



Anita Philyaw. *Where There Are Three of Us* (detail), 2000. Acrylic on canvas, 48" × 34".
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The evolving role of positron emission tomography across a broad range of urologic oncology applications is reviewed.

Positron Emission Tomography in Urologic Oncology

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Background: *Positron emission tomography (PET) is an emerging imaging modality that is being investigated for use in urologic oncology. PET scanning using the radioactive glucose analog FDG has proven to be a highly accurate imaging test for diagnosing and staging a variety of non-urologic cancer types. This review was performed to determine the role of PET imaging in genitourinary malignancies.*

Methods: *A review of the literature focusing on PET and urologic oncology was performed. The role of PET imaging was reviewed in prostate, bladder, renal, and testicular cancer.*

Results: *In testicular cancer, PET has a higher diagnostic accuracy than computed tomography (CT) for both staging and re-staging and should be the test of choice for the assessment of a CT-visualized residual mass following chemotherapy. In prostate, renal, and bladder cancer, the current role of PET is still being defined, but it has a high positive predictive value and can be used for problem solving in patients with indeterminate findings on conventional imaging. Its role in the diagnosis and staging of prostate cancer is hampered by the generally low glycolytic rate of most prostate tumors and their metastases. It has shown promise for staging and re-staging patients with advanced-stage disease and aggressive tumors suspected by a high tumor grade and high prostate-specific antigen velocity. PET has also demonstrated success when applied to renal cell carcinoma in classifying indeterminate renal masses as well as residual renal fossa masses following nephrectomy, gauging response to therapy, and staging and re-staging patients with a known diagnosis of renal cell carcinoma.*

Conclusions: *PET imaging has demonstrated great potential in certain applications, but further investigations are necessary to determine its eventual place as an imaging modality in genitourinary malignancies.*

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Introduction

Positron emission tomography (PET) is a functional imaging modality that has the unique capability of noninvasively studying specific biochemical processes such as tumor glucose metabolism within the body. PET is based on the discovery that certain classes of radioisotopes decay via release of positrons, or positively charged electrons. Examples of these radiotracers and their biological analogs are listed in Table 1. The release of these radioactive substances can be quantified via a nuclear detector and then depicted by means of computed tomography (CT). This technology has been subsequently applied to study the biochemistry and physiology of various tissues within the body by tagging these radioisotopes to naturally occurring substrates.

The major clinical indications for PET have been in the field of oncology. The success of PET imaging in oncology is based on the observation that many types of malignant tumors have an accelerated rate of glycolysis when compared to normal tissue. As a result, the most commonly used radiotracer is the glucose analog 2-deoxy-2-¹⁸F-fluoro-D-glucose (FDG). After being injected intravenously, FDG is preferentially taken up by tumor cells and phosphorylated by hexokinase to FDG-6-PO₄. Unlike glucose-6-PO₄, FDG-6-PO₄ cannot be metabolized in the glycolytic pathway and remains trapped intracellularly. As the cells accrue larger amounts of FDG-6-PO₄, increased activity is detected that delineates the hypermetabolic tumor from the surrounding normal tissues.

Employing the tracer FDG, FDG-PET is now routinely used in clinical practice and has a high diagnostic accuracy for evaluating a variety of cancer types including lung, colorectal, esophageal, breast, lymphoma, and melanoma.^{1,4} The use of PET in urologic

oncology is less well defined and has been investigated with mixed results. While demonstrating great potential in certain applications, PET has proven to be disappointing in others. We reviewed the literature to help demonstrate new advances and delineate successful applications of PET in urologic oncology.

Prostate Cancer

Several studies have investigated different applications of PET in both localized and metastatic prostate cancer. The use of FDG-PET in the diagnosis of localized prostate cancer has proven to be disappointing primarily because most prostate cancers have a relatively low glycolytic rate and therefore do not accumulate high concentrations of the radiotracer FDG. In addition, excreted FDG activity accumulating in the ureters and bladder may limit the evaluation of adjacent structures such as the prostate and pelvic lymph nodes. Numerous studies evaluating methods of removing excreted tracer from the bladder during imaging by means of Foley catheter drainage, continuous bladder irrigation, or furosemide administration have all demonstrated poor results.^{5,6} In fact, Liu et al⁵ demonstrated false-negative PET scans in 23 of 24 patients with biopsy-proven organ-confined prostate cancers.

