Positron Emission Tomography and Positron Emission Tomography/Computerized Tomography of Urological Malignancies: An Update Review

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Purpose: Appropriate imaging in uro-oncology is a crucial component at primary diagnosis, followup and recurrence to achieve an accurate assessment of the disease and determine the most effective treatment. We summarize recent developments in positron emission tomography and positron emission tomography/computerized tomography for prostate, bladder and renal cancer.

Materials and Methods: The recent published literature on positron emission tomography and positron emission tomography/computerized tomography in uro-oncology was searched and reviewed.

Results: For prostate cancer ^{18}F-fluorodeoxyglucose is not highly effective for primary diagnosis but it has a limited role in staging and recurrence detection. Promising results have been shown by ^{11}C-choline, ^{18}F-fluorocholine, ^{11}C-acetate and ^{18}F-fluoride. The role of ^{11}C-methionine, ^{18}F-fluoro-5-alpha-dihydrotestosterone and anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid remains to be elucidated. For bladder cancer ^{18}F-fluorodeoxyglucose positron emission tomography is useful for identifying distant metastases but not for detecting primary tumors due to the urinary excretion of ^{18}F-fluorodeoxyglucose. The role of ^{11}C-choline and ^{11}C-methionine remains to be evaluated further in clinical studies. For renal cancer ^{18}F-fluorodeoxyglucose is of limited use for primary diagnosis but it has a role in staging and restaging of the disease. More clinical data are needed to investigate the roles of ^{18}F-fluoromisonidazole and ^{18}F-fluorothymidine.

Conclusions: Several advances in positron emission tomography and positron emission tomography/computerized tomography for urological cancer have been made in recent years. However, larger clinical trials are needed to establish the role of this imaging method for urological malignancy. In the near future the new radiotracers and further advancement in this imaging technique are expected to improve the performance of positron emission tomography/computerized tomography in uro-oncology.

Key Words: prostate; urinary tract; carcinoma, transitional cell; carcinoma, renal cell; positron-emission tomography

In recent years PET has undergone explosive growth and demonstrated great potential for imaging many primary and metastatic cancers. In urology PET has been one of the slowest areas to develop. This is mainly due to the urinary excretion of many PET tracers and variable tracer uptake in some urological tumors. However, PET and PET/CT in urology have expanded during these years because PET/CT scanners have been improved technically and more favorable PET tracers have been developed.

PET is a unique molecular imaging modality that provides images of physiological and metabolic processes. PET uses positron emitters (positron emitting radionuclides) to provide quantitative tomographic images. Positron emitting radionuclides are produced in a cyclotron optimized for routine clinical use. Biomolecules are labeled with positron emitting radionuclides and the final radiopharmaceuticals are applied to humans after appropriate quality control. All positron emitters have a relatively short half-life, ie 110 minutes for ^{18}F, 20 minutes for ^{11}C, 10 minutes for ^{13}N, 122 seconds for ^{15}O and 75 seconds for ^{82}Rb. In the PET scanner gamma photons are recorded and tomographic images of tracer distribution in the body are reconstructed using mathematical algorithms. PET images are a volumetric set of data that can be displayed as tomographic images in the transaxial, coronal or sagittal planes.

A limitation of PET is the lack of an anatomical reference frame. CT is an excellent morphological imaging modality with anatomical resolution. The combined PET/CT device offers optimal fusion of images, which allows the localization of functional findings detected by PET in morphological structures as shown by CT during 1 imaging procedure.

Most malignant tumors are characterized by enhanced glucose use. Increased cellular proliferation in tumors results in increased FDG use, which can be imaged using PET and ^{18}F-FDG. In urology ^{18}F-FDG PET is a challenge, mainly because of urinary excretion and variable uptake in some urological cancers. Thus, new PET tracers have been investigated in urological malignancies in recent years. These tracers differ in nucleotide labeling, and biochemical uptake mechanisms and pathways, which are characteristics influencing their clinical applicability. The metabolic PET tracer that is most frequently used in oncology scans is ^{18}F-FDG. Regional FDG uptake depends on the cellular

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glucose metabolism. ^{18}F-FDG uptake in the cell is related to several glucose transporters that allow ^{18}F-FDG passage across the cell membrane to the cytoplasm.[1] The radiotracer is first trapped in the cell by rapid phosphorylation without further metabolization but it is later released again after delayed dephosphorylation, followed by clearance via the urogenital system.

Choline is incorporated into the cell membrane.[1] Because cancer cells duplicate rapidly, the biosynthesis of cell membranes is also rapid and it is associated with increased choline uptake. These observations have led to the use of ^{11}C-choline PET for imaging malignancies. ^{11}C has a short half-life of only 20 minutes, which causes logistic problems when a cyclotron is not available on site. Due to the longer half-life of ^{18}F labeled choline (110 minutes) this tracer has been introduced for PET. The major advantage of ^{18}F-FCH vs ^{11}C-choline is the substantially longer half-life, which allows the distribution of this tracer to PET centers without a cyclotron on site, much like the common distribution of ^{18}F-FDG. Because urinary tracer excretion is low, these markers are advantageous in urological malignancies.

Cellular uptake of ^{11}C-acetate in tumor cells is proportional to lipid synthesis and it is incorporated into the cellular lipid pool.[1] An increase in fatty acid synthesis and over expression of the key enzyme fatty acid synthase have been demonstrated in prostate cancer.[1] There seems to be no urinary excretion of ^{11}C-acetate. Other biochemical pathways in cancer cells used for tumor imaging in urology refer to amino acid transport and to some extent protein synthesis, eg ^{11}C-methionine and anti-^{18}F-FACBC, a tumor avid amino acid that is a synthetic l-leucine analogue. To detect accelerated cell division ^{18}F-FLT is a radiotracer that is currently under investigation. Other tumor biology related radiotracer approaches are androgen receptor binding by ^{18}F-FDHT, hypoxic imaging agents such as ^{18}F-FMISO and scanning with ^{18}F-fluoride, which localize in regions with malignant bone lesions and increased bone turnover.[1] We highlight recent findings with regard to the most common urological malignancies, ie prostate, bladder and renal cancer.

PROSTATE CANCER

In the United States prostate cancer is the most common cancer in men.[2] Increased awareness of this cancer as a major cause of male cancer mortality has resulted in a challenge for imaging. It is important at primary diagnosis, followup and recurrence to achieve an accurate assessment of disease stage to determine the most effective treatment strategy. Traditional, morphologically based prostate imaging is now being complemented by functional and molecular imaging techniques for prostate cancer. The initial use of ^{18}F-FDG PET in prostate cancer imaging was disappointing. However, new and more favorable PET tracers have already shown promising results, while other tracers are currently being evaluated.

