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Diagnosis and Monitoring of Urological Tumors Using Positron Emission Tomography

Ch. Hofer[a], H. Kübler[a], R. Hartung[a], J. Breul[a], N. Avril[b]

[a]Urologische Klinik und Poliklinik und [b]Nuklearmedizinische Klinik der Technischen Universität München, Deutschland

Key Words

PET · Renal cell carcinoma · Bladder cancer · Prostate cancer · Testicular tumor

Abstract

The pupose of this article was to critically review the diagnostic value of positron emission tomography (PET) in urological oncology. Urinary tract tumor assessment is hampered by the renal elimination of ^{18}F-fluorodeoxyglucose (FDG), the most commonly used PET radiopharmaceutical. PET imaging offers no significant benefits over conventional imaging modalities for renal cell and bladder carcinomas. As a result of the low metabolic activity of prostate cancer, PET does not differentiate adequately between adenoma and carcinoma, nor detect local recurrence after radical prostatectomy with sufficient sensitivity. However, lymph node staging with FDG-PET, specifically in bladder cancer, has been shown to have a potential clinical benefit. Further studies are required to determine the clinical value of retroperitoneal lymph node staging and recurrent disease detection in germ cell tumors. Finally, encouraging early results exist for the use of serial PET measurements to predict and assess therapy response to chemotherapy which may also be valuable in urological oncology.

Introduction

The sophistication of tomographic imaging techniques has brought about a major advance in oncological diagnosis. Whereas sonography, computed tomography (CT) and magnetic resonance imaging (MRI) provide above all predominantly morphological information, positron emission tomography (PET) permits functional characterization and visualization of (onco)biological processes, above all the noninvasive determination of regional metabolic activity [1,2].

When positron-emitting radioisotopes disintegrate, they release a positron (an antiparticle of the electron) which is very short-lived and in tissue has a range of just a few millimeters. Positrons bond with negatively charged electron and in doing so emit a characteristic annihilation radiation (2 photons of 511 keV energy each, separating in diametrical directions). With the aid of a ring of detectors, this gamma radiation can be registered in a PET scanner as a temporally coincident event in opposite scintillation crystals and hence spatially localized in the body. Another advantage of the use of positron emitters rests on the fact that the most important biochemical atoms, carbon (^{11}C), oxygen (^{15}O), nitrogen (^{13}N) and ^{18}F (as substitute for a proton or hydroxy group) are available for radioactive labelling. This means that virtually any molecule can be radiolabeled and its dis-

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Dr. Christian Hofer
Urologische Klinik und Poliklinik, Technische Universität München
Klinikum rechts der Isar, Ismaningerstrasse 22
D–81675 München (Germany)
Tel. +49 89 4140 2552, Fax +49 89 4140 4818, E-Mail c.hofer@lrz.tu-muenchen.de

tribution or metabolism in the body noninvasively monitored. Most of the positron-emitting radionuclides are produced in a cyclotron. Owing to the relatively short physical half-life, radiochemical synthesis is performed on the spot (in the PET Center). The radiopharmaceuticals are applied to humans after appropriate quality controls. In a PET examination, data is acquired either dynamically, by evaluating the temporal progress of tracer, distribution (derivation of temporal activity graphs) or by the static recording of emission scans. As the detectors of a PET scanner can cover only 10–25 cm of the body simultaneously, only a limited section of the body can be examined dynamically at any one time. Whole-body scans can be obtained by joining together several static images, however. In this case, the PET images are produced approximately 60 min after the tracer injection and last between 40 and 80 min.