To overcome the problems experienced with FDG-PET, investigators have attempted to use ¹¹C-choline, an alternative radiotracer with negligible urinary excretion that is taken up in cancer cells by active transport and retained by phosphorylation.⁷ Hara et al⁸ demonstrated the successful use of this tracer in identifying both locally extensive prostate cancer and associated metastases compared with FDG-PET. The practical clinical use of ¹¹C-choline is limited due to the short half-life of carbon-11, which requires an on-site medical cyclotron for radiotracer production. A fluorinated

Table 1. — Biological Analogs of Radiotracers

Radiotracer	Biological Analog	Measured Biological Process	Half-life (minutes)
[¹⁵ O]water	Water	Tissue perfusion	2
[¹³ N]ammonia	None	Tissue perfusion	10
[¹¹ C]acetate	Acetate	Lipid metabolism	20
⁶⁸ Gallium-ethylenediamine tetra-acetic acid	None	Blood brain barrier	68
[¹⁸ F]tyrosine	Tyrosine	Amino acid metabolism	110
¹⁸ FUdR	Uridine	Nucleic acid metabolism	110
2-deoxy-2- ¹⁸ F-fluoro-D-glucose (FDG)	Glucose	Glucose metabolism	110
[¹⁸ F] fluorodopamine	Dopamine	Amino acid metabolism	110

From Hoh C, Seltzer M, Franklin F, et al. Positron emission tomography in urologic oncology. *J Urol*. 1998;159:347. Reprinted with permission.

choline derivative has been recently been developed that should overcome this limitation.⁹

Detection of localized prostate cancer with FDG-PET is hampered by the inherently low metabolic activity of malignant cells found in these tumors. As a result, the relatively low tracer uptake by localized prostate cancer is difficult to delineate from that of tissue found in benign prostatic hyperplasia.^{6,8,10} A similar problem has been encountered in the attempted use of PET to differentiate between post prostatectomy recurrence vs scar. Hofer et al¹¹ demonstrated that these two entities appear identical (as does benign prostatic hyperplasia) on PET. In contrast, relatively increased uptake of FDG has been demonstrated by primary tumors with high Gleason scores and resultant metastatic disease.¹² This characteristic could make PET imaging useful in determining how aggressive localized tumors are and, hence, help guide treatment decisions.

PET has demonstrated some promise in the preoperative assessment of lymph node and distant metastasis. Hellicapell et al¹³ employed PET to preoperatively image the pelvic lymph nodes of 17 patients with newly diagnosed prostate cancer and then compared the findings with postoperative histopathology. PET was able to accurately diagnose metastatic lymph node involvement in 4 of the 6 affected patients. There were no false-positive results. The two false-negative results were attributed to the small size of the lesions (less than 5 mm). Other small studies (involving 11 to 12 patients) demonstrated sensitivities ranging from 0% to 50% and specificities ranging from 72% to 90% for this indication.^{14,15}

Distant metastases from prostate cancer have also been successfully identified through PET. Seltzer et al¹⁶ evaluated 45 patients with posttreatment (prostatectomy, radiation, or cryotherapy) prostate-specific antigen (PSA) recurrence using PET imaging. Six out of 9 positive PET scans correlated with biopsy proven metastasis, while 2 out of 3 negative scans had negative biopsies (biopsies were taken due to a suspicious finding on CT). Importantly, PET detected evidence of metastases in 50% of patients who had a PSA greater than 4 ng/mL or a PSA velocity greater than 0.2 ng/mL per month compared with only 4% of patients with a lower level PSA or PSA velocity. In addition, they demonstrated similar overall accuracies for CT and PET in detecting distant metastases.

A more recent prospective study by Nunez and associates¹⁷ compared PET with conventional imaging in identifying distant metastases in 12 patients with PSA recurrence following treatment. Using lesions demonstrated on conventional imaging as index lesions, they

demonstrated a relative sensitivity of 48% for FDG-PET and 72% for ¹¹C-methionine PET. Twenty-six percent of lesions demonstrated on conventional imaging were not demonstrated on either PET study. When divided into soft tissue and bony metastasis, FDG-PET demonstrated relative sensitivities of 48% and 34%, respectively, while ¹¹C-methionine PET demonstrated a sensitivity of 70% for both. The study did demonstrate that cervical spinal metastases are more easily detected by PET than by bone scintigraphy. Similarly, Schirrmester et al¹⁸ demonstrated that PET could detect twice as many bony metastases (anywhere) compared to bone scintigraphy. Given these results, some argue that PET can identify very small bone lesions before osteoblastic or osteolytic reactions are visible on radionuclide scintigraphy.¹⁹ The superiority of PET in detecting bone metastasis, however, is contradicted by other studies in the literature.¹⁵

Perhaps the most promising indication for PET with regard to prostate cancer lies in its ability to evaluate changes in tumor burden and location of disease during therapy and, thus, to determine the prognosis of the patient. Studies have demonstrated that changes in PET scanning correlate with changes in PSA.¹⁷ Oyama et al²⁰ demonstrated that in 10 patients undergoing androgen ablation for metastatic prostate cancer, a decrease in PET uptake in the primary tumor and metastatic sites during therapy correlated with a decrease in PSA and decreased size of lesions seen on CT scan. Given this correlation, PET can potentially be employed to both quantify and localize the effects of treatment of metastatic prostate cancer and help guide further therapy.

Bladder Cancer

PET has demonstrated limited utility in the diagnosis and staging of bladder cancer. