1. Introduction on Positron Emission Tomography (PET)

PET is a technique in which an image of a molecular process is obtained. For this purpose a radioactively labeled substance, a radiopharmaceutical, is administered to a patient. The substance will participate in a metabolic or (patho-)physiologic process, and accumulate at the sites the process is most active. Since the substance is radioactively labeled the accumulation, and thus the distribution of the radiopharmaceutical, can be viewed on the outside of the body and be followed in time. So far, there is no difference with conventional nuclear medicine techniques.

The main difference of PET versus conventional nuclear medicine is the type of (radio) isotope used. In conventional nuclear medicine, these radioisotopes are gamma-ray emitters. The energy of the gamma-rays is a characteristic of each radioisotope. The most well known of these isotopes is $^{99m}$Tc (technetium), bound to a large number of substances, e.g. to a diphosphonate. With the resulting $^{99m}$Tc-labeled diphosphonate bone scans are being made, e.g. in the work-up of patients with cancer.

In positron emission tomography a different type of radioisotopes is used, viz. positron emitters. These isotopes are characterized by a surplus of positive charge in the nucleus, creating an unstable...
nucleus. Stability is regained by either capturing an electron (negative charge) into the nucleus, or by emitting the surplus positive charge in the form of a positron. The positron is a particle with the mass of an electron, but with a positive charge. It should be considered the ‘anti-matter’ of an electron.

The positron is expelled from the nucleus with a certain kinetic energy and migrates through the tissue for a few millimeters, losing its kinetic energy when traveling. The distance traveled is depending on the isotope used. When the positron has come to a complete standstill it will form a positronium. Together with an electron in its vicinity the positronium will be annihilated instantly, a process in which the available mass of the particles is converted into energy following Einstein’s formula $E=mc^2$. It has been calculated that the energy present in this system is 1022 kilo-electron Volts (keV). However, in order to fulfill the law on conservation of momentum, this energy is released as 2 gamma-photons with energy of 511 keV which are expelled diametrically. In clinical practice the most often used positron emitters are relatively short-lived, cyclotron-produced. Examples are $^{18}$F, $^{15}$O, $^{13}$N, and $^{11}$C. The last few years also other, often generator-produced, positron emitters are being introduced as $^{68}$Ga, $^{82}$Rb, $^{89}$Zr, and $^{124}$I.

The radiation resulting from this annihilation event can be detected with conventional gamma-cameras, but nowadays dedicated PET-cameras are widely available. The principal difference between conventional cameras and PET-cameras is the presence of coincidence electronics. As stated, an annihilation event produces 2 photons released in opposite directions. This means that when an event is detected in a detector, the other event should be detected within a short time-frame in an opposing detector. Based on these principles modern day cameras consist of a large number of detectors with coincidence electronics, spanning an axial length of 15 cm or more. The newest cameras have detector and electronics characteristics that are thus fast that the time difference between the detection of the 2 photons can be taken into account to locate the exact position of the annihilation. These machines, so-called ‘time-of-flight’ machines, will undoubtedly be the future of PET-cameras.

Second, the specific way of decay allows for a full correction of attenuation of the signal. One can imagine that a signal coming from the deep will be attenuated more than a signal coming from the surface as e.g. the skin. Attenuation can be measured by introducing an external radiation source in the gantry of the camera and comparing the counts obtained in an empty gantry with those obtained with the counts obtained with the patient present. A disadvantage is the relatively long time such a transmission scan for attenuation correction takes (approximately 50% of the whole procedure).

In the past few years a second development occurred, that already has had great impact in clinical routine, viz. the combined PET-CT cameras. In these machines a CT-camera and a PET-camera are combined to one functional unit. In 1 session patients will undergo a CT-scan and a PET-scan directly after each other and thus both anatomical and metabolic information are obtained. The great advantage of these machines is that the metabolic process can be pinpointed to a certain anatomical location. Moreover, the CT-data can replace the transmission scanning for attenuation correction. Since CT-data are obtained in less than a minute, scanning time per patient can be reduced by approximately 50%. However, one has to realize that the CT and the PET-scan are obtained sequentially (be it with a short time interval), not simultaneously. Consequently, there is still the possibility of artifacts due to movement of the patient in between scans. A general tendency in tracer development is the search for more specific tracers, while not losing on sensitivity. The drawbacks of such tracers, viz. problems in locating the tumor, are overcome with the new PET-CT machines. Consequently, the development of these machines itself will form a boost for radiopharmaceutical development.

1.1. Radiopharmaceuticals

1.1.1. $^{18}$F-FDG

The most commonly used radiopharmaceutical for PET in oncology is 2-[$^{18}$F]fluoro-2-deoxy-d-glucose, also called fluorodeoxglucose or FDG. FDG is an analogue of glucose. It is taken up by the cell by glucose transporters (mainly glut-1) and phosphorylated to FDG-6-phosphate by the enzyme glucose-6-phosphokinase. Whereas glucose-6-phosphate finds itself on a crossroads of a vast number of metabolic processes such is not the case of FDG-6-phosphate. Because of the introduction of the fluor-atom, the three-dimensional structure of the molecule changes after phosphorylation changes in such a way that FDG-6-phosphate is not a substrate for other enzymes anymore. As a result, the FDG is trapped in the cell, at least on the time-frame of a normal PET-scan.

The use of FDG in oncology is based on the observation that most cancer cells have a high expression of glut-1 transporters in the cell membrane [1]. It’s use has been established in variety of
carcinomas, e.g. lung cancer, colorectal cancer, and malignant lymphomas [2–4].

Despite the promising results of FDG, the substance also has some drawbacks. First, FDG is also taken up in inflammatory tissue, macrophages in particular [5]. This phenomenon may hamper interpretation of images obtained and results in a reduction of specificity. Second, as FDG is not equal to glucose, the substance is not re-absorbed by the kidneys. As a result, accumulation of FDG in the bladder occurs, causing a high radiation dose to the bladder wall, and hampering interpretation of the pelvic areas. Bladder irrigation or forced diuresis in combination with an indwelling catheter only could solve a part of this problem of FDG PET.

1.1.2. $^{11}$C-choline and analogues
As it was shown that FDG is not suitable for clinical practice of prostate cancer, alternative tracers were developed. The first of these showing clinical potential was $^{11}$C-labeled choline. Choline is one of the components of phosphatidylcholine, which in itself is an essential element of phospholipids in the cell membrane. Cancer is associated with cell proliferation and up regulation of choline kinase (the enzyme which catalyzes the phosphorylation of choline), providing the rationale for the use of choline in oncological PET [6].

A major disadvantage of $^{11}$C-choline is the short half-life of 20.4 minutes. This short half-life will prohibit a widespread use of the tracer, as it is depended on the presence of an on-site cyclotron for the production of $^{11}$C. This has led to the development of $^{18}$F-labeled analogues as $^{18}$F-methyl-choline and $^{18}$F-ethyl-choline.

1.1.3. $^{11}$C-acetate
The mechanism of increased $^{11}$C-acetate accumulation in cancer cells is yet unclear. It has been reported that increased $^{11}$C-acetate uptake in malignant tissue is caused by accelerated lipid synthesis. Based on the assumption that this increased lipid metabolism rate is associated with the accelerated cell membrane synthesis due to tumor growth, $^{11}$C-acetate may be an indicator of this metabolic pathway in cancer tissue [7].

1.2. Radioimmunology and PET
Immuno-PET involves radio labeled monoclonal antibodies bound to an antigen on tumor cells. Targeting of tumor antigens in the treatment of cancer is rapidly progressing. The new classes of biological anticancer agents probably work only in subpopulations of patients, in whom the specific tumor antigens (target) are expressed. Immuno-PET will likely play a greater role in patient selection and tailoring of treatment, monitoring of dosage and response to treatment. Several radio-immunoconjugates are currently studied in for instance prostate cancer, renal cell cancer, colorectal and ovarian cancer. The optimum uptake of such antibody conjugates in tumors is normally several days for the intact immunoglobulin. The half-life of common PET isotopes like $^{11}$C and $^{18}$F is therefore too short for clinical use with antibodies. Positron emitters with longer half-lives are better suited to the slow pharmacokinetics of radio labeled monoclonal antibodies. For this purpose the radioisotopes $^{89}$Zr and $^{124}$I with physical half lives of 78 and 100 hours are commonly used although the ideal radioisotope has not been defined [8].