The metabolic PET tracer most frequently used in oncological scans is ^{18}F-fluorodeoxyglucose (FDG). ^{11}C-methionine or ^{18}F-fluoroethylthyrosine is used to measure the transport of amino acids, ^{11}C-acetate the oxidative metabolism and ^{15}O-water, tissue perfusion. Regional FDG uptake depends on the cellular glucose metabolism. Like glucose, FDG passes the cell membrane via glucose transporters and phosphorylates in the cell to FDG-6-phosphate. Owing to the modification of the second carbon positron, however, FDG-6-phosphate cannot be further metabolized. As the concentration of the dephosphorylating enzyme is low in most cells, FDG accumulation in the cells is dependent on the glucose metabolism (metabolic trapping). Most malignant tumors are characterized by enhanced glucose utilization which can be imaged using PET and ^{18}F-FDG and so used for diagnostic purposes. Enhanced glucose metabolism can be used to detect not only primary tumors but also recurrences and metastases. Numerous studies prove the diagnostic benefits of PET for various tumor entities and especially brain and pulmonary tumors, pancreatic masses and lymphomas [2]. PET has advantages over conventional staging methods in the locoregional lymph node staging of HNO tumors, breast cancer and malignant melanomas and in the mediastinal staging of bronchial carcinomas or prior to the resection of local recurrences or singular liver metastases of colorectal tumors. Regional metabolic activity also permits evaluations of the vitality of any residual masses left after radiation or chemotherapy. Current studies are concerned with therapy monitoring both as a means of characterizing the therapeutic response and of predicting the histological response right at the beginning of chemotherapy [3, 4]. This article provides an overview of the current status of the research on the PET diagnosis of urological tumors.

Renal Cell Carcinoma

The first step, as a rule, is to perform CT or MRI to differentiate between benign and malignant renal masses as are often detected by ultrasound [5]. The staging of renal cell carcinoma is correct in 70–95% of all cases performed using CT and in approximately 80% of those using MRI [6–8]. Excretory urography is often performed to evaluate the urinary tract of patients presenting with symptoms. Diagnostic problems are encountered above all in the differentiation of malignant and benign renal masses [9]. Necrosis and bleeding in renal cell carcinoma can result in the inadequate or nonexistent absorption of the contrast medium and not even the signals produced in T2-weighted MRI ensure a sufficient degree of diagnostic certainty [10]. In selected cases, angiography or percutaneous biopsy can facilitate diagnosis. The use of PET to evaluate a suspect renal mass may also be indicated.

In a study by Bachor et al. [11] 29 patients with solid renal tumors were examined with FDG-PET prior to surgery and the results compared with the histology of the preparation. Of the 26 renal cell carcinomas, 20 were correctly identified using PET, while for 6 patients, the PET scan produced a false-negative result. Diagnostic accuracy turned out to depend also on the degree to which the tumors are differentiated. Only 4 out of 9 (44%) G1 tumors were detected with FDG-PET, for example, whereas an angiomyolipoma, a pericytoma and a pheochromocytoma were false-positive. Lymph node staging was judged true-positive in 3 patients and true-negative in 25 patients. There were no false-negative PET findings. In a study of 21 patients, Goldberg et al. [12] obtained positive PET findings in 9 out of 10 cases of histopathologically proven renal cell carcinoma. A bilateral renal cell carcinoma in a patient with diabetes mellitus was not detected. All the renal cysts manifested themselves as an area of reduced glucose metabolism, although a papillary neoplasia of 4 mm in size was not detected. The imaging of malignant renal tumors is rendered more difficult on account of the renal elimination of ^{18}F-FDG. By increasing diuresis (by hydration or administering diuretics), the tracer is washed out of the efferent urinary tracts and this in turn makes it much easier to evaluate the metabolic activity of the renal parenchyma. In a study of pediatric cases, Shulkin et al. [13] found increased metabolic activity even in the case of histologically proven Wilms' tumors. The number of cases available for an assessment of the diagnostic value of PET is still too small, however. Shreve et al. [14] have reported on their first experiences with ^{11}C-acetate for the diagnosis of various kidney diseases. ^{11}C-acetate enters the citric (tricarboxylic) acid cycle as activated acetyl-CoA and

is used to determine the myocardial oxidative metabolism, for example. This tracer is not eliminated via the efferent urinary tracts. Histopathologically proven renal cell carcinomas did not show any enhanced uptake of ^{11}C-acetate in comparison to the surrounding renal parenchyma, but did have a significantly reduced clearance rate. This meant that clear delimitation was possible only in the course of a dynamic PET scan [14]. It must nevertheless be noted that only a very small group of patients was examined here.

Bladder Cancer

The preoperative staging of bladder cancer, including the detection of regional lymph node metastases, is vital to subsequent therapy. Lymph node or distant metastasis has a highly detrimental effect on the patient's prognosis, with the result that there may be no point in surgical procedures such as cystectomy.

