

REVIEW ARTICLE

Role of positron emission tomography in urological oncology

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- Positron emission tomography (PET) is a diagnostic tool using radiotracers to show changes in metabolic activities in tissues. We analysed the role of PET and PET/computed tomography (CT) in the diagnosis, staging, and follow-up of urological tumours.
- A critical, non-structured review of the literature of the role of PET and PET/CT in urological oncology was conducted.
- PET and PET/CT can play a role in the management of urological malignancies. For prostate cancer, the advances in radiotracers seems promising, with novel radiotracers yielding better diagnostic and staging results than 18F-fluorodeoxyglucose (18F-FDG). In kidney cancer, PET and PET/CT allow a proper diagnosis before the pathological examination of the surgical specimen. For testis cancer, PET and PET/CT have been shown to be useful in the management of seminoma tumours. In bladder cancer, these scans allow a better initial diagnosis for invasive cancer, while detecting occult metastases.
- PET and its combined modality PET/CT have shown their potential in the diagnosis of urological malignancies. However, further studies are needed to establish the role of PET in the management of these diseases. Future applications of PET may involve fusion techniques such as magnetic resonance imaging with PET.

KEYWORDS PET, prostate cancer, bladder cancer, kidney cancer, testicular cancer

INTRODUCTION In recent years, the combination of positron emission tomography (PET) and CT has become a very useful tool referred to as PET/CT. The integration of these two imaging techniques overcomes the limitations of the constituent imaging techniques and allows for precise location of the lesion with a functional registry [1]. This feature is important especially when functional changes precede anatomical ones [2] during treatment response or biochemical progression [3], and for correct and full pretreatment staging, including bone and lymph nodes [4]. PET/CT can be visualized either as a PET scan or as a CT scan through a fusion spectrum with different weights for each technique providing volumetric data; it has the advantage of being able to be presented in any space plane.

We analysed the role of PET and PET/CT in the diagnosis, staging, and follow-up of urological tumours.

A critical, non-structured review of the literature of the role of PET and PET/CT in urological oncology was conducted. We searched for the following keywords in

Medline, MeSH, and Cochrane databases: PET, PET/CT, prostate cancer, renal cell cancer, invasive bladder cancer, and testicular cancer. The European Urology Guidelines [5–10], the European Society of Medical Oncology [11–15], and the National Comprehensive Cancer Network (NCCN) guidelines [16] were also used when applicable.

TABLE 1 The most employed radiotracers in urology: their function and application in urological oncology

Radiotracer by tumour type	Biological analog	Function	Measured effect	Indication
Prostate cancer				
¹⁸ F-FDG	Glucose	Glycolysis	Aerobic and anaerobic glycolysis, glucose consumption	Advanced prostate
¹¹ C-choline	Choline	Choline kinase	Cell membrane metabolism, tumour proliferation	Staging, re-staging, evaluation of salvage therapy
¹⁸ F-choline	Choline	Choline kinase	Cell membrane metabolism, tumour proliferation	Staging, re-staging, evaluation of salvage therapy
¹¹ C-acetate	Acetate	Fatty acid synthase	Lipid synthesis	Staging, re-staging, evaluation of salvage therapy
¹¹ C-methionine	Methionine	A-A transport	Protein synthesis	Staging, re-staging, evaluation of salvage therapy
¹⁸ F-FDHT	Testosterone	Androgen eceptor	Measures androgen receptor	Metastatic prostate cancer, hormone refractory
FACBC		A-A transport		Metastatic prostate cancer
¹⁸ F-NaF	Fluoride	Bone mineralization	Measures bone status	Metastatic prostate, evaluation of bone disease
Kidney cancer				
¹⁸ F-FMISO	NA	Measures hypoxia	Tumour hypoxia	Local staging
¹²⁴ I-cG250	NA	Ab-CalX	Ab-Ag reaction recognizes and joint to CalX	Identification of RCC
¹³¹ I-cG250	NA	Ab-CalX	Ab-Ag reaction recognizes and joint to CalX	Local radio-immunotherapy
GCT				
¹⁸ F-FDG	Glucose	Glycolysis	Aerobic and anaerobic glycolysis, glucose consumption	Retroperitoneal evaluation after chemotherapy
Bladder cancer				
¹⁸ F-FDG	Glucose	Glycolysis	Aerobic and anaerobic glycolysis, glucose consumption	Local staging, recurrence evaluation and metastases
¹¹ C-choline	Choline	Choline kinase	Cell membrane metabolism, tumour proliferation	Initial staging and re-staging
¹⁸ F-NaF	Fluoride	Bone mineralization	Measures bone status	Metastases, evaluation of bone disease

¹⁸F-FMISO, ¹⁸F-fluoromisonidazole; NA, not applicable.

RADIOTRACERS

Radionuclides used in PET scanning are typically isotopes with short half-lives such as carbon-11 (≈20 min), nitrogen-13 (≈10 min), oxygen-15 (≈2 min), and fluorine-18 (≈110 min). They are incorporated into either compounds normally used by the body such as glucose (or glucose analogues), or into molecules that bind to receptors or other sites of drug action. Due to the short half-lives of most radioisotopes, the radiotracers must be produced using a cyclotron in a

radiochemistry laboratory that is in close proximity to a PET-imaging facility. Radiotracers can be divided into two groups, metabolic tracers and receptor-specific radiopharmaceuticals, depending on which pathway is used [17]. The radiotracers used in urological oncology are summarized in Table 1.

Metabolic tracers

The most widely used radiotracer in oncology is fluorodeoxyglucose (2-fluoro-2-deoxy-D-

glucose, FDG), a glucose analogue. Fluorine-18 was chosen to be the positron -emitting radioactive isotope to produce ¹⁸F-FDG. ¹⁸F-FDG is taken up by high-glucose-using cells such as cancer cells, where phosphorylation prevents the glucose from being released intact. FDG cannot be further metabolized as it lacks a 2' hydroxyl group normally found in glucose that is required for further glycolysis. Thus, the FDG-6-phosphate formed does not undergo glycolysis before radioactive decay. As a result, the distribution of ¹⁸F-FDG is a good reflection of the distribution of glucose

uptake and phosphorylation by cells in the body. The fluorine at the 2' position inhibits FDG from metabolic degradation or use, allowing it to accumulate and images to be taken [18]. However, once radioactively decayed, the fluorine from the FDG is converted to ^{18}O after 'picking up' a H^+ from the environment and becomes glucose-6-phosphate labelled with harmless non-radioactive 'heavy oxygen' (^{18}O) at the 2' position. This allows it to be metabolized normally, in the same way as ordinary glucose. FDG-PET can be used for diagnosing, staging, and monitoring

'FDG-PET can be used for diagnosing, staging, and monitoring treatment of various cancers'

treatment of various cancers, including among others: thyroid cancer [19], breast cancer [20], lymphomas [21],

lung cancer [22], head and neck carcinomas [23], and colorectal cancer [24].

Unfortunately, ^{18}F -FDG is not an ideal radiotracer for use in urology due to its urinary elimination, which prevents the proper visualization of the bladder and its surroundings [17]. To minimize this limitation, studies on bladder catheterization and the use of diuretics have been performed and other radiotracers that use different metabolic pathways and are not excreted in the urine are being investigated.

Choline is a necessary compound involved in cellular membrane phospholipid synthesis, transmembrane signalling, and lipid-cholesterol metabolism/transport.

'Targeted molecular imaging of specific surface receptors might be more accurate than molecular pathways'

Radiolabelled choline derivatives (^{11}C -choline, ^{18}F -fluorethyl-choline or ^{18}F -fluormethyl-choline) have been used in several

clinical studies. Choline excretion is mainly intestinal, through the liver, and has reduced renal excretion, making it more useful in urological oncology [25].

Proliferation and up-regulated membrane lipid synthesis are some of the characteristic features in cancer cells. Due to increased fatty acid synthesis in prostate cancer, radiolabelled acetate has been investigated as a tumour-imaging probe [17]. Uptake of acetate across the cellular membrane is mediated by both monocarboxylate transporters and a diffusion-like component. However, the exact mechanism by which acetate is taken up in

cancer cells has not been elucidated thus far. ^{11}C -acetate is the most commonly used radiotracer.

Amino acids are the building blocks of proteins and precursors for many biological molecules. Although all amino acids can be diffused into cells, uptake into cells is mainly achieved through carrier-mediated processes. As there is increased amino acid transport in malignant cells, radiolabelled amino acids have been developed and evaluated. ^{11}C -methionine, a natural radiolabelled amino acid, is a potential tracer for visualizing cellular proliferation and amino acid transport. This radiolabelled amino acid is mainly used in the CNS and it has been successfully applied to urological oncology [26]. Another tracer, ^{18}F -labelled synthetic L-leucine analogue (anti-1-amino-3- ^{18}F -fluorocyclobutyl-1-carboxylic acid, anti- ^{18}F -FACBC) was synthesized and used in prostate cancer [27].

The uptake of the thymidine analogue 30-deoxy-30- ^{18}F fluorothymidine (^{18}F -FLT) correlates very well with malignant cell proliferation. The rate-limiting enzyme for the uptake of ^{18}F -FLT is thymidine kinase 1. Thymidine kinase 1 activity has been shown to be high in proliferating cells and is mainly activated in the S-phase [28].

Receptor-specific radiopharmaceuticals

Targeted molecular imaging of specific surface receptors might be more accurate than molecular pathways. The ^{18}F -labelled androgen analogue, dihydrotestosterone (16β - ^{18}F -fluoro-5 α -dihydrotestosterone, ^{18}F -FDHT) has a good affinity for androgen receptors and has recently been investigated in patients with metastatic prostate cancer [29].

Bombesin is a 14-amino-acid neuropeptide with a high affinity for gastrin-releasing peptide receptors (or subtype 2 bombesin receptor). The four subtypes of the bombesin receptor have been shown to be highly expressed in various human malignancies and their potential use for targeted imaging has been evaluated.

Nitroimidazoles such as ^{18}F -fluoromisonidazole have emerged as a noninvasive technique to measure tumour hypoxia and have been used in the diagnosis of ischaemic tumours [30].

Carbonic anhydrase IX (CAIX) is overexpressed in some tumours, e.g. clear cell carcinomas. The synthetic antibody cG250 recognizes it and reacts against it by means of an antibody-antigen reaction [31].

EQUIPMENT

New technological developments have led to the use of more advanced equipment in all fields of modern medicine, especially benefiting fields such as nuclear medicine. Currently, almost every PET scan includes a fusion technique with CT.

Although it has not been shown in urology, PET/CT scans seem superior to PET scans alone, allowing proper anatomical localization. This superiority has been shown in other specialties, where PET/CT has been superior to bone scintigraphy and PET for lung cancer [32], obviating the need to perform additional examinations and reducing costs. It has also been shown that PET/CT provides a higher diagnostic accuracy by uptake characterization and localization than PET alone [33]. For nodal involvement, the accuracy of PET/CT is higher than PET alone [34].

PROSTATE CANCER

Inaba [35] was the first to use PET to investigate prostate pathology, discovering increased blood flow in malignant hyperplastic prostate tissue compared with BPH tissue. Since then, several studies have been performed to establish the exact role of this imaging technique in the evaluation of patients with prostate cancer.

Primary diagnosis or staging

Information on lymph node status is of key importance when planning appropriate treatment for patients with newly diagnosed prostate cancer. Although the incidence of lymph node metastasis has significantly dropped in the PSA era, it may still range from 1% to 26% depending on the patient population studied, the extent of lymph node dissection, and the quality of the histopathological analysis [36,37]. ^{18}F -FDG PET has a limited role in prostate cancer primary diagnosis and staging because prostate tumours often lack an increased glucose metabolism in contrast to others

tumours. In past years, studies using ^{11}C - or ^{18}F -choline have shown promising results [4,38].

de Jong *et al.* [39] reported excellent results with ^{11}C -choline PET on preoperative lymph node staging in newly diagnosed cases (sensitivity, specificity, and accuracy were 80%, 96%, 93%, respectively). However, it should be noted that the mean preoperative PSA level of patients with lymph node metastases in this study was 123 ng/mL and did not represent the typical high-risk patient.

More recently, in patients with intermediate- to high-risk clinically localized prostate cancer (mean PSA level 28.4 ng/mL) [40], the utility of ^{18}F -choline PET/CT in preoperative staging has been shown to be significantly inferior compared with sentinel lymph node dissection (sensitivity 10% vs 80%). Scher *et al.* [41] used ^{11}C -choline PET and PET/CT in 58 patients suspected of having prostate cancer. Sensitivity and specificity was 86.5% and 61.9%, respectively, for the detection of primary malignancy. The sensitivity and specificity was 81.8% and 100%, respectively, regarding metastatic spread detection.

Testa *et al.* [42] compared ^{11}C -choline PET/CT with MRI, three-dimensional (3D) MR spectroscopy (MRS), and a combination of the latter two techniques in 26 men with biopsy-confirmed prostate cancer who underwent radical prostatectomy (RP). Sensitivity, specificity, and accuracy of the three imaging methods were 55%, 86%, and 67%, respectively, for ^{11}C -choline PET/CT; 54%, 75%, and 61%, respectively, for MRI; and 81%, 67% and 76%, respectively, for 3D MRS. ^{11}C -choline PET/CT had a lower sensitivity than 3D MRS alone or combined with MRI in detecting prostate cancer. Husarik *et al.* [43] used ^{18}F -choline PET/CT in 43 patients at initial diagnosis (mean PSA level 11.6 ng/mL) with discouraging results for initial lymph node staging, especially for detecting small metastases.

Rinnab *et al.* [25] compared ^{11}C -choline PET/CT with TRUS for staging localized prostate cancer. The sensitivity of PET for stages pT3a–pT4 was better than that of TRUS (36% vs 14%). The overall mean staging accuracy was 70% and 26%, respectively. Both methods

under-staged microscopic disease extension and it was concluded that they may not be reliable for guiding treatment decisions.

Giovacchini *et al.* [44] assessed the relationship between ^{11}C -choline PET/CT and PSA level, tumour stage, and antiandrogen therapy in patients with prostate cancer. Sensitivity and specificity for the initial diagnosis was 72% and 43%, respectively. A negative correlation between uptake (maximum standardized uptake value, SUVmax) and antiandrogen therapy was detected. It was concluded that ^{11}C -choline PET/CT is not suitable for initial diagnosis but may be useful to monitor antiandrogen therapy.