Local Prostatic Disease

FDG. There is general agreement that ^{18}F-FDG PET does not have an important role in the primary diagnosis or staging of prostate cancer.[1] This is mainly due to low metabolic glucose activity and urinary excretion of ^{18}F-FDG, which may mask pathological uptake in the prostate. Liu et al found only 4% sensitivity for detecting primary prostate cancer with ^{18}F-FDG PET.[3] In that study no continuous bladder irrigation was used, which may explain the low sensitivity reported. Using continuous bladder irrigation Oyama et al found 80% sensitivity for detecting primary cancer in a small study of 10 patients.[4] This higher sensitivity for ^{18}F-FDG PET may also have been caused by relatively advanced stage and high serum PSA in the patients studied.[4] Figure 1 shows an example of ^{18}F-FDG PET/CT.

Choline. In past years studies using radiolabeled choline (labeled to ^{11}C or ^{18}F) have shown promising results in prostate cancer. Several studies indicated that ^{11}C-choline PET may detect and locate major areas with carcinoma and differentiate segments with cancer from those with benign lesions or normal prostate tissue. Reske et al reported 81% sensitivity and 87% specificity for detecting malignancy in the prostate in 26 patients with prostate cancer.[5] Another study by Scher et al using ^{11}C-choline PET in 48 patients with clinical suspicion of prostate cancer found 86.5% sensitivity and 61.9% specificity.[6] A total of 21 patients had no signs of malignancy and in 8 of these 21 PET was false-positive. Acute prostatitis, chronic prostatitis and BPH were present in these patients. Thus, false-positive findings may occur due to an overlap of ^{11}C-choline uptake between benign and malign processes.

Farsad et al evaluated ^{11}C-choline PET/CT to identify cancer foci in the prostate.[7] Sensitivity, specificity, accuracy, PPV and NPV were reported to be 66%, 81%, 71%, 87% and 55%, respectively. Martorana et al found 83% sensitivity for the localization of cancer nodules 5 mm or greater.[8] However, to assess extraprostatic extension the sensitivity of PET was low in comparison with that of MRI (22% vs 63%, $p < 0.001$). In a study by de Jong et al ^{11}C-choline was found to be avidly taken up in prostate cancer, including the primary tumor and lymph node metastases.[9] In a study of 20 patients with prostate cancer Yamaguchi et al reported that ^{11}C-choline PET showed 100% diagnostic sensitivity for primary lesions, while the sensitivity of MRI and MRS was 60% and 65%, respectively.[10] A small study by Yoshida et al showed no reliable differential ^{11}C-choline uptake of BPH and prostate cancer.[11]

Recently studies using ^{18}F-FCH for prostate cancer imaging were reported. In the study by Schmid et al 10 patients with newly diagnosed prostate cancer and 9 suspected of having recurrence were evaluated with ^{18}F-FCH PET.[12] The study showed that differentiating malignant areas from BPH was not possible with ^{18}F-FCH PET. Conflicting results were reported by Kwee et al, who observed that the distribution of tumors in the prostate gland could be visualized with ^{18}F-FCH PET.[13] Prostate sextant positive for malignancy on biopsy demonstrated significantly higher maximal SUV than biopsy negative sextants. Another study by Kwee et al showed that delayed or dual phase ^{18}F-FCH PET may improve the imaging of malignant areas of the prostate.[14] Dual phase ^{18}F-FCH PET was also used in a study by Cimitan et al.[15]

Acetate. Oyama et al reported marked ^{11}C-acetate uptake in prostate cancer lesions in 22 patients and found that ^{11}C-acetate PET was more sensitive for detecting prostate cancer than ^{18}F-FDG PET.[16] Kato et al investigated the accumulation of ^{11}C-acetate in 30 subjects without prostate cancer, including 21 with a normal prostate and 9

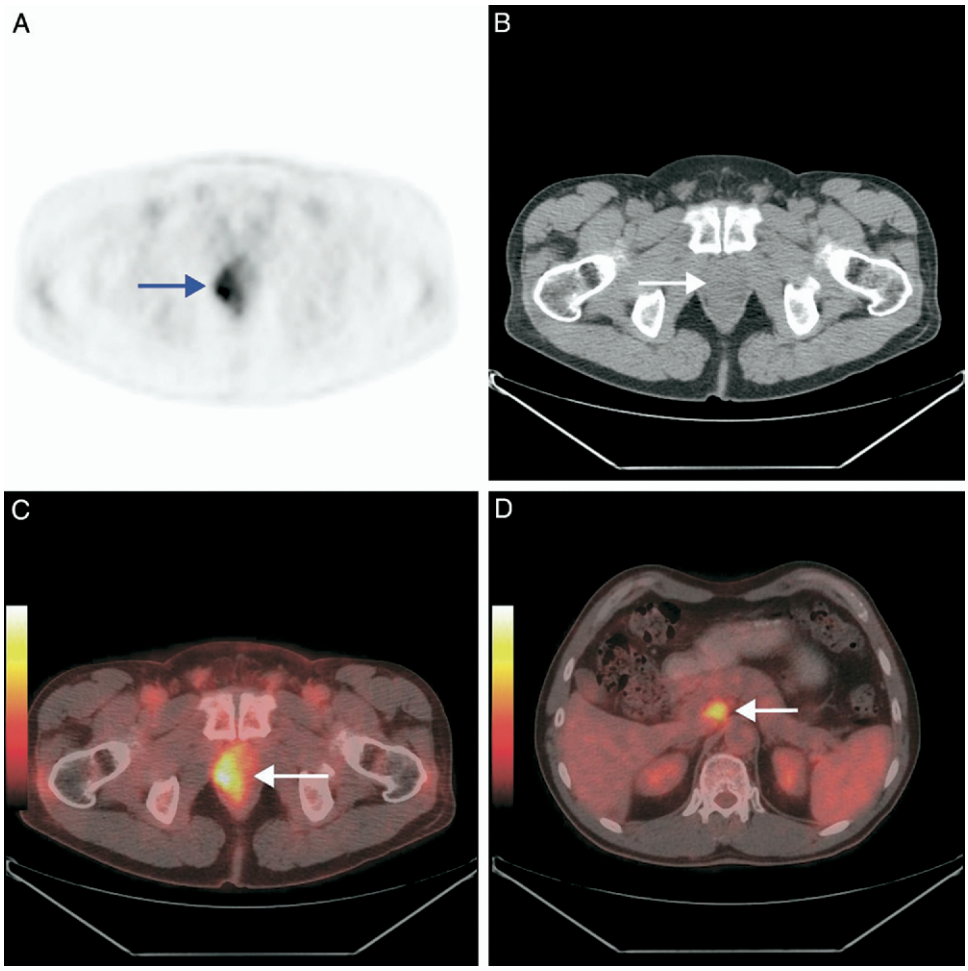

FIG. 1. Staging in 56-year-old man with prostate cancer and serum PSA 61 ng/ml. No metastases were found on conventional bone scintigraphy. CT showed enlarged abdominal lymph nodes. Biopsies from abdominal lymph nodes failed and patient was referred for PET/CT. Transaxial PET (*A*), CT (*B*) and PET/CT fusion images (*C*) show pathological tracer accumulation in prostate. Increased ^{18}F-FDG uptake is visible in enlarged abdominal lymph node on fusion image (*D*). In this case ^{18}F-FDG PET revealed tracer uptake in prostate and abdominal lymph node but increased ^{18}F-FDG uptake is relatively rare in prostate cancer.

with BPH, and in 6 patients with prostate cancer.[17] All patients with prostate cancer had positive findings on ^{11}C-acetate PET. However, the difference in SUV between patients 50 years or older with a normal prostate or BPH and patients with prostate cancer was not statistically significant. The group recommended careful interpretation of ^{11}C-acetate PET images because the SUV may overlap for prostate cancer, a normal prostate and BPH.

