of RCC (118) and it permits quantification of antibody binding and estimation of a therapeutic radiation dose. A recent study of the diagnostic efficacy of I-124 girentuximab (I-124 G250) that was carried out in 195 patients resulted in an overall sensitivity of 86 % and specificity of 86 % (75).

Research studies carried out in nude mice showed highest therapeutic efficacy with ¹⁷⁷Lu labeled cG250 leading to treatment trials in patients with RCC. The recently published results of the Phase 1 trial showed that in patients with metastatic clear cell RCC ¹⁷⁷Lu-cG250 was well tolerated up to a dose of 2405 MBq /m² (65 mCi/m²). Most patients demonstrated stable disease up to 3 months after the first treatment, and one patient showed a partial response that lasted for 9 months. Mean tumor growth was reduced from 40% to 5.5% at 3 months after the first treatment cycle (116). In the trial In-111 labeled cG250 was used for selection of patients eligible for treatment.

RENAL INJURY

Molecular Biology

Acute kidney injury (AKI) has many etiologies including ischemia-reperfusion, infection and acute radiation. Development of injury is rapid and changes in renal function occur early. Fast determination of the cause and rapid intervention are essential to minimize risk of nephron loss. The number of nephrons in the human kidneys is set at birth and can only decrease with aging and illnesses (119). Increased serum creatinine or decreased creatinine clearance may not be sensitive enough to detect AKI in a timely fashion.

Chronic kidney disease (CKD) such as diabetic nephropathy or transplant nephropathy develops more insidiously. The loss of nephrons may be masked for a long time by compensatory mechanisms so that decreased GFR (glomerular filtration rate) may be detected in a phase of the illness when a considerable number of nephrons is lost irreversibly. The first response of the kidneys to injury includes changes in the expression of genes and molecular pathways. Potential diagnostic circulating biomarkers for early tubular injury are the kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and interleukin-18 (IL-18). On the other hand, biomarkers sensitive to glomerular injury are β_2 microglobulin and cystatin C. After acute injury there is a response delay of 2-6 h for NGAL and 6-12 h for IL-18. This delay also underlines the need for molecular imaging biomarkers which are sensitive, quantitative and capable of showing small regional changes before release of biomarkers into bloodstream or urine.

AKI and CKD are treated differently but they are often interrelated (120). Treatment delay for AKI will result in loss of nephrons and facilitate the development of CKD. On the other hand preexisting CKD (for example caused by diabetes) increases the risk of AKI (for example caused by intravenous administration of a contrast agent). In this situation AKI acts as an accelerant of CKD. An episode of dialysis-requiring AKI is associated with a 28 fold increased risk of advanced CKD (120).

Functional and structural manifestations of CKD include hypertension, hyperfiltration, tubular hypertrophy, arteriosclerosis, tubulointerstitial fibrosis and glomerulosclerosis. There is also loss of balance of hormonal interactions at the tissue level, most important of which is dysregulation of the renin angiotensin system (RAS). Hyperfiltration and glomerular hypertrophy occur at first as compensatory mechanisms; chronically they will result in irreversible remodeling which includes glomerulosclerosis and tubulointerstitial fibrosis (120).

Recovery after functional or structural renal injury is possible and either spontaneous or facilitated by proper therapy. Examples are recovery after post-infectious glomerulonephritis, pyelonephritis, ureteral obstruction, ATN. Early functional recovery is the result of compensatory mechanisms (hyperfiltration) and may or may not be followed by structural recovery (121).

Kidney injury at the cellular level includes DNA damage, apoptosis and necrosis. Mechanisms of cellular repair include mitosis of neighboring cells, dedifferentiation-proliferation-redifferentiation of epithelial cells, recruitment and differentiation of resident stem cells as well as transdifferentiation and immigration of extrarenal mesenchymal stem cells (121).

Recent research has focused on replacement of lost renal tissue by stem cells. Mesenchymal stem cells derived from bone marrow, adipose tissue or human fetal tissue including umbilical cord blood and amniotic fluid. Stem cells may help regenerate tubular cells,

podocytes, mesangial cells and endothelial cells of the glomerular capillary (122). Facilitation of these processes and monitoring of stem cells by imaging are important for future applications of stem cell therapy. Stem cells can not only repopulate lost cells but also restore paracrine functions which promote mitogenesis and suppress apoptosis. This includes release of growth factors such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (122). In vivo biodistribution of mesenchymal stem cells in small animals has been successfully monitored by bioluminescence imaging (123). The technique has helped demonstrate that the damaged kidneys preferentially recruited donor cells in glomeruli, around mesangial cells (124). In animals renal recruitment of mesenchymal stem cells has been studied with MRI after their labeling with superparamagnetic oxide (SPIO) (125).