Schiavina *et al.* [45] evaluated the accuracy of ^{11}C -choline PET/CT for lymph node staging preoperatively in intermediate- to high-risk patients with prostate cancer and compared it

‘PET/CT scans seem superior to PET scans alone, allowing proper anatomical localization’

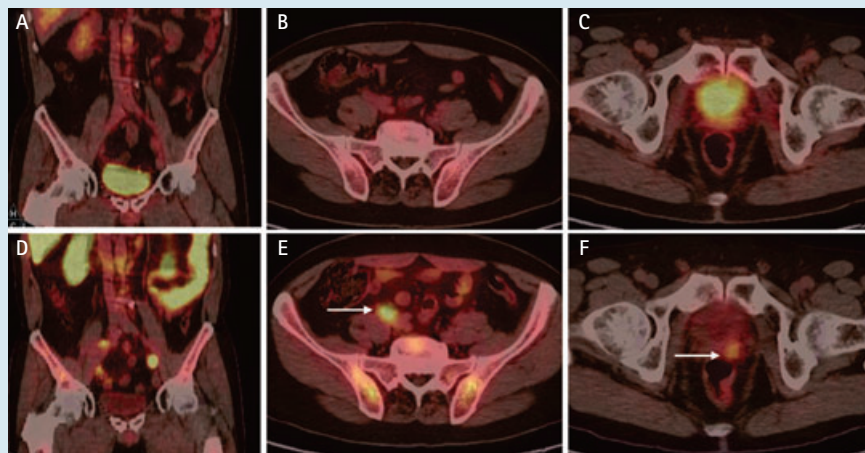
with the accuracy obtained from using two current nomograms [37,46]. The sensitivity and specificity of PET/CT for lymph node staging was 60% and 97.6%, respectively. In the per-node analysis, the respective values were 41.4% and 99.8%. PET/CT showed a higher specificity and accuracy than the nomograms, although the areas under the curve did not differ significantly.

Although studies on other radiotracers (^{11}C -acetate and ^{11}C -methionine PET) are scarce, it has been reported that they are more sensitive than ^{18}F -FDG in primary prostate cancer detection and the detection of regional lymph node or bone metastases [26,47,48]. Studies show ^{11}C -choline, ^{11}C -acetate, and ^{11}C -methionine to be better than ^{18}F -FDG for primary staging due to their better biodistribution pattern. Only one study compared ^{11}C -choline with ^{11}C -acetate and found a similar performance [49]. However, more studies are needed to determine which of these tracers performs best [50].

Re-staging, follow-up, and progression

Until 1999, ^{18}F -FDG has been the most commonly used radiotracer. However, it has been clearly shown that the ability of ^{18}F -FDG to detect lymph node involvement in organ-

FIG. 1. Comparison of PET with ^{18}F -FDG (A, B, C) and ^{11}C -choline (D, E, F) in a patient with biochemical failure after external beam radiotherapy. With biochemical failure with a PSA level of 2.1 ng/mL. No pathological uptake was seen with (A, B, C). However, in the choline study (D, E, F), there was a metastatic uptake in the seminal vesicle, in both external iliac lymph nodes, and right ilio-obturator.



confined tumours [2] and in patients with low PSA levels [51] is minimal; therefore, it is no longer recommended in clinical practice [52]. Larson and Schoder [53] retrospectively evaluated ^{18}F -FDG PET images performed between 1997 and 2003 at Memorial Sloan-Kettering Cancer Center, and calculated the PSA level and PSA velocity thresholds for best clinical performance at 2.4 ng/mL and 1.3 ng/mL/year. The use of these best thresholds resulted in a sensitivity of 80% and 73%, respectively, and a specificity of 71% and 77%, respectively.

Several studies have shown the diagnostic advantages of ^{11}C -choline over ^{18}F -FDG in re-staging patients after RP and biochemical failure [54,55]. Currently, prostate cancer studies have shown ^{11}C -choline to be better than ^{18}F -FDG (Fig. 1).

One of the most difficult clinical problems urologists face is to assess biochemical relapse after RP, and to decide whether to treat it by means of salvage or systemic therapy. ^{11}C -choline PET/CT has been

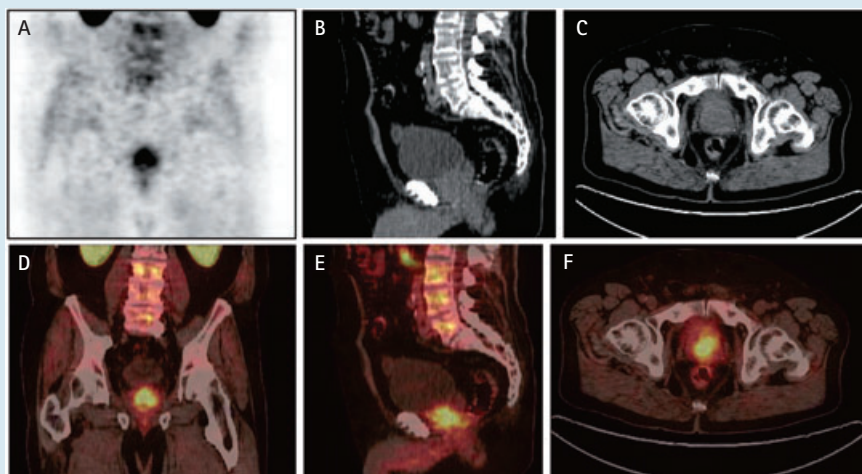
used for this purpose. Reske *et al.* [55] assessed the value of ^{11}C -choline PET/CT for detecting occult relapse after RP in 49 patients. In patients with biochemical relapse with a mean (range) PSA level of 2.0 (0.3–12.1) ng/mL, PET/CT showed true positive (with histological confirmation) lesions with increased ^{11}C -choline uptake in the prostatic

fossa in 70% of the cases. Similar results were achieved by Rinnab *et al.* [25] who studied this technique in patients after RP, external radiotherapy, and interstitial brachytherapy. The sensitivity for detecting recurrence was 91% with a specificity of 50% at PSA levels of <2.5 ng/mL. The same group of investigators studied the diagnostic value of ^{11}C -choline PET/CT for targeted salvage lymph node dissection in biochemical relapse after primary curative therapy [56]. A positive histology was reported in eight of 15 patients, only one patient had PSA nadir of <0.1 ng/mL after salvage surgery, three patients developed metastases during follow-up, and one patient had stable disease with a PSA level of 0.5 ng/mL. Krause *et al.* [57] assessed the relationship between the detection rate of ^{11}C -choline PET/CT and serum PSA level in biochemical failure. The detection rate was 36% for a PSA level of 1 ng/mL, 43% for a PSA level of 1 to <2 ng/mL, 62% for a PSA level of 2 to <3 ng/mL and 73% for a PSA level of ≥ 3 ng/mL. Our group has been using a dual radiotracer method, with ^{18}F -FDG and ^{11}C -choline PET/CT, showing that there is an increase in detection when using both markers, and this has a role for PSA levels of <5 ng/mL [58] with a sensitivity for PSA >1 ng/mL of 96.2% and a specificity of 44.4%.

According to Scattoni *et al.* [59], ^{11}C -choline PET/CT can be used as a diagnostic tool for the detection of lymph node metastases in recurrent prostate cancer. In that study, 25 patients were evaluated (mean PSA level 1.98 ng/mL). Of four patients with a negative

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FIG. 2. Image of a study performed with ^{11}C -choline on a patient with prostate cancer (T2NxM0) treated with radiotherapy and hormonal treatment, with PSA relapse at 48 months. A, PET images; B and C, CT; D–F, PET/CT images. Diagnosis was confirmed by biopsy.



^{11}C -choline PET/CT and positive MRI, none had nodal metastases. Of 21 patients, 19 patients (90%) with positive ^{11}C -choline PET/CT had nodal involvement. A lesion-based analysis showed that the sensitivity, specificity, and accuracy of ^{11}C -choline PET/CT was 64%, 90%, and 86%, respectively.

^{18}F -choline has also been used for studying recurrence after primary treatment. Heinisch *et al.* [60] evaluated the role of ^{18}F -choline for re-staging patients with biochemical failure after RP. The median PSA level for positive and negative ^{18}F -choline PET/CT was 6.1 ng/mL and 2.3 ng/mL, respectively. When the PSA threshold was set at 5 ng/mL, 41% of the examinations were true positive. Therefore, ^{18}F -choline PET/CT should not be restricted to patients with PSA levels of >5 ng/mL. Moreover, Vess *et al.* [61] assessed the value of ^{18}F -choline and ^{11}C -acetate PET/CT for residual or recurrent tumours after RP in 20 consecutive patients with a mean (range) PSA level of 0.33 (0.08–0.76) ng/mL. There was an abnormal uptake in five and six patients in each radiotracer group. Thus, PET/CT detected residual or recurrent disease in about half of the patients with a PSA level of <1 ng/mL. Recently, Pelosi *et al.* [62] reported that the detection rate in patients with biochemical failure after RP was related to PSA level, with a sensitivity of 20%, 44%, and 88.8% for PSA levels of ≤ 1 ng/mL, >1 to ≤ 5 ng/mL, and >5 ng/mL, respectively.

Albrecht *et al.* [63] studied ^{11}C -acetate PET potential in the diagnosis of prostate cancer

recurrence after radiotherapy (17 patients, median PSA level of 6 ng/mL) and RP (15 patients, median PSA level of 0.4 ng/mL). Local recurrence was confirmed via histology in biopsies obtained from all patients after radiotherapy (six patients). In the post-surgical group, ^{11}C -acetate PET was positive or equivocal for local recurrence in nine of 15 patients. Even in the subgroup of 11 patients with PSA level of >0.8 ng/mL, there was evidence for local recurrence in a similar percentage.

Very few studies have been conducted on the use of ^{11}C -methionine. Nilsson and *et al.* [64] reported ^{11}C -methionine uptake in most of the lesions in patients with androgen-independent prostate cancer. In another study, Nuñez *et al.* [26] compared the diagnostic yield of ^{11}C -methionine and ^{18}F -FDG in patients with rising PSA levels. They reported that ^{11}C -methionine not only detected more lesions than ^{18}F -FDG, but the intensity of ^{11}C -methionine uptake in these lesions was significantly higher than ^{18}F -FDG. The sensitivity of ^{11}C -methionine for the detection of soft tissue and bone metastases was equal (70%), while ^{18}F -FDG showed a sensitivity of 48 and 34%, respectively.

Recently, anti- ^{18}F -FACBC has shown promising results [27]. In all, 15 patients

with a recent diagnosis of prostate cancer (nine) or suspected recurrence (six) and a mean PSA level of 15 ng/mL were included in this study. Anti- ^{18}F -FACBC PET/CT images were compared with clinical, conventional images and pathological follow-up. In newly diagnosed prostate cancer, anti- ^{18}F -FACBC correctly identified malignancy in 40 of 48 prostate sextants. Pelvic node metastases were identified in seven of nine patients and were undetermined in two of nine. In all, four patients who had proven recurrence, anti- ^{18}F -FACBC identified malignancy. Larger clinical studies are needed to evaluate the role of anti- ^{18}F -FACBC PET in prostate cancer.

Progressive metastatic disease

The correct staging of metastatic prostate cancer is highly valued in monitoring treatment response and disease progression (Fig. 2). Conventional imaging techniques, namely scintigraphy, CT, or MRI, are usually used in this respect. Nuñez *et al.* [26] compared ^{18}F -FDG, ^{11}C -methionine PET, and conventional imaging techniques. The respective sensitivities were 48%, 72%, and 100%. More than 95% of metabolically active metastases metabolized ^{11}C -methionine, while only 65% metabolized ^{18}F -FDG.

For patients with metastatic disease, performed tests are important if they can effect disease management decisions. Tuncel *et al.* [65] showed that ^{11}C -choline PET/CT is a very useful tool in staging and re-staging patients with advanced prostate cancer. The result of PET/CT changed disease management in 24% of the patients.

To evaluate the best method for bone metastases detection, Beheshti *et al.* [66] performed a comparative study between ^{18}F -

^{11}C -choline PET/CT is a very useful tool in staging and re-staging patients with advanced prostate cancer'

choline and ^{18}F -fluoride PET/CT. It was concluded that ^{18}F -choline PET/CT might be superior for early detection (bone marrow involvement) of metastatic disease, while ^{18}F -fluoride PET-CT seemed to be superior in the diagnosis of sclerotic lesions.

Summary

^{18}F -FDG has little accuracy in diagnosing or staging prostate cancer. However, ^{11}C -acetate or ^{11}C -choline radiotracers proved to be good alternatives due to increased lipid metabolism and biosynthesis of cell membranes and their association with increased uptake of ^{11}C -acetate or ^{11}C -choline. ^{11}C -choline and ^{18}F -choline have been successfully used for staging primary and recurrent disease [67]. ^{18}F -fluoride seems promising in the study of bone disease. Currently, FDG-PET is only recommended for metastatic evaluation in equivocal cases [5]. Further testing is needed on other radiotracers, such as ^{11}C -methionine, anti- ^{18}F -FACBC, and ^{18}F -FDHT. Extensive research is needed to clarify the exact role PET/CT plays in the treatment of prostate cancer. It should not be used outside of clinical trials settings. Table 2 lists the studies performed [25,26,40–45,52–56,58,59,62].

KIDNEY CANCER

Initial diagnosis and staging

The detection of RCC with PET is often hampered because most radiotracers are excreted through the kidneys. While ^{18}F -FDG PET has not been useful in the primary diagnosis of RCC, it has been more effective in the detection of distant metastases [4], thus influencing therapeutic decisions. Dilhuydy *et al.* [68] showed that a positive ^{18}F -FDG PET affected decision-making in up to 20% of patients, while a negative result did not modify decision-making, especially for surgery due to its sensitivity.

^{11}C -acetate, another radiotracer, was studied for RCC. Sherve *et al.* [69] reported that RCCs accumulate more ^{11}C -acetate than normal kidney parenchyma, but this was contradicted by Kotzerke *et al.* [70] who reported the opposite.

Preoperative identification of tumour type could have important implications for the choice of treatment for RCCs, prompting several radiotracers to be studied. AS RCC

behaves like a hypoxic tumour and is resistant to chemotherapy and radiotherapy, studies on nitroimidazoles, a noninvasive technique to measure tumour hypoxia, have been conducted. ^{18}F -fluoromisonidazole has been explored as a potential tool for staging RCC by Lawenschuck *et al.* [30]. There was mild uptake increase in seven of 11 tumours. The identification of hypoxia in RCC and its impact on tumour biology and prognosis is an area of ongoing research.

The antibody cG250 reacts against CAIX, which is overexpressed in clear cell carcinomas. The value of ^{124}I -cG250 in predicting this type of RCC has been recently investigated in a phase I trial [31]. Twenty-six patients with renal masses scheduled for surgery underwent ^{124}I -cG250 PET-CT. PET accurately identified 15 of 16 clear cell carcinomas. Sensitivity and specificity of ^{124}I -cG250 PET-CT was 94% and 100%, respectively. Despite being a phase I study, the results are very promising, with the potential to help decide between treatment options.

Radioimmunotherapy is based on the use of a radiotracer, and uses β particles to destroy cellular DNA rather than to provide images. A study was conducted using ^{131}I -G250 to target RCC [71]. While modest, the results were promising in predicting who might respond to treatment with fractionated radiolabelled G250. It should be noted that the study was performed before the use of PET/CT, therefore the location of the deposits was not ideal.