Anti-FACBC. The synthetic L-leucine analogue anti-^{18}F-FACBC showed excellent in vitro uptake in prostate cancer cell lines and in implanted prostate tumors in nude rats.[18] Recently Schuster et al used anti-^{18}F-FACBC PET in a small pilot study of 15 patients with newly diagnosed (9) and recurrent (6) prostate carcinoma.[18] Anti-^{18}F-FACBC PET correctly identified the presence or absence of focal neoplastic involvement in 40 of 48 prostate sextants. In all 4 patients in whom there was proven recurrence anti-^{18}F-FACBC PET was successful for identifying disease in the prostate bed in 1 and at extraprostatic sites in 3.

Lymph Node Involvement

Choline and acetate. The use of ^{18}F-FDG PET for primary staging of prostate cancer has been limited from the beginning. Proper staging of prostate cancer is particularly important in high risk primary disease and it has important implications for optimal treatment. Studies of ^{11}C-choline have shown promising results for detecting lymph node metastasis in prostate cancer. In a study by de Jong et al 67 consecutive patients with prostate cancer were included.[19] The results of ^{11}C-choline PET were compared with histological findings of the pelvic lymph node and with followup data. The study showed 80% sensitivity for ^{11}C-choline PET, 96% specificity and 93% accuracy. A study by Oyama et al indicated that ^{11}C-acetate PET was more effective for detecting nodal and bone metastasis than ^{18}F-FDG PET.[16]

Schmid et al reported that ^{18}F-FCH PET also may be promising for detecting local recurrence and lymph node metastases.[12] Similar results were reported by Cimitan et al.[15] The study showed that ^{18}F-FCH PET was useful for detecting lymph node involvement. In contrast, Hacker et al recently reported that ^{18}F-FCH PET was not useful for preoperatively detecting regional lymph node metastases in their study.[20] Fricke et al compared ^{11}C-acetate PET with ^{18}F-FDG PET for detecting lymph node involvement and found that ^{11}C-acetate PET was more useful for detecting regional lymph node metastases than ^{18}F-FDG PET.[21]

Bone Metastases

FDG. The most common organ for distant metastasis in prostate cancer is bone. ^{18}F-FDG PET is variable in the detection of bone metastasis and it was reported to be less sensitive for detecting bone metastasis than conventional imaging.[22] Nunez et al reported 48% sensitivity for detecting bone metastasis.[22] Morris et al examined a total of 157 bone lesions in 17 patients with progressive metastatic prostate cancer.[23] In patients with progressive metastatic prostate cancer ^{18}F-FDG PET discriminated active osseous disease from quiescent lesions on scintigraphy but it was limited for detecting soft tissue metastases. All lesions seen on ^{18}F-FDG PET proved to be active disease on subsequent bone scans. Oyama et al reported a decrease in ^{18}F-FDG uptake in prostate cancer and metastatic lesions after endocrine therapy, suggesting that glucose use by tumors was suppressed by androgen ablation.[4]

Choline, acetate and methionine. Cimitan et al reported that ^{18}F-FCH PET was useful for detecting bone metastases.[15] Fricke et al compared ^{11}C-acetate PET with ^{18}F-FDG PET for detecting bone involvement.[21] The lesion sensitivity of ^{11}C-acetate PET and ^{18}F-FDG was 83% and 75%, respectively. Kotzerke et al used ^{11}C-acetate and ^{11}C-choline to detect bone metastases in their preliminary study.[24] Uptake of the 2 radiotracers in prostate cancer or its metastases was almost identical in 12 patients. Nunez et al found that ^{11}C-methionine was more effective than ^{18}F-FDG PET for detecting bone metastasis in patients with prostate cancer.[22] They combined ^{18}F-FDG and ^{11}C-methionine PET in 12 patients with newly progressive metastatic cancer and compared the scans with conventional imaging. The sensitivity of ^{18}F-FDG PET and ^{11}C-methionine PET was 48% (167 of 348 lesions) and 72.1% (251 of 348), respectively, with conventional imaging used as the 100% referent. In this study a significant portion of lesions (26%) had no detectable metabolism of ^{18}F-FDG or ^{11}C-methionine.

FDHT. A new imaging agent that binds to androgen receptors,^{18}F-FDHT, was recently developed. This new radiotracer may be used for monitoring the treatment response. Two groups have reported that ^{18}F-FDHT PET can detect metastatic and recurrent prostate cancer. In 7 patients with a median PSA of 69 ng/ml Larson et al found that ^{18}F-FDHT detected 78% of the lesions that were identified by conventional imaging, while ^{18}F-FDG detected 97%.[25] Dehdashti et al investigated the feasibility of androgen receptor imaging with ^{18}F-FDHT PET in patients with advanced prostate cancer and a mean PSA of 86.9 ng/ml.[26] This study showed 63% sensitivity on a patient by patient basis (12 of 19) and 86% sensitivity on a lesion by lesion basis (24 of 28). However, in these 2 studies the androgen receptor content of prostate cancer tumors was not investigated. Further studies are needed to evaluate whether ^{18}F-FDHT PET is predictive of the response to hormonal therapy in patients with prostate cancer.

Fluoride. In a prospective study Even-Sapir et al performed bone scintigraphy, SPECT and ^{18}F-fluoride PET/CT on the same day in 44 patients with high risk prostate cancer.[27] The sensitivity, specificity, PPV and NPV of planar bone scintigraphy were 70%, 57%, 64% and 55%, respectively. For multiple field of view SPECT the values were 92%, 82%, 86% and 90%, respectively. For ^{18}F-fluoride PET the values were 100%, 62% 74% and 100%, respectively. For ^{18}F-fluoride PET/CT the values were 100% for all parameters.