Perfusion and Function

Perfusion imaging is an important tool for detection of renal injury. All forms of renal injury result in some loss of vascularization, attenuation of perfusion reserve and, in end effect, tissue hypoxia with activation of hypoxia-inducible pathways that promote inflammation and fibrosis (120). Single photon imaging with [^{99m}Tc]MAG3 or [^{99m}Tc]DTPA has been used extensively in the clinic but the resulting planar gamma camera images cannot separate overlapping structures of the anterior and posterior renal cortex. Correction for radioactivity arising from surrounding tissue (background correction) is also challenging. Dynamic quantitative tomographic imaging with single photon computerized tomography (SPECT) is at present technically not feasible due to the rapid renal distribution of the radiopharmaceuticals and slow speed of SPECT. Renal uptake of [^{99m}Tc]DTPA is low and corresponds to glomerular filtration fraction. Renal extraction of [^{99m}Tc]MAG3 is 3 times higher but it does not represent effective renal plasma flow (ERPF) due to a high and variable plasma protein binding of the radiopharmaceutical.

A significant step in functional imaging of the kidneys represents positron emission tomography (PET). PET signals are quantitative and can be obtained in list mode and reconstructed at the desired temporal sampling rate (126). The radiopharmaceutical p[^{18}F]fluorohippurate ([^{18}F]PFH) is stable under both *in vitro* and *in vivo* conditions and its renal clearance is suppressed by the organic anion transporter blocker probenecid (127). In rats plasma protein binding of [^{18}F]PFH is acceptable, PET images and renographic curves are of exquisite quality and outperform both ^{125}I -hippurate and ^{99m}Tc -MAG3 (128).

The other fluorine-18 labeled hippurate m-cyano-p-[^{18}F]fluorohippurate ([^{18}F]CNPFH) also demonstrates high *in vivo* stability with no metabolic degradation, minimal plasma protein binding and red blood cell uptake. However, unlike [^{18}F]PFH, a minor (about 12%) fraction of [^{18}F]CNPFH is eliminated via the hepatobiliary route (129). Hippurate excretion depends not only on kidney perfusion but also on the performance of the organic cation tubular membrane transporters. A renal blood flow study independent of membrane function can be performed with O-15 labeled water (H^2_{15}O) if a cyclotron is available for its production. Renal blood flow measured with H^2_{15}O decreases linearly with increasing renal artery stenosis and correlates with the degree of CKD. Renal blood flow measured with H^2_{15}O is 1.82 mL/min/g in healthy kidneys, 1.26 mL/min/g in chronic kidney disease and 1.49 mL/min/g in renal artery stenosis. Interestingly, follow up measurements in the stenosis group after revascularization by percutaneous transluminal renal angioplasty (PTRA) revascularization actually decreased to 1.40 mL/min/g tissue (130). For comparison, renal blood flow measurements in healthy dogs carried out with O-15 water resulted in renal blood flow values of ~2.0 mL/min/g (131).

The myocardial perfusion imaging agent, Rubidium-82 chloride has only recently been introduced for imaging renal perfusion (126). The first results show that accumulation of ^{82}Rb in the kidneys is high and the quality of PET images is excellent (Figure 5).

Impulse response functions (Figure 6b) calculated by regularized least squares deconvolution analysis (132) of the time activity curves show a peak at the first point which represents vascular onset of Rb-82 which due to the effect of deconvolution contracted to a Dirac δ function (a single point) weighted by tissue uptake parameter K_1 . The second and third points represent tracer extraction while the slow washout component represents tissue clearance. This part of the impulse response function can be fitted with a simple monoexponential function $f(t)=K_1e^{-k_2t}$, where the rate constants represent tissue uptake (K_1) and washout (k_2). Figure 6b shows that tissue uptake was 8 times higher while the distribution volume calculated as $DV=K_1/k_2$ was 3 times higher in the renal cortex than in the myocardium.