Follow-up after treatment

^{18}F -FDG PET has been more successful in monitoring RCC progression. Safei *et al.* [72] used this method for re-staging advanced RCC. ^{18}F -FDG PET correctly staged 32 of 36 patients (89%) and missed four patients (11%), with 87% sensitivity and 100% specificity. The accuracy of PET for classifying lesions that were biopsied was also investigated. PET correctly classified 21 of 25 lesions biopsied with 88% sensitivity and 75% specificity. Additionally, Ramdave *et al.* [73] proved ^{18}F -FDG PET to be superior to CT in the evaluation of suspected RCC recurrence (accuracy 100% vs 88%).

A recent meta-analysis investigated the role of ^{18}F -FDG PET in RCC [74] and concluded

‘detection of RCC with PET is often hampered because most radiotracers are excreted through the kidneys’

^{18}F -FDG PET has been more successful in monitoring RCC progression’

TABLE 2 Summary of the PET studies on prostate cancer

Reference	Radiotracer	% Sensitivity	Specificity	Accuracy	Summary
Primary diagnosis and staging					
de Jong <i>et al.</i> [54]	¹¹ C-choline	80	96	93	Median PSA before surgery 130 ng/mL
Scher <i>et al.</i> [41]	¹¹ C-choline	86.5	61.9		For primary tumour detection
		81.8	100		For metastases spread detection
Testa <i>et al.</i> [42]	¹¹ C-choline	55	86	67	Comparison between MRI, MRS and PET/CT
Rinnab <i>et al.</i> [25]	¹¹ C-choline	36		70	Local staging, data referring for detecting pT3–pT4 disease
Schiavina <i>et al.</i> [45]	¹¹ C-choline	60	97.6		Detecting lymph nodes
		41.4	99.8		Per lymph node analysis
Giovanchini <i>et al.</i> [44]	¹¹ C-choline	72	43		Negative correlation between uptake (SUVmax) and androgenic therapy
Häcker <i>et al.</i> [40]	¹⁸ F-choline	10			Mean PSA 28.4 ng/mL compared with sentinel node (80% sensibility)
Husarik <i>et al.</i> [43]	¹⁸ F-choline	33.3	100		For detecting positive lymph nodes before surgery
Nuñez <i>et al.</i> [26]	¹¹ C-methionine	72.1			Mean PSA 11.58 ng/mL
	¹⁸ F-FDG	48			¹¹ C-methionine ¹⁸ F-FDG (compare conventional imaging as standard reference)
Re-staging, follow-up, and progression					
de Jong <i>et al.</i> [54]	¹¹ C-choline	38.4	100		For surgery patients
		77.7	100		For external beam radiation patients
Reske <i>et al.</i> [55]	¹¹ C-choline	63.8	92.3		PSA relapse after biochemical recurrence. Mean PSA positive studies 2.6 ng/mL
Rinnab <i>et al.</i> [25]	¹¹ C-choline	91	50		For detecting recurrence after primary treatment with surgery or radiation
Rinnab <i>et al.</i> [56]	¹¹ C-choline	34.7			Data for PSA < 2.5 ng/mL
Scattoni <i>et al.</i> [59]	¹¹ C-choline	64	90	86	For salvage lymphadenectomy after primary treatment
					Detection of lymph node metastases of recurrent prostate cancer
Pelosi <i>et al.</i> [62]	¹⁸ F-choline	20			PSA ≤ 1 ng/mL
		40			PSA > 1 ng/mL ≤ 5 ng/mL
		88.8			PSA > 5 ng/mL
Larson and Schoder [53]	¹⁸ F-FDG	80	71		For a PSA 2.4 ng/mL
		73	77		For a PSA velocity of 1.3 ng/mL/year
Picchio <i>et al.</i> [52]	¹¹ C-choline vs ¹⁸ F-FDG				Abnormal focal increases were noted in 47% of patients on ¹¹ C-choline-PET and in 27% on ¹⁸ F-FDG-PET. No positive PSA ≤ 5 ng/mL
Nuñez <i>et al.</i> [26]	¹¹ C-methionine vs ¹⁸ F-FDG	Soft tissue 70 vs 48 bone 70 vs 34			¹¹ C-Methionine diagnosed a higher number of lesion than ¹⁸ F-FDG in total
Rioja Zuazu <i>et al.</i> [58]	¹¹ C-choline vs/and ¹⁸ F-FDG	91			For PSA levels of 4.3 ng/mL for combined PET (¹¹ C-choline and ¹⁸ F-FDG) 5.15 ng/mL ¹¹ C-choline and 6.51 ng/mL for ¹⁸ F-FDG
Nuñez <i>et al.</i> [26]	¹¹ C-methionine vs ¹⁸ F-FDG	72 vs 48			95% of metabolically active ¹¹ C-methionine while only 65% metabolize ¹⁸ F-FDG

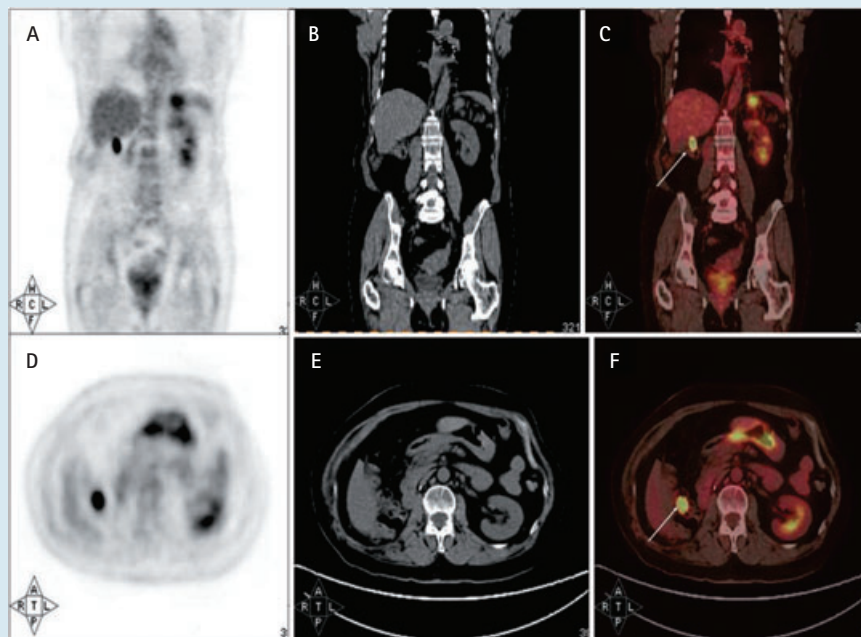
that ¹⁸F-FDG PET is useful in the diagnosis and staging of metastatic lesions with a sensitivity of 0.87 (95% CI 0.75–0.95) and a specificity of 0.93 (95% CI 0.86–0.97) but presents limitations when diagnosing primary tumours. Using PET/CT may

overcome these limitations (Fig. 3). From our experience, it is more advantageous to use PET/CT in kidney cancer for staging recurrent disease or new metastases after initial therapy, than for initial diagnosis and staging.