Recurrence

FDG. Patients showing increasing PSA after definitive local therapy for prostate cancer represent a diagnostic dilemma. PET with ^{18}F-FDG may identify local recurrence and distant metastases, and the probability of a positive image increases with increasing PSA.[28] Chang et al evaluated whether ^{18}F-FDG could detect pelvic lymph node metastases in patients with prostate cancer who had increased PSA after initial treatment.[29] The study showed 75% sensitivity, 100% specificity and 83.3% accuracy. However, the sensitivity of recurrent disease detection is higher with ^{11}C-acetate than with ^{18}F-FDG.[21,30]

Choline. In a study by de Jong et al ^{11}C-choline was used to evaluate treatment in 36 patients with prostate cancer after initial treatment with radical prostatectomy (20) or external beam radiotherapy (16).[31] Results were compared with the results of histology or followup. The site of recurrence was detected correctly in 78% of patients after external beam radiotherapy compared to 38% after radical prostatectomy. No positive scans were observed in patients with PSA less than 5 ng/ml. Using ^{18}F-FCH PET Schmid et al reported promising results for detecting local recurrence and lymph node metastases.[12] Heinisch et al found that, when restaging cases of prostate cancer, ^{18}F-FCH PET yielded positive findings even at PSA less than 5 ng/ml.[32] Recently Cimitan et al performed a large study of 100 patients with prostate cancer with a persistent increase in PSA after radical prostatectomy (58), radiotherapy (21) or hormonal therapy (21).[15] They reported that ^{18}F-FCH PET is not likely to have a significant impact on the therapeutic management of prostate cancer with biochemical recurrence until PSA increases to above 4 ng/ml, especially in patients with well/moderately differentiated primary tumors (Gleason score 7 or less). Figure 2 shows an example of recurrence detection by ^{18}F-FCH PET/CT.

Acetate. ^{11}C-acetate PET has also shown promising results for the early detection of prostate cancer recurrence in patients with increasing PSA after initial radiotherapy or radical surgery.[21,30,33–35] In the study by Sandblom et al pathological uptake was seen in patients with PSA as low as 0.5 ng/ml after radical prostatectomy.[35] However, in this study false-positive uptake was seen in 3 patients. Oyama et al investigated the effectiveness of PET with ^{11}C-acetate for evaluating patients with increasing PSA after radical prostatectomy or radiation therapy.[30] The study demonstrated marked uptake in prostate cancer. ^{11}C-acetate PET had higher sensitivity than ^{18}F-FDG PET for detecting recurrent prostate cancer. In this study ^{11}C-acetate PET was not able to detect recurrent tumors below PSA 3.0 ng/ml. In the study by Fricke et al ^{11}C-acetate was more useful than ^{18}F-FDG for detecting local recurrence and regional lymph node metastases.[21] However, in the same study ^{18}F-FDG appeared to be more accurate for visualizing distant metastasis.

To assess the clinical value of CT and MRI image fusion with ^{11}C-acetate PET for the detection and exact localization of clinically occult recurrence Wachter et al investigated

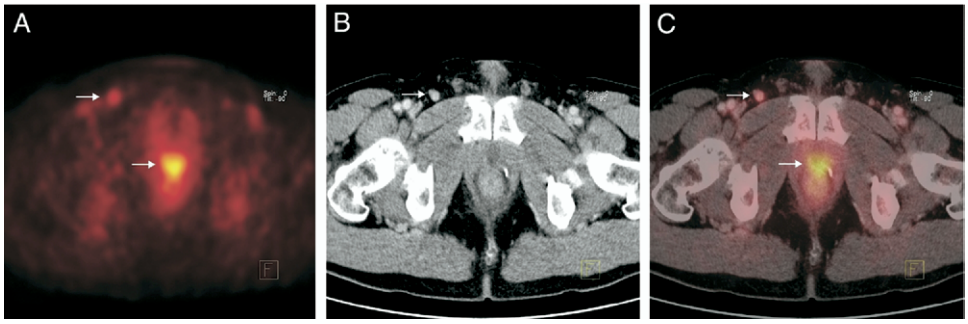

FIG. 2. Prostate cancer recurrence in 56-year-old man with history prostatectomy and later radiation therapy because of increasing PSA. Transaxial PET (*A*), CT (*B*) and fusion PET/CT images (*C*) reveal focal ^{18}F-FCH uptake in prostate bed and enlarged lymph node in right inguinal area.

50 patients with increased/increasing PSA after radical therapy.[34] Image fusion changed the characterization of equivocal lesions as normal at 5 of 51 sites (10%) and abnormal at 9 (18%). It precisely defined the anatomical location of abnormal uptake at 37 of 51 sites (73%). ^{11}C-acetate PET findings influenced treatment in 14 of 50 patients (28%). The investigators concluded that retrospective fusion of ^{11}C-acetate and CT/MRI is feasible.

Summary

Regarding prostate cancer, metabolic ^{18}F-FDG has little accuracy for diagnosing or staging this malignancy. However, increased lipid metabolism and biosynthesis of cell membranes, and their association with increased uptake of acetate or choline radiotracers was shown to be an alternative approach. Most evidence comes from studies of choline. ^{11}C-choline and ^{18}F-FCH have been successfully applied to prostate cancer for staging primary and recurrent disease. In addition, ^{18}F-fluoride has shown promising results as a marker of bone metabolism due to metastases. ^{11}C-methionine, ^{18}F-FDHT and anti-^{18}F-FACBC remain to be elucidated further. Table 1 lists current PET tracer studies in prostate cancer, including diagnostic results for select clinical purposes.

BLADDER CANCER

Bladder cancer is the fourth most commonly diagnosed cancer in the United States.[2] The detection of bladder cancer is still based on direct visualization by cystoscopy and subsequent biopsy/resection. Urinary markers still cannot replace cystoscopy for diagnosing bladder cancer. Invasive disease confined to the pelvis is treated with radical cystectomy and pelvic lymphadenectomy. Given the importance of neoadjuvant chemotherapy, preoperative identification of patients at high risk with extravesical spread would help identify candidates for combined modality treatment.

CT and MRI are widely used for preoperatively staging bladder cancer. However, these imaging modalities have limitations. Metastases of bladder cancer frequently replace normal nodes, causing little if any enlargement, and false-negative rates may be recorded on CT and MRI. Thus, there is a need for a noninvasive imaging modality for more accurately staging bladder cancer.

Local Disease and Staging

FDG. The role of ^{18}F-FDG PET for detecting localized bladder cancer is limited due to urinary excretion of ^{18}F-FDG.[1] However, occasionally ^{18}F-FDG PET/CT may detect unknown primary bladder cancer (fig. 3). On the other hand, ^{18}F-FDG PET may have a role in identifying locoregional lymph node metastasis and other distant metastasis. Figure 4 shows an example of preoperative staging and figure 5 shows an example of recurrence detection.

Drieskens et al evaluated the preoperative use of ^{18}F-FDG PET for detecting lymph node metastasis and distant metastasis in 55 patients with bladder cancer.[36] For the diagnosis of metastatic disease the sensitivity, specificity and accuracy of ^{18}F-FDG PET were 60%, 88% and 78%, respectively. Liu et al investigated the value of ^{18}F-FDG PET for detecting metastatic disease in 46 patients.[37] The investigators reported 76.9% sensitivity in 36 patients who received no prior systematic chemotherapy. However, in 10 patients who were imaged after receiving chemotherapy sensitivity decreased to 50%. The group recommended that ^{18}F-FDG PET should be interpreted with caution in patients who have received prior chemotherapy.