The classical staging methods for bladder cancer are cystoscopy, biopsy or transurethral resection, bimanual examination under anesthetic, sonography, excretory urography, CT or MRI and skeletal scintigraphy. In an overview by Husband [15], CT has an accuracy of 64–92% for pelvic lymph node staging, while the equivalent figure for MRI is between 72 and 96%. In a study by Paik et al. [16] CT had an accuracy of 55%, although extravesical tumor spread and lymph node involement were each detected in only 5% of all the cases examined. The most serious diagnostic limitations of CT result from the underestimation of tumor spread, both locally and in the case of locoregional lymph node involvement. Other methods of examination to improve the accuracy of preoperative staging are therefore desirable.

Kosuda et al. [17] examined 12 patients with histologically proven bladder cancer with FDG-PET and obtained a true-positive result for 8 patients. In addition to this, 17 distant metastases were correctly identified with PET, as were 2 out of 3 lymph node metastases. In 2 cases, it was possible to delimit a local recurrence of radiation-induced changes with the aid of PET. As in the case of renal cell carcinoma, the most serious diagnostic limitation of FDG-PET in primary tumor diagnosis was the elimination of FDG via the efferent urinary tracts. This made the results difficult to evaluate, despite continuous retrograde bladder irrigation. For the PET diagnosis of bladder cancer, therefore, the radiopharmaceutical used in addition to ^{18}F-FDG was ^{11}C-methionine, which is not renally eliminated. Ahlström et al. [18] showed on a group of 23 patients with biopsy-proven bladder cancer, that it is possible to image tumors of >1 cm in size using ^{11}C-methionine. The authors nevertheless conclude that methionine-PET is no better at staging bladder cancer than are conventional methods. The study with the largest number of cases for the lymph node staging of bladder cancer using FDG-PET compared to histology after cystectomy was published by Bachor et al. [19]. In a group of 64 patients, 14 cases of lymph node metastasis were correctly identified, while a false-negative result was obtained for 7 patients. For 37 patients, the lymph nodes were classified as true-negative, while there were 6 false-positives. This translates into a sensitivity of 67%, a specificity of 86% and accuracy of 80%. The authors showed that PET results are better than those of classical staging examinations, even though it was not possible to detect micrometastases using PET. Similar results were obtained by Heicappell et al. [20] who, in a study of 8 patients with bladder cancer, was able to detect 2 out of 3 histologically positive lymph nodes using FDG-PET, the smallest metastasis being 9 mm in diameter.

Prostate Cancer

In the case of prostate cancer, it would be interesting to find out whether PET can be used to distinguish benign prostate hyperplasia from malignant tissue as this would permit better, and perhaps noninvasive, primary diagnosis. Among the other important diagnostic questions are those concerning extracapsular growth and lymph node or distant metastasis. The most important concern after radical prostatectomy is to be able to differentiate between scare tissue and local recurrence.

Various studies have shown, however, that FDG is not suitable for diagnosing changes of the prostate gland as prostate cancer often does not go hand in hand with an increase in glucose metabolism. In a study of biopsy-proven primary prostate cancer, Effert et al. [21] discovered only low metabolic activity in most tumors, without any correlation of tumor degree and stage. Our own data from 11 patients with localized prostate cancer and 2 with benign prostate hyperplasia confirm these results [22]. After radical prostatectomy and an increase in PSA, there can be no differentiation of scar tissue and local recurrence using FDG-PET. Of 6 patients with a local recurrence diagnosed by biopsy, 5 produced false-negative results in the PET scan [23]. At the same time, 2 out of 4 patients with a negative biopsy showed enhanced FDG uptake. Here, too, our own study produced comparable results [22]. The metabolic activity of local recurrences diagnosed by biopsy after radical prostatectomy cannot be distinguished from scar tissue.

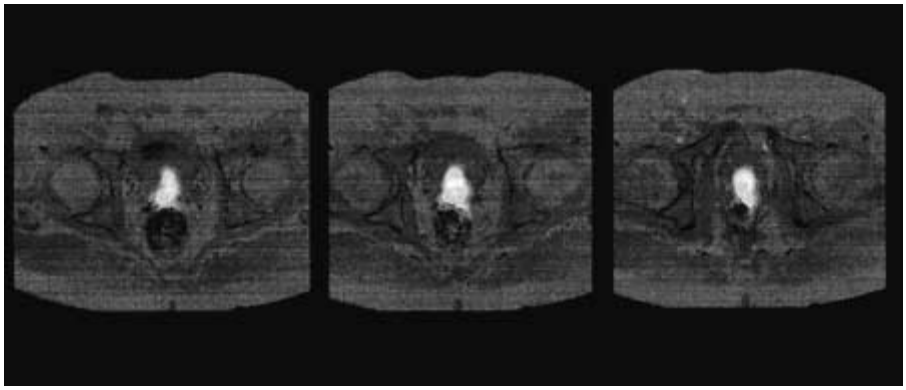

Fig. 1. PET with ^{11}C-acetate on a patient with locally advanced prostate cancer. The photograph shows transversal slices of an overlay between MRI and PET with a clear accumulation of ^{11}C-acetate in the prostate bed.

In a study of Effert et al. [21], increased FDG accumulation was detected in some patients with lymph node metastasis of prostate cancer. Heicappell et al. [20] compared PET of regional lymph nodes to histopathological examination of 17 patients with prostate cancer. Increased uptake was found in 4 of 6 patients with metastasis. The smallest detected metastasis was a micrometastasis with a diameter of 0.9 cm. In 2 additional patients who all had histopathologically proven micrometastases ($\leq$0.5 cm), FDG uptake was within the normal range [20]. Evaluation of pelvic lymph node metastases of prostate cancer is severely limited by bladder tracer activity [24].

In a study of 34 patients with metastasized prostate cancer, Shreve et al. [24] examined the value of FDG-PET for the diagnosis of bone metastases using CT, bone scintigraphy and clinical follow-up as a reference. Among the 22 untreated patients, there were 202 bone metastases in all, only 131 of which were detected using FDG-PET. In the case of small metastases, the low sensitivity of 65% is at least in part the result of partial volume effects. The most important cause, however, is the low metabolic activity and hence the low FDG accumulation of prostate tumors and their metastases. Despite this, a high positive-predictive result of 98% was obtained for metabolically active lesions. The results obtained by Shreve et al. [24] have been confirmed by other studies of smaller groups. In a comparison with positive foci identified using skeletal scintigraphy, Yet et al. [25] found only some 18% of the lesions in 13 patients with pretreated bony prostate metastases, previously classified as hormone refractory.

Recently, a Japanese research team used ^{11}C-choline, a precursor of cell membrane phospholipids, for the diagnosis of histologically proven prostate cancer [26]. Compared with FDG, 10 patients showed a much higher uptake of ^{11}C-choline in the prostate gland. As there is also significant tracer accumulation in the normal prostate, however, there could be no differentiation of carcinomas using ^{11}C-choline. Kotzerke et al. [27], on the other hand, report the successful use of ^{11}C-choline for staging lymph node and bone metastases. All the metastases known from other imaging techniques were identified using PET with ^{11}C-choline too. One out of the 10 negative PET examinations proved to be a false-negative as a nonenlarged tumor-involved lymph node was not detected. The use of the ^{11}C-marked 5-hydroxytryptophan used to show neuroendocrine tumors also led to the positive imaging of bone metastases in 10 patients with hormone refractory prostate cancer [28]. Shreve [29] recently reported using ^{11}C-acetate. In 18 patients with biopsy-proven local recurrences or regional metastases, the uptake of ^{11}C-acetate in malignant tissue (SUV 2.8–10.6; mean value 5.9) was significantly higher than in normal prostate tissue (SUV 1.6–2.5; mean value 1.9). In addition to this, tumor-involved lymph nodes of $\geq$8 mm in size were also detected. A Japanese team arrive at similar results and in 12 cases of prostate cancer reported increased tracer uptake [30]. There is no biochemical explanation for the increased accumulation of ^{11}C-acetate as yet. Figure 1 shows a positive PET scan with ^{11}C-acetate on a patient with locally advanced prostate cancer.