Summary

The usefulness of PET in RCC remains unclear. In local staging, there is no evidence to support its use, but novel radiotracers are showing promising results regarding the

FIG. 3. Coronal images (A, B, C) and axial (D, E, F) of PET-FDG (A, D), CT (B, E), and fusion images (C, F) of a patient with a record of right radical nephrectomy for RCC. A recurrence was suspected at 1 year after surgery and a PET/CT was performed. A hypermetabolic deposit is visualized (arrow) in the surgical area, compatible with local recurrence.



identification of RCC before surgery. In monitoring and re-staging advanced disease, PET has already shown good results, which might lead a potential role for this technique within the 'targeted therapy' era. Further research is needed before clinical use of PET/CT, as current results show that it cannot be used in primary diagnosis or follow-up outside of clinical trials. Additionally, its role in monitoring response with target therapy has to be examined.

[4,50,75] have investigated the clinical role of ^{18}F -FDG PET in primary tumour staging and in guiding therapy in both seminomatous GCT and nonseminomatous GCT (NSGCT). ^{18}F -FDG PET has several major limitations:

- Inflammatory and granulomatous tissues show extensive ^{18}F -FDG uptake
- lesions of <1 cm are often not detected
- mature teratoma is indistinguishable from normal and necrotic tissue [75].

GERM CELL TUMOURS (GCTS)

PET is a promising tool in testicular cancer, as three major diagnostic problems have yet to be solved by conventional techniques, including: correct staging of patients classified as stage I, evaluation of residual masses after chemotherapy, and the study of rising markers without clinical evidence of disease.

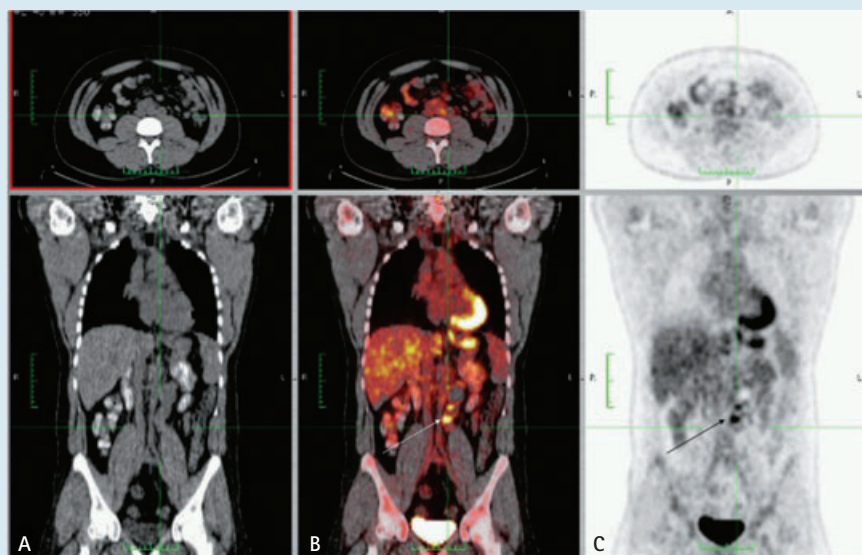
To date, ^{18}F -FDG is the only radiotracer used for imaging GCTs. Several clinical studies

NSGCTS

There is a lot of controversy about the use of ^{18}F -FDG PET in the evaluation and staging of NSGCT [76]. In a prospective trial conducted by Huddart *et al.* [77], they investigated the ability of ^{18}F -FDG to identify patients with no occult metastatic disease for whom surveillance was an attractive option. In that multicentre study, 111 high-risk patients with NSGCT underwent ^{18}F -FDG PET scanning within 8 weeks after orchidectomy or marker normalization. Positive scans were excluded from the study; negative scans were observed in the surveillance programme. The trial was prematurely stopped in 2005 due to an

' ^{18}F -FDG is the only radiotracer used for imaging GCTs'

FIG. 4. CT image of a suspicious lesion in a patient with seminoma. A ^{18}F -FDG was performed to visualize the activity of the lesion which confirmed an active tumour. (A, CT; B, fusion PET/CT; C, PET) Note the physiological uptake of the cardiac muscle in non-fasting adults. This physiological uptake can be easily diagnosed from the other hypermetabolic statuses.



unacceptably high relapse rate in PET-negative patients. Of the 88 PET-negative patients, one requested adjuvant chemotherapy, while 87 proceeded to surveillance. Within a median follow-up of 12 months, 33 of 87 patients in the surveillance program relapsed. Although ^{18}F -FDG PET identified some patients with disease not detected by CT, the relapse rate among PET-negative scans remained high. It was concluded that ^{18}F -FDG PET is not sufficiently sensitive to identify patients at low-risk of relapse to guide management decisions. In another prospective trial with confirmatory histology, Oechsle *et al.* [78] reported that ^{18}F -FDG PET was unable to provide additional information to that which CT scan and serum markers provided.

However, there were several previous studies reporting positive results for ^{18}F -FDG PET in NSGCT. Kollmannsberger *et al.* [79] reported that PET alone properly identified 32 lesions of 85, with 29 true-positives and only three false-positives. In a later study using PET alone, Johns Putra *et al.* [80] had similar results with six teratoma lesions and only one recurrent disease out of 12 negative studies. In addition, other radiotracers have been successfully used in the study of other GCTs, such as the brain with promising results [81].

Seminomatous GCTS

Results from several studies suggest that ^{18}F -FDG may be used as a standard tool in evaluating seminoma residuals in patients with seminomatous GCT after chemotherapy. De Santis *et al.* [82] studied 56 patients with metastatic pure seminoma who had either the histology of the resected lesion or the clinical outcome documented by CT, tumour markers, and/or physical examination during follow-up. The sizes of the residual lesions on CT (>3 cm or ≤ 3 cm) were correlated with the presence or absence of a viable residual tumour. The diagnostic values of ^{18}F -FDG PET were as follows: specificity 100% (95% CI 92–100%), sensitivity 80% (95% CI 51–95%), positive predictive value 100%, and negative predictive value 96%, respectively; vs values of specificity 74% (95% CI 58–95%), sensitivity 70% (95% CI, 34–90%), positive predictive value 37%, and negative predictive value 92%, respectively, for CT for discrimination of the residual tumour by size (>3 cm or ≤ 3 cm). These results confirm that ^{18}F -FDG PET is the best predictor of viable residual tumour in post-chemotherapy seminoma residual masses and should be used as a standard tool for clinical decision-making

in this patient group. The above results were reproduced by Becherer *et al.* [83], corroborating that PET contributes to the management of residual seminoma lesions especially in terms of avoiding unnecessary surgery for patients with lesions of ≥ 3 cm (Fig. 4).

Summary

While poor PET results from the Huddart *et al.* [77] study show that it cannot be considered a validated diagnostic tool for NSGCT, PET seems to be one of the most promising tools in the evaluation of patients with testicular tumours. Currently, the only established role for PET in urological oncology is for follow-up of patients with seminomas GCT [7,12]. Smaller studies have shown the potential for PET to be used as an adjunct to CT and serum tumour markers in the management of NSGCT, but further studies are necessary. The development of newer radiotracers with different metabolic pathways may be promising in the evaluation of NSGCT.

BLADDER CANCER

Invasive bladder cancer confined to the pelvis is treated by means of radical cystectomy and pelvic lymph node resection. Preoperative accurate staging would help to identify patients at high-risk for extraperitoneal spread for whom a combined treatment may be offered.