Methionine and choline. Some investigators have attempted to improve the sensitivity of PET for detecting primary tumors in the bladder by using tracers other than FDG. ^{11}C-methionine PET has been reported to be superior to ^{18}F-FDG PET.[1] Another relevant tracer is ^{11}C-choline since a small amount of tracer is found in urine. de Jong et al used ^{11}C-choline PET in 18 patients to evaluate bladder cancer.[38] In the normal bladder wall tracer uptake was low and in 10 patients tumor was detected correctly by ^{11}C-choline PET. Gofrit et al evaluated ^{11}C-choline PET for preoperative staging in 18 patients.[39] They noted that ^{11}C-choline PET was highly positive for primary and metastatic bladder cancer, and in all primary transitional cell carcinomas ^{11}C-choline uptake was found. The study included 3 patients with refractory bladder carcinoma in situ, which was visualized in all 3. In 6 patients ^{11}C-choline uptake in a lymph node as small as 5 mm was visualized. Picchio et al reported that ^{11}C-choline PET was comparable to CT for detecting residual cancer after transurethral bladder cancer resection but it appeared to be superior for detecting lymph node metastasis.[40]

Summary

^{18}F-FDG PET is useful for identifying distant metastases but not the primary tumor because of urinary excretion of FDG. Generally increased FDG uptake in these tumors allows the assessment of metastatic disease. However, only a limited number of studies have been published and many

TABLE 1. *Prostate cancer*

References	PET Tracer	No. Pts	Purpose	% Sensitivity	% Specificity	% PPV	% NPV	Comments
Liu et al[3]	^{18}F-FDG	24	Diagnosis	4	—	—	—	PET, compared to prostate histology, furosemide washout, no continuous bladder irrigation, PET failed to show pos prostate Ca imaging
Oyama et al[4]	^{18}F-FDG	10	Treatment evaluation	80	—	—	—	PET before + after initiation of endocrine therapy, retention of ^{18}F-FDG in bladder minimized by continuous bladder irrigation
de Jong et al[9]	^{11} C-choline	30	Staging	100	—	—	—	PET before surgery, additional CT or MRI, histology, prostate Ca in 25 pts + BPH in 5, moderate uptake in all BPH
Kato et al[17]	^{11}C-acetate	30	Diagnosis	—	—	—	—	PET, compared to CT or MRI, normal prostate in 21 pts, BPH in 9, prostate Ca in 6, normal prostate showed age related accumulation of ^{11}C-acetate uptake, SUV in normal prostate or BPH overlapped that of prostate Ca in pts 50 yrs or older
Morris et al[23]	^{18}F-FDG	17	Staging	—	—	—	—	PET, compared to bone scan, CT or MRI
Nunez et al[22]	^{11}C-methionine (^{18}F-FDG)	12 (12)	Staging	72.1 (48)	—	—	—	PET, 2 tracers in all 12 pts, compared to bone scan, CT or MRI, Lesion based sensitivity reported
Oyama et al[16]	^{11} C-acetate (^{18}F-FDG)	22 (18)	Staging	100 (83)	—	—	—	PET, compared to CT or MRI, 2 tracers in 18/22 pts, problematic was SUV based sensitivity comparison of different pt Nos. + without indication of respective specificities.
de Jong et al[19]	^{11}C-choline	67	Staging	80	96	—	—	PET, additional CT or MRI, compared to lymph node histology, 93% accuracy
de Jong et al[31]	^{11}C-choline	36	Treatment evaluation	38/78	—	—	—	PET, PSA greater than 0.2 ng/ml additional CT or CT + bone scan, 2 groups of radical prostatectomy in 20 pts + external beam radiotherapy in 16
Chang et al[29]	^{18}F-FDG	24	Staging	75	100	100	67.7	PET, compared to lymph node histology, additional CT, retrospective study, 83.3% accuracy
Fricke et al[21]	^{11}C-acetate (^{18}F-FDG)	24 (15)	Restaging	83 (75)	—	—	—	PET, 2 tracers in 15/24 pts, compared to histology, MRI, CT +/or TRUS, lesion based evaluation
Kotzerke et al[24]	^{11}C-acetate, (^{11}C-choline)	12 (12)	Staging					PET, 2 tracers had almost identical results
Oyama et al[30]	^{11}C-acetate (^{18}F-FDG)	46	Restaging	—	—	—	—	PET, bone scan or conventional CT when available, biopsies only in 3 pts, 2 groups of prostatectomy in 30 pts + radiation therapy in 16, 59% sensitivity at PSA greater than 3 ng/ml
Larson et al[25]	^{18}F-FDHT (^{18}F-FDG)	7 (7)	Staging	78 (97)	—	—	—	PET, compared to conventional imaging, advanced prostate Ca with median PSA 69 ng/ml, lesion based evaluation
Dehdashti et al[26]	^{18}F-FDHT	20	Staging	63	—	—	—	PET, compared to conventional imaging, advanced prostate Ca with mean PSA 86.9 ng/ml, 86% sensitivity on lesion by lesion basis (24/28)
Farsad et al[7]	^{11}C-choline	41	Diagnosis	66	81	87	55	PET/CT, 216 sextant biopsies, lesion based sensitivity reported, 71% accuracy, prostate Ca in 36 pts, 5 controls had bladder cancer, ^{11}C-choline not recommended for first line screening for prostate Ca in men at high risk
Kwee et al[13]	^{18}F-FCH	17	Diagnosis/ staging	93	48	—	—	PET, correlated with histology, CT, plain x-ray + bone scan, tracer uptake in prostate sextants, max SUV greater than 3.3 based evaluation
Schmid et al[12]	^{18}F-FCH	19	Staging/ restaging	100 Restaging	—	—	—	PET/CT, newly diagnosed prostate Ca in 10 pts, recurrent disease in 9, compared to histology + initial staging, tumor detection also possible at PSA 5 ng/ml or less
Schoder et al[28]	^{18}F-FDG	91	Restaging	31	—	—	—	PET, Compared to bone scan, CT+MRI when available, retrospective study, PSA relapse after radical prostatectomy, pts at relative low risk + mean PSA 4.6 ng/ml
Yamaguchi et al[10]	^{11}C-choline	20	Diagnosis	100	—	—	—	PET, compared with MRI/MRS, sensitivity 60% for MRI + 65% for MRS
Yoshida et al[11]	^{11}C-choline	13	Staging/ restaging	56.3	12.5	—	—	PET, compared to CT + bone scan, primary staging in 6 pts, radical prostatectomy in 5, radiotherapy in 3, small pt No. for sensitivity + specificity

(table continues)

TABLE 1. *Continued*

References	PET Tracer	No. Pts	Purpose	% Sensitivity	% Specificity	% PPV	% NPV	Comments
Albrecht et al[33]	^{11}C-acetate	32	Restaging	82 Local recurrence	—	—	—	PET, image fusion with CT, endorectal MRI, compared to unknown, radiotherapy in 17 pts + radical prostatectomy in 15, PET 1 hr after injection allowed better differentiation between benign + malignant tumors than early imaging
Cimitan et al[15]	^{18}F-FCH	100	Staging	98	100%	Unknown	Unknown	PET/CT, early + delayed scans in 43 pts, radical prostatectomy in 58, radiotherapy in 21 + hormonal therapy in 21, mean PSA 48.28 ng/ml pos PET/CT group, 1.98 ng/ml in PET/CT neg group
Even-Sapir et al[27]	^{18}F-Fluoride	44	Staging	100	100	100	100	PET/CT, compared to planar + SPECT bone scan, + PET alone, high risk of bone metastases (Gleason score 8 or greater, PSA 20 ng/ml or greater), planar bone scan: 69% sensitivity, 64% specificity, 69% PPV, 64% NPV
Hacker et al[20]	^{18}F-FCH	20	Staging	10	80%	—	—	PET/CT before intraop sentinel + extended lymph node dissection
Heinisch et al[32]	^{18}F-FCH	34	Restaging	—	—	—	—	PET/CT, compared to CT, MRI + histology, radical prostatectomy in 31 pts + radiotherapy in 3
Kwee et al[14]	^{18}F-FCH	26	Diagnosis/ staging	60 Initial, 88 delayed	90 (both)	—	—	Dual phase PET, sextant analysis, compared to histology, newly diagnosed in 15 pts, recurrence in 2, no recurrence sign in 6 + normal prostate in 3, small pt No.
Martorana et al[8]	^{11}C-choline	43	Diagnosis	66	84	—	—	PET/CT before biopsy, sextant analysis. TRUS sensitivity 61% + specificity 97%, extraprostatic extension sensitivity PET/CT 22% + MRI 63%
Reske et al[5]	^{11}C-choline	26	Diagnosis	81	87	86	83	PET/CT, sextant analysis, compared to histology, 84% accuracy
Sandblom et al[35]	^{11}C-acetate	20	Restaging	—	—	—	—	PET/CT, compared to histology when available, pos PET at low PSA
Scher et al[6]	^{11}C-choline	58	Diagnosis/ staging	86.5 (81.1)	61.9	—	—	PET in 25 pts + PET/CT in 33, compared to histology, sensitivity for primary Ca 86.5% + for metastasis 81.1%
Wachter et al[34]	^{11}C-acetate	50	Restaging	—	—	—	—	PET with retrospective CT/MRI fusion, PET findings influenced treatment in 28% of pts
Schuster et al[18]	^{18}F-FACBC	15	Staging/ restaging	—	—	—	—	PET/CT, sextant analysis, histology, newly diagnosed in 9 pts + suspected recurrence in 6

included few patients. ^{11}C-choline and ^{11}C-methionine may prove to be more effective than ^{18}F-FDG but this remains to be elucidated further. Table 2 lists current PET tracer studies in bladder cancer, including diagnostic results for select clinical purposes.

RENAL CANCER

In the United States RCC represents approximately 3% of all adult malignancies.[2] The increasing use of CT and ultrasound to help diagnose various medical conditions has led to the incidental diagnosis of RCC in a higher proportion of patients. At diagnosis RCC is often advanced and unresectable. Approximately a third of patients present with metastatic disease and are usually not curable. Thus, there is a need for more accurate imaging modalities for diagnosis and staging to optimize and develop new and more effective treatment for RCC.

Primary Diagnosis

FDG. ^{18}F-FDG PET imaging is a challenge in RCC. The major difficulty with diagnosing lesions by ^{18}F-FDG PET is false-negative imaging due to difficult urinary excretion, leading to the variable detection of primary tumors. Thus, there is general agreement that ^{18}F-FDG PET has a limited role in the initial diagnosis of renal tumors compared to standard imaging modalities. Ramdave et al reported that the accuracy of ^{18}F-FDG PET and CT was similar at 94% in patients with known or suspected primary RCC.[41] Compared with CT ^{18}F-FDG PET detected local recurrence and distant metastases more accurately, and it differentiated recurrence from radiation necrosis. Kang et al found 60% sensitivity and 100% specificity for ^{18}F-FDG-PET in 17 patients with primary RCC, whereas the sensitivity of abdominal CT was 91.7% and its specificity was 100%.[42]

FMISO. ^{18}F-FMISO-PET is a recognized noninvasive method for detecting hypoxia in tumors. Most often RCC is

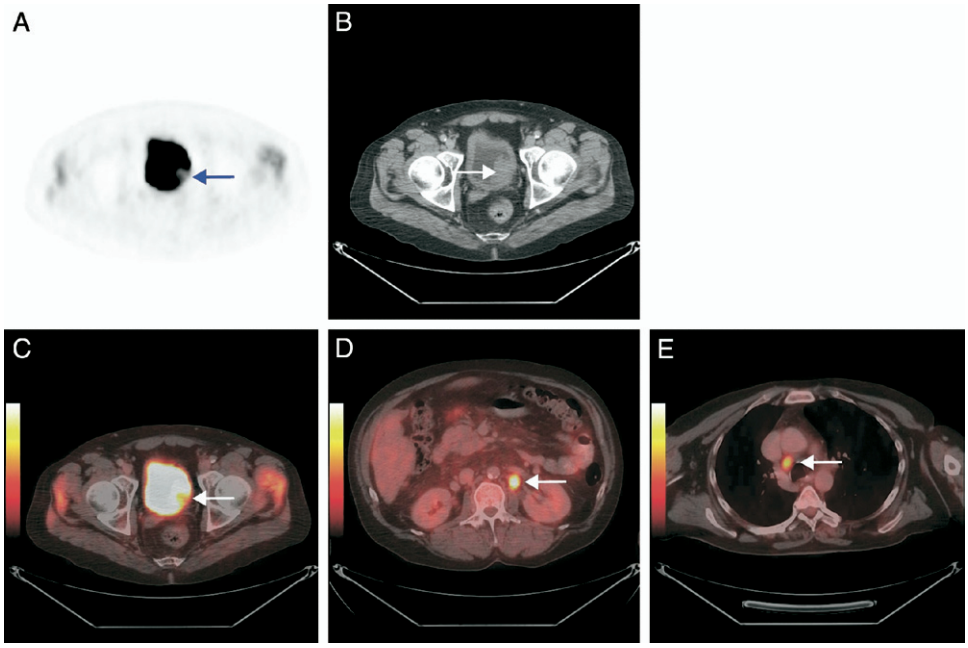

FIG. 3. Unknown primary tumor and bladder cancer staging in 54-year-old man with tumor on right side of neck. Transaxial ^{18}F-FDG PET (*A*), CT (*B*) and PET/CT fusion images (*C*) demonstrate tumor on left side of bladder, which was later confirmed by cystoscopy. Axial PET/CT fusion images reveal foci with tracer accumulations in retroperitoneal and mediastinal lymph nodes (*D* and *E*). As expected, PET/CT showed tumor on right side of neck but no other pathological tracer uptake in head/neck region (data not shown).

resistant to treatment with radiation and chemotherapy, which may be due to malignant hypoxic areas in the tumor. In a study by Lawrentschuk et al 17 patients were evaluated with ^{18}F-FMISO-PET before nephrectomy for presumed RCC.[43] Of these patients 11 had histologically confirmed RCC and in these 11 a total of 7 tumors had mildly increased ^{18}F-FMISO uptake. However, this tendency toward greater uptake in tumor vs that in normal tissue was not statistically significant.