2. PET in oncological urology

2.1. Bladder cancer
The mainstay of patients with transitional cell carcinoma of the bladder present with non-invasive form of the disease. Local therapy combined with adjuvant installations of chemo- or immunotherapeutic agents prevent progression in terms of recurrence and grade. Optimal treatment for invasive bladder cancer without (lymph node) metastases is surgery. Apart from transurethral resection to determine depth and grade, computerized tomography is mainly used to determine presence of lymph node metastases. This technique relies on anatomic distortion for instance enlargement. However is has been shown that although metastases are present enlargement does not have to occur. It has been proposed that metabolic imaging through PET could provide extra information on the presence of metastatic sites even outside local lymph node regions. One of the first tracers to be studied that did not excrete into urine was $^{11}$C-methionine. However, the initial results using this radiopharmaceutical were poor, only tumors of more than 1 cm in diameter being visualized with PET [9]. It was also shown that L-methyl-$^{11}$C-methionine PET was unsuitable for monitoring of neo adjuvant chemotherapy in bladder cancer [10].

Although a commonly applied tracer in oncology, FDG has very limited application in bladder cancer. The rapid excretion via the kidneys into the urinary tract hampers evaluation of the pelvic region and in particularly the bladder For this reason FDG PET was not useful in local staging [11,12]. Recently Drieskens et al. studied FDG PET for detection
of nodal or distal metastases in a large series of patients comparing FDG PET with PET CT using histology as reference. FDG PET/CT was superior to CT alone for the diagnosis of metastatic disease with a sensitivity, specificity and accuracy of PET/CT of 60%, 88% and 78%, respectively. Diagnostic discordances between PET/CT and CT alone were found in 9/40 patients, among whom PET was correct in six (15%): three with true-positive and one with true-negative distant metastases, and two with true-negative lymph nodes. The authors concluded that metabolic imaging using FDG PET added to the diagnostic accuracy but the sensitivity of 60% needs to be improved before routine clinical use [13].

$^{11}$C-choline PET has already shown potential for the detection and staging of tumors in areas where FDG lacks sensitivity, such as the brain and the prostate. In a pilot study by de Jong et al. 18 patients with invasive bladder cancer were studied with $^{11}$C-choline PET. All 10 patients with residual tumor were identified by $^{11}$C-choline PET. One false-positive scan was attributed to an indwelling catheter. Pre-malignant and non-invasive tumors were not visualized [14]. Pichio et al studied $^{11}$C-choline PET in 27 patients with bladder cancer prior to cystectomy and confirmed the high detection rate of residual tumor. Next $^{11}$C-choline PET was slightly superior to CT in identifying nodal metastases with a detection rate of 5/8 for PET/CT vs 4/8 for CT only [15]. In a recent study by Gofrit et al. in 18 patients using $^{11}$C-choline PET/CT, all 6 patients with proven lymph node metastases were detected by PET/CT [16]. Larger studies on pre-operative staging are lacking at present. Thus the clinical value of PET in bladder cancer still has to be determined. With the present data PET does not have a role in the primary diagnosis or in local staging of bladder cancer.

### 2.2. Prostate cancer

The incidence of prostate cancer increases yearly. This can be mainly attributed to increased use of sensitive diagnostic tools such as prostate specific antigen (PSA). 75% of patients present with localized disease. Prognosis is dependent on accurate staging and treatment selection. Widely used transrectal ultrasound in combination with sextant biopsies gives accurate diagnosis and grading. However determination of capsular penetration and metastases detection has remained a challenge with current imaging modalities. CT and magnetic resonance imaging (MRI) has been used with variable but reproducible results [17,18]. With addition of an endocoil and ultra small super paramagnetic iron oxide particles an increased sensitivity of MRI in local staging and detection of lymph nodes was achieved [19].

#### 2.2.1. Staging primary prostate cancer

$^{18}$F-FDG – Prostate cancer is the most researched urological tumor with PET. FDG is the most applied tracer in the oncological field. Its accumulation is dependent on the glycolytic activity of the tumor. However prostate cancer displays little glycolytic activity. The added effect of urinary excretion makes it very difficult to determine uptake of FDG in primary prostate cancer. Even under continuous bladder irrigation FDG was not able to distinguish between scar tissue, BPH and prostate carcinoma [20–22]. The detection of metastases of prostate cancer with FDG varies (20–65%) but uptake of FDG seems to signify progression of disease [22,23]. At the moment FDG does not seem to be the tracer of choice in the primary staging of prostate cancer.