CT and MRI are widely used for preoperatively staging bladder cancer. However, these

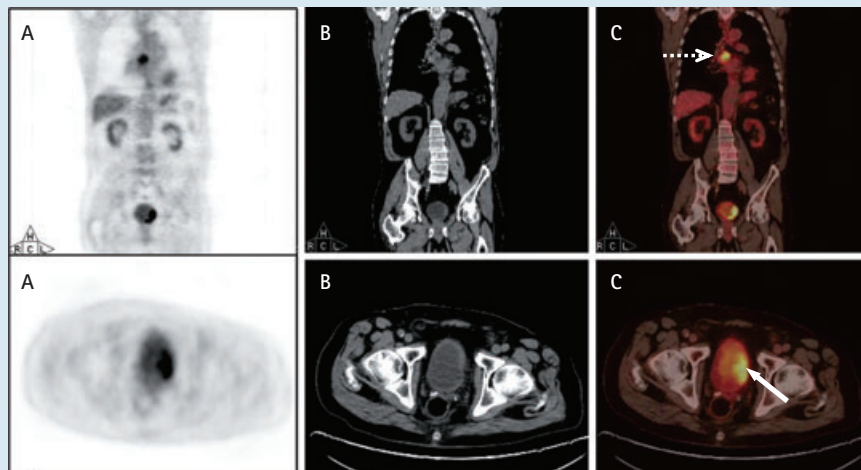
‘there is a need for a noninvasive imaging method to more accurately stage bladder cancer’

imaging methods have limitations. Metastatic lymph nodes are rarely substantially enlarged causing false-negative rates to be recorded on CT and MRI. Thus, there is a need for a noninvasive imaging method to more accurately stage bladder cancer.

Local disease and staging

The role of ^{18}F -FDG PET for the detection of localized disease is limited due to the urinary excretion of ^{18}F -FDG [50]. However, occasionally, ^{18}F -FDG PET/CT may detect unknown primary bladder cancer. Additionally, ^{18}F -FDG PET may have a role in

FIG. 5. Preoperative ^{18}F -FDG-PET scan of a suspicious lesion on the chest CT, consistent with metastasis; a biopsy was taken which confirmed the result. A, PET images; B, CT images; C, PET/CT fusion images.



identifying loco-regional lymph node and other distant metastases (Fig. 5). A major drawback to this technique is urinary elimination of ^{18}F -FDG, which can be avoided by using a bladder washing-rinsing system that uses diuretics and i.v. fluids [84].

Drieskens *et al.* [85] evaluated the preoperative use of ^{18}F -FDG PET for detecting lymph node and distant metastasis in 55 patients with bladder cancer. For the diagnosis of metastatic disease, the sensitivity, specificity, and accuracy of ^{18}F -FDG PET was 60%, 88%, and 78%, respectively. Liu *et al.* [86] investigated the value of ^{18}F -FDG PET for detecting metastatic disease in 46 patients. 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 be interpreted with caution for patients who have received prior chemotherapy.

In an effort to improve PET results, researchers have studied other radiotracers. Ahlström *et al.* [87] reported ^{11}C -methionine to be superior to ^{18}F -FDG; however, sensitivity was only 78%. In another study, de Jong *et al.* [88] used ^{11}C -choline PET in 18 patients to evaluate bladder cancer. Normal bladder wall tracer uptake was low and in ^{11}C -choline PET correctly detected tumours in 10 of the patients. Gofrit *et al.* [89] evaluated ^{11}C -choline PET for preoperative staging in 18 patients. They noted that ^{11}C -choline PET was highly positive for primary and metastatic

bladder cancer, and in all primary TCCs there was ^{11}C -choline uptake. Picchio *et al.* [90] reported that ^{11}C -choline PET was comparable to CT for detecting residual cancer after transurethral bladder cancer resection and it appeared to be superior for detecting lymph node metastasis.

^{18}F -FDG application in upper urinary tract TCC is limited to a case report in which a difficult diagnosis was made with the help of ^{18}F -FDG [91]. ^{18}F -fluorothymidine is a radiolabelled compound based on the nucleic acid thymidine, and has emerged as an important radiotracer that mirrors cellular proliferation in PET. Early studies in human tumours are promising. Recently, Lawrentschuk *et al.* [30] reported a difficult case of renal TCC in a long-standing cyst, which was clearly identified with the use of this radiotracer.

Summary

^{18}F -FDG PET is useful for identifying distant metastases due to increased ^{18}F -FDG uptake by the lesions, but it is not useful in detecting primary tumours because urinary excretion of ^{18}F -FDG interferes with local staging. ^{11}C -choline and ^{11}C -methionine may prove to be more effective than ^{18}F -FDG, but further studies are needed.

OTHER APPLICATIONS IN UROLOGICAL ONCOLOGY

One of the most wide-spread indications of PET in oncology is the study of haematological tumours such as lymphomas

FIG. 6. PET scan of a prostate lymphoma that shows systemic involvement. Solid-lined arrows point to thoracic lymph nodes; dashed-lined arrows points to iliac lymph nodes; and arrowheads point to sacrum lymph nodes

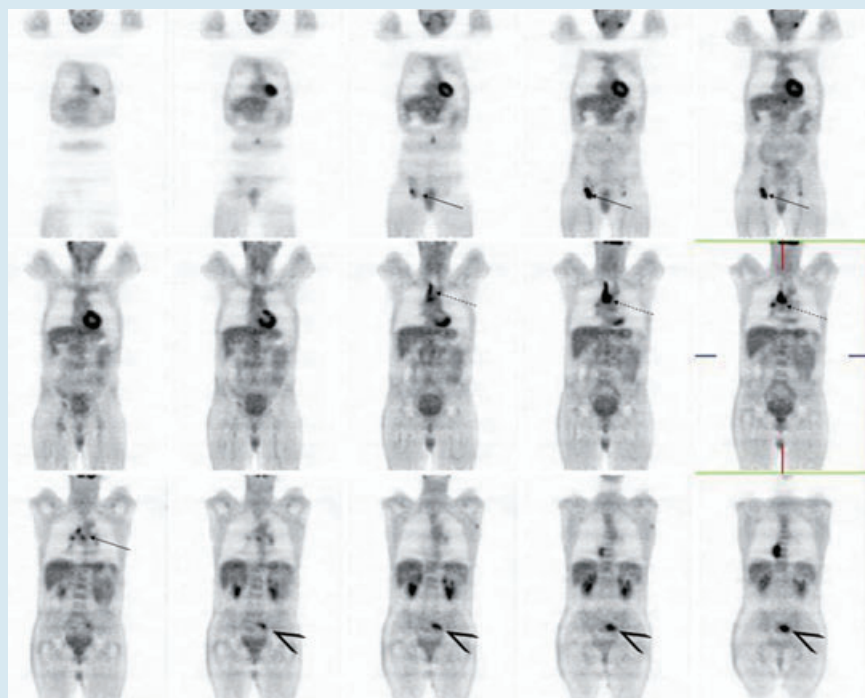


FIG. 8. Optimal use of PET scans with various tracers in urological oncology

Prostate	-Biochemical Recurrence	→	C^{11} -Acetate or C^{11} -Choline
	-Metastatic Disease	→	C^{11} -Choline
Kidney	Initial Diagnosis	→	^{124}I -cG250
	Follow-up	→	^{18}F -FDG
Testis	Monitoring Retroperitoneum disease	→	^{18}F -FDG
Bladder	Metastatic disease	→	^{18}F -FDG

[92]. Such tumours may arise in the genitourinary system, e.g. in the testes or prostate. Although treatment and follow-up of these rare entities is done by haematology oncology specialists, urologists are involved in the diagnosis, which can be facilitated by PET (Fig. 6).