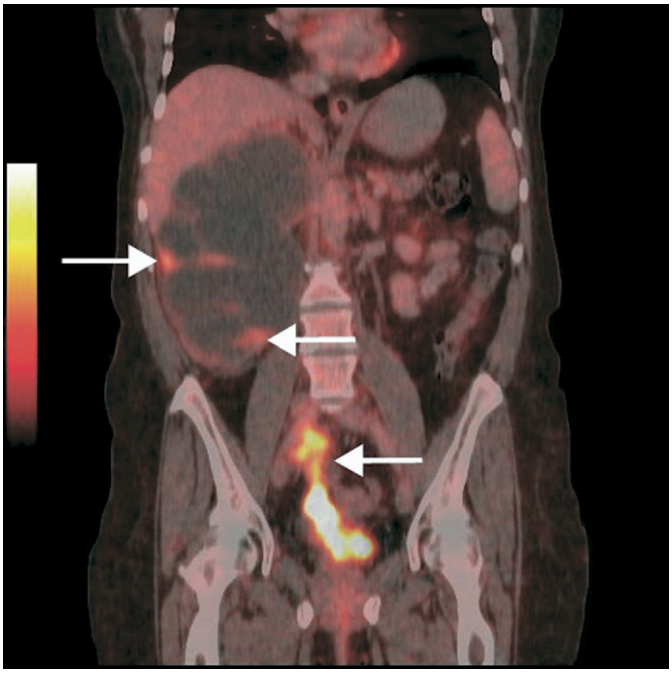

FIG. 4. Bladder cancer staging and ureteral tumor infiltration in 52-year-old woman with newly diagnosed bladder cancer and no right kidney function referred for ^{18}F-FDG PET/CT for preoperative staging. Coronal PET/CT fusion image reveals pathological accumulation in distal ureter on right side (lower arrow) and large hydronephrosis at same site containing several foci with tracer accumulation (upper arrows).

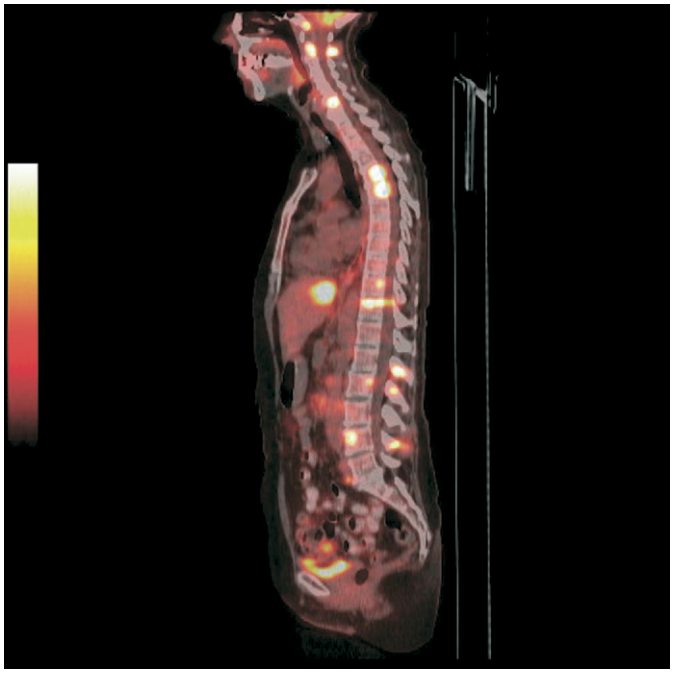

FIG. 5. Bladder cancer recurrence in 57-year-old woman with history of cystectomy 6 years previously. Ultrasound revealed hydronephrosis on left side and 3 processes in liver. Patient was referred for ^{18}F-FDG PET/CT for further evaluation. Sagittal PET/CT fusion image demonstrates extensive metastatic disease with multiple foci in bones, liver and abdominal lymph nodes.

TABLE 2. *Bladder cancer*

References	PET Tracer	No. Pts	% Sensitivity	% Specificity	Comments
de Jong et al[38]	^{11}C-choline	23	55.5	—	PET before cystectomy in pts with bladder Ca, bladder Ca in 18 + 5 healthy volunteers
Drieskens et al[36]	^{18}F-FDG	55	60	88	PET before cystectomy, correlative imaging of PET with CT, 78% accuracy
Gofrit et al[39]	^{11}C-choline	18	100	—	PET/CT before cystectomy, 100% sensitivity for tumor + lymph node metastases, visualized carcinoma in situ in 3 pts
Liu et al[37]	^{18}F-FDG	46	76.9	97.1	PET, compared to conventional imaging + histology, prior systemic chemotherapy in 10 pts, 50% sensitivity after chemotherapy
Picchio et al[40]	^{11}C-choline	27	96	—	PET, compared to histology, additional CT + bone scan, lymph node sensitivity 62%, accuracy 88.9% for bladder + lymph node

Imaging was done for staging, and PPV and NPV were not available.

FLT. ^{18}F-FLT is a radiolabeled compound based on the nucleic acid thymidine. It has emerged as an important tracer that mirrors cellular proliferation in PET. Early studies in human tumors are promising. Recently Lawrentschuk et al reported a difficult case of RCC in a longstanding cyst, which was clearly delineated using ^{18}F-FLT.[44]

Staging With FDG

Studies have demonstrated the usefulness of PET for detecting the metastatic spread of RCC compared with other imaging modalities. Ak and Can used ^{18}F-FDG and dual head coincidence mode PET in 19 patients who had suspected primary renal tumors according to conventional imaging techniques, including CT and ultrasound.[45] The overall sensitivity, specificity and accuracy of ^{18}F-FDG coincidence mode PET for RCC were 86% (13 of 15 cases), 75% (3 of 4) and 84% (16 of 19), respectively. For RCC the PPV was 92% and the NPV was 60%. Aide et al compared ^{18}F-FDG PET to CT to assess efficiency in the primary staging of suspicious renal masses in 53 patients.[46] When characterizing renal masses, a high rate of false-negative results was observed, leading to 47% vs 97% sensitivity, 80% vs 0% specificity and 51% vs 83% accuracy for ^{18}F-FDG PET vs CT. ^{18}F-FDG PET detected all sites of distant metastasis revealed by CT as well as 8 additional metastatic sites, leading to 94% accuracy vs 89% accuracy for CT. Brouwers et al evaluated 20 patients with metastatic RCC using ^{18}F-FDG PET and radioimmunoscintigraphy with the chimerical monoclonal antibody ^{131}I-cG250.[47] Of the 112 tumor lesions that were documented ^{18}F-FDG PET detected 69%, whereas radioimmunoscintigraphy detected only 30%. When considering 12 bone lesions, Kang et al found 100% specificity for ^{18}F-FDG PET for differentiating between benign lesions and bone metastases.[42] This makes ^{18}F-FDG PET a complementary problem solving tool when conventional scans are suspicious for metastatic RCC but equivocal. Overall ^{18}F-FDG-PET had 77% sensitivity and 100% specificity for bone metastases compared to 93.8% and 87.2%, respectively, for combined CT and bone scan.