$^{11}$C-acetate – Oyama and co-workers reported in a series of 22 patients that all primary prostate carcinoma could be visualized [24]. The main advantage over FDG is that prostate imaging could be achieved without hindrance by urinary excretion. In the same group of patients five presented with lymph node metastases detected with Acetate against 2 positive with FDG. However there seems to be an overlap in patient with uptake of acetate due to BPH and prostate carcinoma [24].

$^{11}$C-choline – Several studies have confirmed that $^{11}$C-choline with PET is able to visualize carcinoma of the prostate although there is ‘non specific’ uptake observed in both benign hyperplasia as well as in high grade prostatic intraepithelial neoplasia [25–28].

$^{11}$C-choline has several advantages over FDG. Although bowel uptake can disturb reading, generally there is intense and clear uptake of choline in primary and metastatic prostate cancer. There is hardly any urinary excretion and its serum clearance is fast. The short half life of $^{11}$C does limit the application of this tracer to institutions with production systems. The application of $^{18}$F with choline could overcome this problem. However urinary excretion of $^{18}$F poses challenges in determining uptake of choline in urinary tumors. In a group of 67 patients preoperative staging revealed that of 15 patients positive on PLND 12 had a positive choline PET scan (sensitivity 80%). The 3 false-negative findings are thought to be on the basis of micro metastases [29]. This inability to detect metastases is that the spatial resolution of current PET scanning is approximately 5 mm due to physical restraints of modern PET scanning.
$^{11}$C-methionine – At first the uptake of $^{11}$C-Methionine could be demonstrated in patients with prostate cancer [30]. In a more recent study in twenty patients with elevated PSA (average 9.36 ng/mL) a sensitivity in detection of tumor could be demonstrated in 75% of patients with repeat negative biopsies. In 5 patients with negative PET findings no carcinoma could be shown on biopsy [31].

$^{18}$F-Fluorodihydrotestosterone (FDHT) – Ongoing research must further elucidate the knowledge of the role of the androgen receptor in prostate cancer. In an initial study performed in 7 patients a lesion to lesion comparison with FDG PET. FDHT showed 78% of lesions whereas FDG detected 97%. However an uptake decrease was noticed in patients with hormonal therapy which might indicate a use in therapy monitoring [32]. In another study of twenty patients, nineteen patients that had known metastases of which 12 patients showed positive scans (sensitivity 63%). These patients showed decreased uptake on flutamide administration with repeat PET scan [33]. These results probably indicate that FDHT PET can be used to distinguish androgen dependent prostate cancer and undifferentiated forms. This could have implications for tailoring treatment in near future.

2.2.2. Recurrent prostate cancer
PSA relapse most commonly preludes clinical manifestations of recurrent or residual prostate cancer. This group of patients has a very varied outcome and therefore it is difficult to predict clinical significance. Ten years after prostatectomy 30–50% of patients show biochemical recurrence. The mean interval between biochemical recurrence and clinical symptoms is approximately 8 years. During this period imaging recurrent disease can be difficult [34].

$^{11}$C-acetate – In the 31 patients studied by Kotzerke et al. it was shown that of the 18 patients with recurrence $^{11}$C-acetate PET identified 15 patients (83%) with recurrence. In the three false-negative cases patients had small recurrent lesions (<15 mm) [35]. These limitations were reproduced by Oyama et al. [36]. In this study $^{11}$C-acetate was compared with FDG PET. Fricke and co-workers showed that $^{11}$C-acetate was able to visualize 80% of local and distant recurrence whereas FDG demonstrated recurrence in only 66% of 25 patients. FDG (75%) was superior to $^{11}$C-acetate in showing distant metastases (50%) [37].

$^{11}$C-choline – In a pilot study by de Jong et al. in 36 patients with 13 of the patients with biochemical recurrence, $^{11}$C-choline showed a sensitivity of 38% in detecting recurrence after radical prostatectomy. $^{11}$C-choline PET displayed a higher sensitivity in patients with biochemical recurrence after curative radiotherapy (7 of 9 patients) (Fig. 1). No positive PET-scans were obtained in patients with a serum PSA < 5 ng/ml [38]. Picchio et al. studied 100 patients with biochemical recurrence after radiotherapy (N = 77) and radical prostatectomy (N = 23) with $^{11}$C-choline and FDG. $^{11}$C-choline showed greater sensitivity (47%) compared to FDG (27%). Only one $^{11}$C-choline PET scan was false-negative [39].