The difference between the first and second points of the renal impulse response function is small indicating very high radiopharmaceutical extraction as high as 100 %. This high extraction value still needs to be tested in diseases of the kidney. In comparison, the difference between the first and second points of the myocardial impulse response function is low which may indicate low radiopharmaceutical extraction. Accurate estimation of extraction from the myocardial impulse response function is hampered by significant vascular activity which results from spill over from the ventricular lumen into the myocardial voxels. Although effective uptake is less, washout is about 3 times slower from the myocardium ($k_2=0.118$; mL/min/g) than from the renal cortex ($k_2=0.322$; mL/min/g). This is also clearly reflected by the shape of the impulse response function.

Receptor Imaging

The renal renin angiotensin system is clearly involved in the pathophysiologies of both AKI and CKD. There is a close relationship between hypoxia and the AT1R. In cultured vascular smooth muscle cells hypoxia significantly upregulates AT1R; high environmental glucose has the same effect (133). In human fibroblasts hypoxia elevates the expression of hypoxia-inducible factor 1 α (HIF-1 α) and increases the expression of genes regulated by the hypoxia-responsive element (HRE) and upregulates both angiotensin converting enzyme (ACE) and AT1R (134).

Integrity of the podocytes is essential for a physiological, selective glomerular filtration and lack of this selectivity with protein loss plays an essential role in the development of CKD. This can happen with increased glomerular capillary pressure which is a compensatory mechanism in response to the loss of nephrons. Mechanical strain increases angiotensin II production and upregulates the expression of AT1R in podocytes which results in inhibition of nephrin expression and impairment of the glomerular sieving function (135). Protein load stimulates podocytes to release TGF- β inducing mesangial cells into myofibroblasts, an early but significant event in the development of fibrosis. Tubular cells in response to protein overload release cytokines and growth factors which promote interstitial accumulation of inflammatory cells, extracellular matrix collagen and fibronectin and other components leading to interstitial fibrosis. The importance of proteinuria and of the RAS is confirmed by the observations that both dietary protein restriction and blocking of the RAS with ARBs (angiotensin receptor blockers) or ACEIs (angiotensin converting enzyme inhibitors) have renoprotective effects (135). These renoprotective effects are manifested in delayed progression from micro- to macroalbuminuria and delayed development of interstitial fibrosis. More importantly, ARBs and ACEIs not only prevent progression of renal injury but can also induce regression of glomerulosclerotic, tubulointerstitial and vascular lesions (135). A cautiously uptitrated treatment with RAS inhibitors has also been

recommended for kidney transplant patients where it has been shown that RAS inhibitors decrease graft failure and mortality (136).

Antibodies to AT1R have been associated with hypertension in preeclampsia, malignant hypertension and non-anti-HLA mediated acute kidney graft rejection (137). AT1R antibodies bind to the second extracellular loop while angiotensin II and ARBs bind to transmembrane domains of the AT1R. Thus, imaging of the AT1R with PET should not be hampered in transplant patients with AT1R antibodies. AT1R antibodies may have agonistic effects (64) and can instigate allograft injury by activation of AT1R and triggering of the receptor's signal transduction pathways rather than by antibody induced complement directed cytotoxicity as anti-HLA antibodies do. To attenuate the pathophysiological cascades triggered by AT1R antibodies the best therapeutic approach includes plasmapheresis combined with ARBs and intensified immunosuppression. Particularly severe pathology may develop in subjects with upregulated AT1R either due receptor gene polymorphism or hypoxia (138). The AT1R may be also be upregulated inside the donor's organism after brain death (139) or in the recipient's organism due to cyclosporin treatment (140).

There is also an increased incidence AT1R antibodies in patients with diabetic nephropathy as compared to controls and diabetes mellitus without nephropathy which correlates with the presence of β 1 adrenergic receptor antibodies and increased plasma cystatin C levels. In patients with positive antibodies against both the AT1R and β 1 adrenergic receptor combined therapy with the ARB valsartan and the β adrenergic antagonist metoprolol resulted in significant reduction of urinary albumin excretion (141).