Germ Cell Tumors

CT has a rather low accuracy when used for staging retroperitoneal lymph node involvement in patients with germ cell tumors. A recurrence rate of approximately 20% within the first 5 years is to be expected among patients who undergo surveillance for a clinical stage I seminomatous germ cell tumor (SGCT) or nonseminomatous germ cell tumor (NSGCT) [31, 32]. It is therefore standard practice for patients with a stage I SGCT to receive additional radiation therapy [33]. For cases of NSGCT, the recovery rate for

retroperitoneal lymphadenectomy (RLA), a watch-and-wait strategy or adjuvant chemotherapy is more or less the same, but with differing morbidity and rates of recurrence [32]. Given this situation, a diagnostic procedure which recognizes occult metastases and so can differentiate between stages I and II and perhaps even spare patients unnecessary therapy would therefore be highly desirable.

Any residual retroperitoneal masses remainging after chemotherapy in patients with SGCT constitute a therapeutic dilemma with regard to the question of vital tumor cells, especially when the residual mass is >3 cm. Motzer et al. [34] recommend surgical resection on the basis of a significant number of patients with malignant residual tissue, while other authors [35], in the absence of any growth tendency, consider regular follow-up as part of a surveillance strategy to be adequate. In contrast, a resection is always recommended when it comes to residual masses in pretreated NSGCT patients, as surgery also removes any remaining vital residual germ cell tumors, teratomas or non-germ cell portions [36]. What are needed when imaging any residual masses remaining after the chemotherapy of germ cell tumors, if unnecessary surgery is to be avoided, are examination methods which can differentiate between vital residual tumors and fibrosis or necrosis.

Wilson et al. [37] examined 21 patients with metastasized NSGCT and SGCT using FDG-PET compared to CT. While metastases of both types of germ cell tumor showed clear metabolic activity, the metabolic activity in necrosis, fibrosis and even in the mature teratoma was comparable with that of normal tissue. Three patients who responded to therapy also showed a decline in metabolic activity in the tumor, while 2 nonresponders did not show any change. In a study of 54 patients (27 with SGCT and 27 with NSGCT), Müller-Mattheis et al. [38] compared the PET results with the findings of abdominal CT, tumor markers and the histopathological findings obtained after primary or post-chemotherapeutic retroperitoneal lymphadenectomy. In 21 patients with a stage I SGCT, the results of the PET scan were identical with the results of the CT. As the patients had received radiation therapy and the results could not be histopathologically validated, the value of PET in this group remains unclear. In 2 of the 7 patients with a stage I NSGCT, metastases which had not been detected by CT were detected using PET, while in 4 of the 7 patients, micrometastases went undetected by PET. In 3 out of the 4 patients who underwent surgery for a pure seminoma in stages IIB and IIC, PET correctly identified tumor-free lymph nodes after chemotherapy. In 1 case, the histological examination of a mass which persisted even after chemotherapy revealed a ganglioneuroma, even though the PET scan had been negative. In another study, 19 patients with NSGCT in stages II and III were examined. FDG-PET was used to show the influence of chemotherapy on pretherapeutic hypermetabolic foci. After chemotherapy, the PET scan showed a true-negative result in 11 cases, the histological examination of which revealed either scan tissue or necrosis. In 6 patients with a negative PET scan, the histological examination revealed a mature teratoma and in 1 other patient, an active residual tumor. One false-positive PET scan was caused by inflammatory changes in the histological specimen. The authors conclude from these findings that FDG-PET cannot be used as a routine method of examination for germ cell tumors, whereas it does have its uses for the evaluation of post-chemotherapeutic residual tumors. Despite this, it is still not possible to use PET instead of RLA for staging lymph nodes. Hain et al. [39] prove in their study that when used for primary staging, FDG-PET can detect metastases which are overlooked by conventional diagnostic methods. In a recent study, Albers et al. [40] report correct retroperitoneal staging using PET in 34 out of 37 cases, compared with just 29 out of 37 using CT. Seven out of ten distant metastases were revealed by PET, while CT identified only four lesions. The PET scans did not produce any false-positive results, although neither malignant lesions of <5 mm in size nor mature teratomas, irrespective of size, were detected. The results of the two studies mentioned above were assessed on the basis of histology or clinical follow-up. Cremerius et al. [41] examined 50 patients and obtained comparable results for histopathologically proven GCT. In a direct comparison of CT and FDG-PET, the same research team found PET to have significant advantages in the evaluation of residual masses [42]. With comparable sensitivity , PET was significantly more specific than CT. The authors nevertheless point out that PET scans should not be performed until at least 2 weeks after the completion of therapy as only then can vital malignant tissue be recognized. In a study involving 29 patients, however, Ganoo et al. [43] did not find PET to have any advantages in the evaluation of residual masses in bulky SGCT.

We examined 22 patients with a primary diagnosis of germ cell tumor (14 of them with NSGCT before RLA, 3 with SGCT before radiation therapy, 4 with NSGCT before chemotherapy and 1 with SGCT before chemotherapy) and also performed PET scans on 11 patients after primary chemotherapy (9 of them with subsequent, secondary RLA). The PET and CT results were correlated with the histology after RLA or clinical progress. In the primary diagnosis, PET produced false-negative findings for 2 patients, both of whom had histologically proven metastases. One patient who was evaluated positive by CT, but negative by

PET, was histologically negative. PET yielded false-negative results for 2 patients after primary chemotherapy. A 2.5-cm large residual mass detected by CT in 1 patient was found to be a mature teratoma in the histological examination. The second patient had small foci (<1 cm) of vital residual malignant tissue. PET produced false-positive findings for 2 patients, probably as a result of reparative inflammatory changes.

Discussion

While the clinical indications for PET with ^{18}F-FDG for various malignant tumors have already been specified [1, 2], the status of the data for urological tumors is not as unequivocal. In primary tumor diagnosis, the elimination of FDG via the efferent urinary tracts impairs the value for diagnostic purposes. FDG-PET does not have any advantages over classical examination methods in the primary diagnosis of renal cell carcinoma. In the case of small and highly differentiated tumors in particular, PET findings are unreliable. Nor does PET have the necessary relevance for the diagnosis of primary tumors in bladder cancer. When it comes to prostate cancer, FDG-PET is neither suitable for the differentiation of benign prostate hyperplasia and carcinoma nor for the detection of distant metastases or local recurrence after radical prostatectomy. One of the main reasons for this is the low metabolic activity of such tumors. Other tracers such as ^{11}C-choline, ^{11}C-acetate and ^{11}C-5-hydroxytryptophan have so far been tested on only small groups of patients, although the first results do indeed point to a potential clinical application.

PET does not have any advantages over CT and MRI for the staging of retroperitoneal lymph nodes in renal cell carcinoma. With a sensitivity of 67% and a specificity of 86% for lymph node staging, FDG-PET appears better than the classical staging methods used for bladder cancer. The consensus conference 'PET in Oncology' held under the auspices of the Deutsche Gesellschaft für Nuklearmedizin (German Society of Nuclear Medicine), believes such a clinical application of PET could prove helpful [44]. The primary diagnosis of germ cell tumors using FDG-PET is no better than that using classical methods as far as subsequent therapy is concerned, as false-negative findings effectively prevent any significant improvement in the differentiation of stages I and II. As mature teratomas have only low metabolic activity, it is not yet possible to differentiate them adequately from scar tissue and necrosis when examining residual masses diagnosed by CT after primary chemotherapy. This means that in our view, secondary RLA cannot be dispensed by PET imaging. Whether PET can detect vital residual tumors in the residual masses remaining after the chemotherapy of an SGCT cannot yet be finally determined, given the small number of patients examined. At least the enhanced metabolic activity of tumor recurrences means that they can be distinguished from any changes caused by therapy. Large trials with histologic controls are ongoing, that will provide answers about the benefit of PET in germ cell tumors in a more valid way than it is possible with the informations currently published.

PET offers certain advantages in the evaluation of the retroperitoneum, the lymph nodes of which are often involved in urological cancers [45]. When using CT, the size of such lymph nodes is of decisive importance, although even lymph nodes which are normal in size can be tumor-involved, just as lymph nodes can be nonspecifically enlarged. In principle, PET permits the recognition of positive lymph nodes independent of size, but with limited sensitivity in the evaluation of microscopically small tumors. Resolution is an important factor here, as existing PET scanners do not have a high resolution to permit the detection of micrometastases. The further development of PET scanners and new imaging processes should improve spatial resolution in future.

To summarize, it can be said that as there are diagnostic advantages to the use of FDG-PET in urological oncology only in a few, very specific areas, it cannot be regarded as a routine examination procedure at this point in time.

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