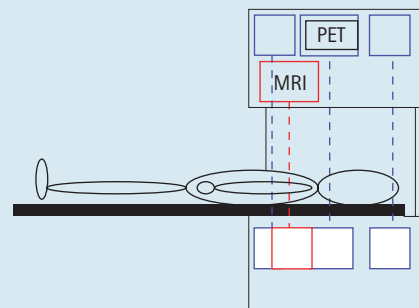
FUTURE

The unrivaled advantage of PET stems from its ability to track radiolabelled biomarkers with detection sensitivity below the picomolar range for functional imaging, whereas MRI and CT provide high-resolution anatomical information. MRI also permits a large variety of tissue contrasts, diffusion imaging,

MRS, and functional MRI [93]. Thus, the combination of two or more imaging methods to get complementary information, such as morphology and function, is a worthwhile goal.

Although combining PET and CT has already been achieved [94] in clinical and preclinical scanners, PET/CT has many limitations. Its major drawback is that imaging is performed sequentially rather than simultaneously. In preclinical studies, this adds considerable time for studying subjects and eliminates any temporal correlation between the two methods, such as CT

FIG. 7. Scheme of PET/MRI fusion. One of its major advantages is that both the functional image (PET) and the morphological image (MRI) are taken simultaneously rather than sequentially (like in the PET/CT)



perfusion measurements and PET tracer kinetics. Furthermore, CT has limited soft-tissue contrast, and the necessary dose of radiation can be high enough to affect the animal model under study. Hence, a preferred choice would be the PET/MRI technique. Its advantages include:

- the absence of ionizing radiation
- excellent soft-tissue contrast
- flexible scan protocols
- the capability to perform functional MRI and MRS

The simultaneous acquisition of different functional parameters using PET, functional MRI, or MRS, in addition to high-resolution anatomical MRI information, creates enormous possibilities and provides new opportunities to study pathology and biochemical processes *in vivo* [95,96] (Fig. 7). PET/MRI provides a powerful tool for studying biology and pathology in preclinical research and has great potential for clinical applications. Combining functional MRI and MRS with PET paves the way for a new perspective in molecular imaging.

‘preferred choice would be the PET/MRI technique’

CONCLUSIONS

The use of PET and PET/CT is widespread in oncology, with ^{18}F -FDG as the most commonly used radiotracer (Fig. 8). PET/CT in urological oncology is challenging because of the urinary excretion of many tracers. While it is of great help in some difficult cases, the

only widely accepted indication for ^{18}F -FDG is on seminomatous GCT. The rapid development of the new radiotracers together with technological advances has improved the visualization of urological malignancies. However, further studies are needed to establish the role of PET in the management of these diseases. The future belongs to fusion techniques, like the current PET/CT, where anatomical and biological imaging is provided. Further research in this field may allow combining of other techniques.

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CONFLICT OF INTEREST

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Abbreviations: PET, positron emission tomography; FDG, fluorodeoxyglucose (2-fluoro-2-deoxy-D-glucose); NCCN, National Comprehensive Cancer Network; anti-¹⁸F-FACBC, anti-1-amino-3-¹⁸F-fluorocyclobutyl-1-carboxylic acid; ¹⁸F-FLT, 30-deoxy-30-[¹⁸F]fluorothymidine; ¹⁸F-FDHT, ¹⁸F-dihydrotestosterone (16β-¹⁸F-fluoro-5α-dihydrotestosterone); CAIX, Carbonic anhydrase IX; 3D, three-dimensional; MRS, MR spectroscopy; RP, radical prostatectomy; (NS)GCT, (nonseminomatous) germ cell tumours; SUVmax, maximum standardized uptake value.

A biomarker is a biological molecule found in blood, body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease that may also be used to monitor treatment response [1,2]. In the context of imaging the term 'biomarker' may even be supplemented by the term 'biological signature' taking into account the tumour microenvironment and vascularity rather than a singular biomarker itself. Positron emission tomography (PET) combined with CT (PET/CT) has shown great promise for obtaining a biological signature of tumours by allowing us to focus on the functioning and anatomy of tumours and certainly not just with traditional oncology imaging with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), which exploits only tumour metabolism of glucose. The timely review by Rioja *et al.* [3] in this edition provides a comprehensive summary of the current role of PET in urological oncology.

Perhaps the most promising imaging biomarker in urological oncology involves immuno-PET for clear-cell RCC. In this case the monoclonal antibody (mAb) to the membrane-associated antigen carbonic anhydrase IX (CAIX) called G250 ([¹²⁴I]-cG250-PET/CT) is used to exploit the over-expression of this antigen in such tumours with >90% accuracy [4,5]. We eagerly await the results of a Phase III multicentre comparative study evaluating this method in presurgical patients with renal masses (clinicaltrials.gov NCT00606632). Radiolabelled glucose is certainly still relevant in urological oncology as we understanding how PET-CT may not be relevant for diagnosis, but has an important role in staging of penile, bladder and renal tumours. Interest has emerged specifically recognizing the functional value of PET/CT in monitoring of tumour response specifically after tyrosine kinase inhibitors, in part due to responses seen in RCC [6]. The Response Evaluation Criteria In Solid Tumors (RECIST 1.0) [7] criteria using only size change has even been deemed inadequate in favour of PET/CT or PERCIST: PET Response Criteria in Solid Tumors (PERCIST) which uses quantitative and qualitative approaches to metabolic tumour response assessment with ¹⁸F-FDG PET/CT [8].

In other developments choline exploiting cell membrane construction in prostate cancer [9,10] and thymidine [11] exploiting DNA turnover in urothelial tumours are but a few examples of where the imaging is headed in the next decade. PET/CT is already accepted in

guidelines to investigate post-seminoma retroperitoneal masses. Furthermore, labelling the biomarker representing the therapeutic mechanism directly so it may be imaged in context (e.g. bevacizumab which binds to vascular endothelial growth factor expressed in clear-cell RCC) [12], although yet to be fully evaluated in human patients would be an exciting development, as would radiolabelling of other tyrosine kinase inhibitor and small molecules.

Certainly, barriers to functional imaging of tumours in the urinary tract remain such as the excretion of radiotracer altering background levels making interpretation difficult and relatively limited resolution of masses smaller than ≈5 mm. Over time, more suited markers and better software and machines will improve both of these issues. Advantages such non-invasiveness, ability to repeat and tumours remaining *in situ* and metabolically active thus not being subject to significant bias by tissue processing, storage, and analysis when compared with traditional blood or tissue biomarkers [13,14]. Ultimately it is the ability of an imaging method to alter clinical decision-making (e.g. in RCC [15,16]) that is the hallmark of success.

Although examples now abound even with conventional imaging methods such as MRI where intracellular lipid content, intratumoral haemosiderin deposition and enhancement patterns may be exploited to interrogate a potentially malignant lesion, PET/CT is at the forefront of 'biological signatures'. The key will remain the resolution, sensitivity, costs, ability to obtain data in a single scan and above all influence management. We await future studies that will delineate which biological signatures will be most relevant in urological oncology, but certainly, the era of tailored imaging is well and truly upon us, so urologists must remain educated as to the current role of PET/CT. With careful selection of patients being matched to the correct sophisticated imaging techniques such as PET/CT, we have the potential to improve treatment outcomes.

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EDITORIAL COMMENT

ROLE OF POSITRON EMISSION TOMOGRAPHY IN UROLOGICAL ONCOLOGY

Urological oncology has benefited from advances in medical imaging, perhaps more so than other specialties particularly in renal and adrenal tumours where imaging remains the cornerstone of management. Testicular, bladder and penile cancer staging have similarly benefited. However, 'grey' areas remain, particularly prostate cancer for the staging of high-risk and locally advanced tumours and for localization of low- to intermediate-risk tumours. To improve in the grey areas and to enhance even those where imaging is highly sensitive, the era of biomarker imaging has emerged.