$^{18}$F-fluorocholine – Heinisch et al. studied 34 patients with prostate cancer who had undergone initial local therapy using $^{18}$F-fluorocholine (FCH) PET/CT during follow-up in case of demonstrable or rising PSA levels. This study aimed at the use in patients with low PSA levels. In eight of 17 examinations (47%) with PSA < 5 ng/ml, at least one FCH-positive focus was detected. Follow up and additional imaging and or histology confirmed

Fig. 1 – $^{11}$C-choline PET and PET/CT fusion images in a patient with recurrent prostate cancer after external beam radiotherapy. A pathological lymph node is identified on PET (arrow) and corresponds with the enlarged node in the left iliac region. Histology confirmed the nodal metastases after PLND.
recurrent prostate cancer in 7/8 patients. In re-
staging patients with prostate cancer, FCH PET/CT is able to yield true positive findings even at PSA < 5 ng/ml [40]. But as long as the decision for salvage radiotherapy after radical prostatectomy is directed by a PSA at a level of 1.0 ng/ml the clinical utility of PET/CT in stratification of patients has to be proven in the low PSA ranges.

2.2.3. Distant metastases

About 20% of patients presents with distant (bone) metastases. The incidence in hormone refractory prostate cancer patients reaches 100%. The current standard for screening is (di)phosphonate bone scanning. It has well-known high sensitivity and low specificity. It is becoming increasingly clear that as much as 17% of metastases are not seen on bone scanning [41]. One cause could be that for a positive bone scan there needs to be cortical involvement. Micro metastases do not cause this reaction at that time.

FDG - Prostate cancer is considered as a cancer with false-negative results on FDG-PET. A limited number of studies have looked at FDG PET and bone metastases. In a study from Yeh et al only 18% of bone scan lesions were positive on FDG-PET [42]. Shreve et al evaluated 34 patients in which PET was compared with the isotope bone scan, computed tomography (CT), and clinical follow up for the presence of skeletal metastases. FDG-PET identified 131 of 202 untreated metastases in 22 patients with a sensitivity of 65%. In only 1 out of 7 patients receiving hormonal treatment FDG uptake was seen in only 4 of the 131 metastases seen on bone scan [22]. Although the authors concluded that FDG PET did not perform as well as bone scintigraphy in the identification of skeletal metastases, a question can be raised on the biological activity of FDG negative lesions. In a recent study by Morris et al. in 17 patients with progressive metastatic prostate cancer, bone scans were compared with FDG PET. Of 134 bone lesions considered to be metastases identified on either FDG-PET or bone scans, 95 were seen on both FDG-PET and bone scan whereas 8 were seen on FDG-PET only and 31 on bone scan only [43]. FDG PET had a sensitivity of 77% in this group of progressive patients. The interest in this study was that all but one lesion seen on bone scan alone were “stable” on follow-up when compared with the baseline bone scan, whereas all FDG-PET lesions reflected active disease on subsequent studies. So the authors concluded that FDG-PET can discriminate active osseous disease from quiescent lesions on bone scintigraphy in patients with progressive metastatic prostate cancer. Future studies will be needed to answer the question if these FDG-PET negative but bone scan positive lesions have clinically relevancy.

18F-Fluoride – Sodium fluoride (NaF) can be been used in combination with PET for imaging of bone metastases using 18F as radioisotope (Fig. 2). Even-Sapir et al. studied 18F-Fluoride PET/CT in comparison with planar and SPECT bone scintigraphy in 44 patients with high-risk prostate cancer. 18F-Fluoride PET/CT is more sensitive and specific modality for detection of bone metastases. It is more specific than 18F-Fluoride PET alone and more sensitive and specific than planar and SPECT BS. Detection of bone

Fig. 2 – 18F-fluoride PET showing multiple bone metastases in a patient with prostate cancer.
metastases is improved by SPECT compared with planar bone scintigraphy and by \(^{18}\text{F}\)-Fluoride PET compared with SPECT. This added value of \(^{18}\text{F}\)-Fluoride PET/CT may beneficially impact the clinical management of patients with high-risk prostate cancer and a negative bone scan [44].

2.3. PET and Renal Cell Carcinoma (RCC)

2.3.1. Tumor detection and initial staging

Only a limited number of studies have investigated the utility of PET in the assessment of renal masses and primary staging of RCC. The first pilot study by Wahl et al in five patients with RCC prompted further investigation as all primary tumor and metastases were visualized by FDG-PET [45]. In a second study of 29 patients by Bachor et al. PET was compared with histology after nephrectomy. FDG PET was true positive in 20 of 26 with confirmed disease, but the primary tumor was missed in 6 cases. An angiomyolipoma, a pericytoma, and a pheochromocytoma showed a false-positive PET result [46]. In a more recent study by Ramdave et al. PET was compared with histology and CT. The primary RCC was identified by FDG PET in 15 of 17 patients with suspicious renal masses. There were no false-positive results reported in this study. FDG PET showed an accuracy of 94% which was identical to CT in this study [47].

Kang et al. have published the largest study in RCC so far. A total of 66 patients with renal mass were studied with FDG PET. Sixteen patients had proven RCC. FDG PET exhibited a sensitivity of 60% and specificity of 100% for primary RCC tumors which was unfavorable to abdominal CT (92% sensitivity and 100% specificity). The authors concluded that the role of FDG PET in the detection of RCC is limited by low sensitivity [48].

This conclusion is supported by the results from the study of Aide et al. In a subgroup of 35 patients FDG PET studies were performed for both characterization and staging of a suspicious renal mass. A high rate of false negative FDG PET results was observed, leading to a sensitivity, specificity and accuracy of 47%, 80% and 51% respectively, versus 97%, 0% and 83% respectively for CT [49].

Results on immuno-PET have to be awaited but could lead to improved results on primary staging targeting hypoxia using \(^{18}\text{F}\)-Fluoride-misonidazole [50] or carbonic anhydrase- IX activity using the G250 monoclonal antibody.

In general FDG PET has not shown any advantage over CT for the characterization of renal masses, initial staging and treatment planning of renal cell carcinoma.

2.3.2. Recurrent and metastatic disease

Metastatic disease is a strong predictor of poor survival in patients with RCC [51]. Patients with advanced metastatic disease have a 0% to 2% 5-year survival rate whereas solitary metastases can be resected surgically in selected patients, with a 5-year survival rate of approximately 30% [52]. Early detection and management of metastases has the potential to improve prognosis and quality of life. Currently CT, sometimes supplemented by a bone scan if indicated, is the most commonly used imaging test for follow-up of patients with RCC. Although FDG-PET did not appear to contribute much to the initial staging of RCC, the detection of local recurrence or metastases should not be affected by some of the FDG-inherent limitations in imaging the urinary tract [47,48,53,54].

The study by Ramdave et al. included eight patients with suspected local recurrence or metastatic disease. FDG PET was true positive in seven patients and true negative in one, yielding a diagnostic accuracy of 100% (CT: 88%). Of eight patients in whom CT suggested potentially resectable metastatic disease, FDG PET revealed widespread metastases in four. In one patient, PET accurately distinguished between post radiation changes and local recurrence. The findings lead to a change in treatment in four of eight patients (50%) by avoiding or altering planned surgical procedures [47].

Safaei and coworkers studied FDG PET in 36 patients with advanced renal cell cancer who were referred for restaging. 85% of confirmed lesions were assessed accurately (sensitivity 88%, specificity 75%). They concluded that FDG PET could be useful in characterizing anatomic lesions of unknown significance [53].

Majhail and coworkers studied 24 patients with RCC and suspected recurrence at distant sites. Of the 33 sites of histologically proven metastatic sites, 21 (64%) were identified by FDG PET. Sensitivity and specificity were 64% and 100%. These findings were independent of initial Fuhrman grade, prior immuno- or chemotherapy, or the site of distant metastases. However, the average size of metastatic lesions correctly identified by FDG PET was larger than that for false-negative findings (2.2 cm versus 1.0 cm; \(P < 0.01\)). In no case did FDG-PET identify distant metastases that had not been visualized by CT or MRI [54].

In the larger study by Kang and coworkers a total of 172 soft tissue and bone lesions were confirmed as metastatic RCC either by subsequent imaging studies or histopathology, and 115 of these (67%) were identified by PET. Specifically FDG PET detected 89 of 139 soft tissue metastases (64%)
and 26 of 33 bone metastases (78%). Lung metastases were detected with a sensitivity of 75% and specificity of 97%. As expected, CT was more sensitive than FDG PET in detecting lung metastases (91%) (Figs. 3 and 4). In addition, the combination of CT and bone scan showed higher sensitivity for detecting osseous metastases (94%).

For retroperitoneal nodal metastases, FDG PET was 75% sensitive and 100% specific (CT: 93% and 98%). Multiple lesions within a single patient often exhibited differing levels of FDG uptake and some were undetectable: In 44% of studies FDG PET detected all metastatic lesions, in another 44% only some lesions, and in 12% PET failed to detect any metastasis. Overall, the specificity of FDG PET was generally higher than that of any other test or a combination of CT and bone scan (for bone lesions) [48].

2.4. PET and testicular cancer

2.4.1. Initial diagnosis and staging

FDG-PET was studied by Albers et al. for initial staging of lymph nodes in 37 patients with stage I and II germ cell tumors (CGT) [55]. PET was compared with CT and final histology after retroperitoneal lymph node dissection. FDG-PET was 70% sensitive and 100% specific in the detection of nodal metastases, compared with 40 and 78% for CT, respectively. Three false-negative PET results were seen in 2 small (<0.5 cm) nodal metastases and a mature teratoma. PET did not improve staging in comparison with CT in clinical stage 2 GCT. Cremerius et al studied FDP PET in 50 patients with GCT [56]. CT, tumor markers and histology (in 12/50 patients) were used as reference. FDG-PET was 87% sensitive and 94% specific in the detection of nodal metastases, compared with 73% and 94% for CT, respectively. Quantification of uptake of FDG resulted in a wide range from 1.8 to 17.3. Metastases below the size of 10 mm were not identified with PET. Again teratoma failed to show uptake of FDG. Hain and workers studied FDG PET in the initial staging of both seminoma and nonseminoma in a retrospective study in 31 cases. CT scan, clinical follow up and histology were used as reference. In this study FDG PET showed a sensitivity of 67%. Lack of histology
interfered with proper judgment in 5 cases with retroperitoneal mass on CT [57]. In a subset of 12 patients with stage I and II nonseminoma by Spermon et al. equivalent results for PET and CT in initial staging were reported [58].

FDG PET was also studied for staging after orchiectomy in stage I NSTCGT in a study by Lassen and coworkers. In a cohort of 46 patients FDG PET was superior to CT in the prediction of tumor recurrence in retro peritoneal lymph nodes with a PPV and NPV of 92% and 100% [59].

In general, the majority of the studies suggested that PET is slightly superior to CT. However, clinical decision making is not influenced in all cases by FDG PET.

2.4.2. Restaging of residual and recurrent disease
A majority of patients with bulky nodal disease have residual mass on CT scan after chemotherapy. Differentiation between viable tumor cells inside the mass versus fibrosis and/or necrosis is essential for further treatment versus a watchful follow-up. Unnecessary additional radiotherapy or chemotherapy can potentially increase toxicities. Considering the fact that these individuals are young and most of them will live more than 15 to 20 years when cured, both short term and long-term toxicities are likely to occur. Although the serum tumor markers are very useful in this regard, occasionally they may be misleading and not helpful to locate the site of recurrence/residual. Therefore imaging has a central role in locating the residual/recurrent disease. Conventional imaging modalities including CT cannot confirm the presence of viable tumor cells in a residual mass. FDG PET was first studied by Stephens et al. as a feasibility study in 30 nonseminomatous GCT patients before surgical resection of residual masses. PET was able to differentiate viable tumor from residual necrosis/fibrosis or teratoma. Unfortunately PET did not differentiate necrosis/fibrosis from teratoma [60]. In a series of 70 patients by Hain et al. the sensitivity, specificity, PPV, and NPV of 88, 95, 96, and 90%, were calculated respectively for FDG PET in differentiating viable tumor from fibrosis or necrosis or mature teratoma [61].