Another study confirmed the superiority of ^{18}F-FDG PET over bone scan for detecting active osseous metastases.[48] The diagnostic sensitivity and accuracy of FDG-PET were 100% and 100%, while bone scan sensitivity and accuracy were 77.5% and 59.6%, respectively. Lymph node staging was accurate in 9 patients without metastases and in 2 with metastases. Majhail et al reported overall 63.6% sensitivity, 100% specificity and 100% PPV for FDG PET for detecting distant RCC metastases.[49]

Followup With FDG After Treatment and Recurrence

FDG-PET has been used successfully to monitor RCC progression in the form of local recurrence or metastasis. A study by Safaei et al used whole body ^{18}F-FDG PET for restaging 36 cases of advanced RCC.[50] ^{18}F-PET classified clinical stage correctly in 32 of 36 patients (89%) and it was incorrect in 4 (11%) with 87% sensitivity and 100% specificity. Safaei et al also investigated the accuracy of PET for classifying lesions that were later biopsied. They found that PET correctly classified 21 of 25 biopsied lesions (84%) with 88% sensitivity and 75% specificity.

Ramdave et al similarly observed the superior value of ^{18}F-FDG PET over CT in the evaluation of patients with suspected recurrent RCC.[41] PET was 100% accurate for demonstrating local tumor recurrence and metastases as opposed to 88% for CT. Jadvar et al reported that the diagnostic performance of PET for detecting recurrent and metastatic RCC revealed 71% sensitivity, 75% specificity, 72% accuracy, 33% NPV and 94% PPV.[51] Dilhuydy et al investigated 24 patients and a total of 26 ^{18}F-FDG PET scans.[52] Sensitivity was 75% and PPV was 92.3%. The investigators concluded that, when it is positive, ^{18}F-FDG PET may modify the decision but, when it is negative, it should not modify decision making especially for surgery due to its sensitivity.

Summary

Because of renal excretion, ^{18}F-FDG is not useful for primary diagnosis but it has a role in staging and restaging disease when evaluating especially visceral, lymph node and bony disease. ^{18}F-FMISO and ^{18}F-FLT may be useful but more clinical data are needed. Table 3 lists recent PET tracer studies in renal cancer, including diagnostic results for select clinical purposes.

CONCLUSIONS

The use of PET and PET/CT in oncology is rapidly expanding with ^{18}F-FDG the most commonly used radiotracer. PET/CT in uro-oncology is a challenge, mainly because of the

TABLE 3. *RCC*

References	PET Tracer	No. Pts	Purpose	% Sensitivity	% Specificity	% PPV	% NPV	Comments
Ramdave et al[41]	^{18}F-FDG	25	Diagnosis/staging	88	—	—	—	PET, compared to conventional imaging, accuracy for primary tumor 94% + for metastasis/ local recurrence 100%
Safaei et al[50]	^{18}F-FDG	36	Restaging	87	100	—	—	PET, compared to conventional imaging, including CT, 89% accuracy
Wu et al[48]	^{18}F-FDG (^{99m}Tc bone scan)	18	Staging	100 (77.5)	—	—	—	PET, 52 bone lesions, including 40 metastatic + 12 benign bone lesions, PET 100% + bone scan 59.6% accuracy
Brouwers et al[47]	^{18}F-FDG (^{131}I radioimmunoscintigraphy)	20	Restaging	69 (30)	—	—	—	PET, 112 lesions investigated
Aide et al[46]	^{18}F-FDG	53	Staging	47	80	—	—	PET, for distant renal Ca metastasis PET appeared more efficient than CT (accuracy 94% vs 89%)
Jadvar et al[51]	^{18}F-FDG	25	Restaging	71	75	94	33	PET, compared to histology in 2 pts, + clinical followup + conventional imaging for up to 1 yr in 23
Majhail et al[49]	^{18}F-FDG	24	Staging/restaging	63.6	100	100	20	PET before surgery, additional CT, MRI, RCC suspected of metastasis or recurrent disease, accuracy for distant metastasis 66.7%
Kang et al[42]	^{18}F-FDG	66	Diagnosis/staging	60	100	—	—	PET, compared to histology or at least 1-yr followup, retrospective study, primary RCC 60% sensitivity, 100% specificity, lymph nodes 75% sensitivity, 100% specificity, bone 77.3% sensitivity, 100% specificity
Ak and Can[45]	^{18}F-FDG	19	Diagnosis	86	75	92	60	To assess role of ^{18}F-FDG imaging with dual head coincidence mode gamma camera
Lawrentschuk et al[43]	^{18}F-FMISO	17	Hypoxia	—	—	—	—	PET, study on the relationship between ^{18}F-FMISO + hypoxia in RCC, only mild ^{18}F-FMISO uptake in the present RCCs
Dilhuydy et al[52]	^{18}F-FDG	24	Staging	75	50	92.3	33.3	PET before treatment, additional CT, Follow-up every 3–4 months
Lawrentschuk et al[44]	^{18}F-FLT	1	Diagnosis	—	—	—	—	PET/CT, case report

urinary excretion of many radiotracers and often moderate uptake in some urological tumors. However, ^{18}F-FDG PET was recently demonstrated to be useful when applied to specific indications in select patients. The rapid development of new metabolic PET tracers with more favorable properties has improved the ability to visualize these urological malignancies and several advances in PET/CT have been made in recent years. However, larger clinical trials are needed to further establish the role of PET/CT in the management of urological malignancy. New radiotracers and further advancement in PET/CT techniques are expected to further improve the performance of PET/CT in uro-oncology. Thus, PET/CT in urological malignancies will continue to expand.

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia
CT = computerized tomography
FACBC = fluorocyclobutane-1-carboxylic acid
FCH = fluorocholine
FDG = fluorodeoxyglucose
FDHT = fluoro-5-alpha-dihydrotestosterone
FLT = fluorothymidine
FMISO = fluoromisonidazole
MR = magnetic resonance
MRI = magnetic resonance imaging
MRS = MR spectroscopy
NPV = negative predictive value
PET = positron emission tomography
PPV = positive predictive value
PSA = prostate specific antigen
RCC = renal cell carcinoma
SPECT = single photon emission CT
SUV = standardized uptake value
TRUS = transrectal ultrasound

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