In aging upregulation of the renal medulla AT1R receptors has been observed together with an increase in the AT1R/AT2R ratio in the renal cortex, upregulation of the (pro)renin receptor and cortical ACE while the protective antioxidant enzyme manganese superoxide dismutase and the endothelial nitric oxide synthase are downregulated (142). Development of glomerulosclerosis and tubulointerstitial fibrosis have been linked to age-dependent activation of the RAS which increases the risk of both AKI and CKD. Upregulation of renal AT1R has been described in animal models of hypertension (143) and cardiorenal syndrome (144), glomerulonephritis (145) subtotal nephrectomy (146). Progression of renal and cardiac failure and atherosclerotic disease are less frequent in premenopausal women than age matched men. This is in part contributed to the effects of estrogen on the RAS (147). Using AT1R PET it has been shown in dogs that estrogen downregulates the AT1R (148).

Due to the significance of the AT1R multiple AT1R selective radioligands have been synthesized including [^{11}C]MK-996, [^{11}C]-159,884, [^{11}C]irbesartan, [^{11}C]eprosartan, [^{11}C]methyl-losartan, [^{11}C]telmisartan and [^{11}C]methyl-candesartan (149-151). Extensive experience with PET has been collected in animal models of physiology and renal pathology. *In vivo* AT1R PET demonstrated AT1R upregulation with ACEI treatment (152) and with high salt intake (131). Effect of high salt intake resulted in upregulation of both renal and adrenal AT1R (153). Particularly interesting is increased *in vivo* binding of the AT1R in animal models of renovascular hypertension (154). The technology is ready for clinical translation.

Bladder cancer

Bladder carcinoma is the most frequent type of tumor of the urinary tract and is most prevalent in the fifth to seventh decade of life (1). A systematic review and meta-analysis of application of FDG PET and PET/CT in urinary bladder cancer was published by Lu et al. in 2010 (155). This study reviewed studies published from 2000 through 2010 and selected six eligible studies for meta-analysis which found good diagnostic accuracy of FDG PET and

PET/CT for detection of metastatic bladder cancer. The pooled sensitivity and specificity of FDG PET or PET/CT for bladder cancer staging or restaging (metastatic lesions) of bladder cancer were 0.82 (95% CI: 0.72–0.89) and 0.89 (95% CI: 0.81–0.95), respectively. However, there were too few eligible studies to adequately assess the utility of FDG PET or PET/CT for diagnosis and localization of the primary urinary bladder cancer which can be limited in some instances due to urinary FDG excretion and accumulation in the bladder (156).

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Figure 1. FDG PET/CT in a patient with advanced metastatic prostate cancer with (A) metastases and (B) pelvic and lower lumbar bone metastases.

Figure 2.
 ^{18}F -NaF PET/CT in a man with prostate cancer with right iliac bone metastasis. Central activity corresponds to benign endplate degenerative change of the L5-S1 junction.

Figure 3.
 ^{18}F -DCFBC low molecular weight PSMA-based PET/CT imaging of castration-resistant metastatic prostate cancer. (A) MIP, (B) Right Iliac bone metastasis, (C) Small Aorto-caval lymph node.

Figure 4.

Coronal view of an FDG PET/CT scan of a patient with right kidney RCC. There is moderately increased FDG activity fusing to a soft tissue mass at the lower pole of the right kidney. There is also intensely FDG avid linear expansile lesion with cortical destruction in the left lateral seventh rib consistent with bone metastasis. The uptake in the primary tumor is similar to uptake in kidney parenchyma but less than in renal collecting system.

Figure 5.

Coronal PET/CT images of the heart and kidneys in a healthy human subject 2-5 minutes post IV injection of 500 MBq Rb-82 chloride. Images of the heart and the kidneys were acquired after separate but technically identical bolus injections of ^{82}Rb . Image maximum was set at 400kBq/mL. Time activity curves (Figure 6a) showed that uptake in the kidneys was much higher than uptake in the myocardium.

Figure 6a.

Time activity curves derived from a dynamic PET study of the myocardium and kidneys 0 – 5 min after injection of 500 mBq Rb-82 chloride. Dots represent the average of the two kidneys, circles represent the myocardium and the unmarked line represents the input function from the left ventricle.

Figure 6b.

Impulse response functions of Rb-82 in the myocardium and kidneys. Dots represent the average of the two kidneys, circles represent the myocardium and unmarked lines represent the monoexponential curve fits to the slow decreasing component of both impulse response functions.