FDG PET is also used for the evaluation of response to chemotherapy. Bokemeyer et al. studied PET in comparison with CT, serum tumor markers and prognostic groups. FDG-PET accurately predicted the successful outcome of high-dose chemotherapy in 91%; in comparison CT and serum markers predicted successful outcome in 59% and 48% of the cases. PET identified all failures of chemotherapy in the low-intermediate and high risk groups. A negative FDP PET correctly predicted favorable outcome in the low and intermediate prognostic groups [62].

In a study of 54 patients with post chemotherapy seminoma residual by Becherer and De Santis et al. FDG PET was superior to CT in the detection of viable residual tumor. The PPV and NPV for FDG PET was 100% and 96% versus CT 37% and 92% respectively. FDG PET is recommended for treatment evaluation in advanced seminoma after chemotherapy with residual mass >3 cm [63].

2.5. Penile cancer
The use of PET for the staging of penile cancer is very limited. So far there is one feasibility study by Scher et al. in 13 patients with suspected (recurrent) penile cancer using a PET/CT system in combination with FGD [64]. PET/CT data were compared with histopathological reference at biopsy or during surgery. The primary tumor and regional lymph node metastases exhibited a increased uptake of FDG. Sensitivity in the detection of primary lesions was 75% and specificity was 75%. The sensitivity and specificity in the detection of nodal metastases on a per-patient basis were 80% and 100% respectively.

On a nodal-group basis, PET/CT showed a sensitivity of 89% in the detection of metastases in the superficial inguinal lymph node basins and a sensitivity of 100% in the deep inguinal and obturator lymph node basins. The use of PET/CT provided additional information, useful for planning surgery. The clinical value of FDG PET cannot be determined before additional studies with increased number of patients have been performed.

3. PET in non-oncological urology
The only non oncological area in which PET is currently studied is the central control of bladder function, detrusor overactivity and the female pelvic floor. Cerebral blood flow, measured by $\text{H}_2^{15}\text{O}$ is used for functional imaging of the brain and brainstem. From the initial studies by Blok et al. the specific areas in brain stem and higher brain who were involved in micturition control in healthy human volunteers were identified [65,66]. Kitta et al. reported on detrusor overactivity in 9 patients with Parkinson’s disease. In this study an alteration of brain activation sites in response to bladder filling was noticed compared to the know areas in healthy men [67]. The pelvic floor musculature plays an important role in behaviors such as defecation, micturition, mating behavior, and vomiting. Blok et al. studied brain structures involved in the
voluntary motor control of the pelvic floor with PET. The results revealed the major areas involved on the motor cortex. No activations were found in subcortical structures belonging to the emotional motor system [68].

So the feasibility for monitoring the central nervous system and micturition reflexes with PET has been demonstrated.

4. Conclusion

The developments in both imaging systems with PET/CT as current standard and in the development of specific (targeted) radiopharmaceuticals will improve molecular imaging using PET in the coming years. Based on the current literature no additional value for PET compared to conventional imaging has been shown in tumor detection and initial staging of prostate, bladder and renal cancer. In metastatic disease the studies are ongoing. In restaging of prostate cancer PET or PET/CT using choline or acetate are able to identify the site of recurrence. However the value in clinical decision making seems limited at low PSA values. At present there are two accepted clinical indications for FDG PET, i.e. restaging of renal cell cancer and treatment evaluation after chemotherapy in seminomatous germ cell tumors.

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CME questions

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1. The main difference between Positron Emission Tomography and conventional nuclear imaging is for:
   A. The use of molecular processes to obtain images
   B. The type of radiation the camera system detects
   C. The isotopes used to obtain images
   D. The spectrum of clinical applications

2. Which of the statements is correct on immuno-PET?
   A. The technique is widely used for patient stratification
   B. The use of monoclonal antibodies in combination with the radioisotope 18 fluoride
   C. The use of monoclonal antibodies in combination with radioisotopes with a long half life
   D. The technique offers an universal imaging technique in different specific cancers

3. Clinical indication of PET in oncological urology is currently relevant in:
   A. Recurrent prostate cancer
   B. Recurrent renal cancer
   C. Primary prostate cancer
   D. Primary testicular cancer

4. Which of the statements on radiopharmaceuticals for PET in urology is not correct?
   A. Universal radiopharmaceuticals are not available
   B. The background of uptake of choline and acetate in cancer cells are not well known
   C. Targeted immuno-radiopharmaceuticals can offer patient tailored treatment
   D. FDG-PET/CT has overcome the limitations of FDG-PET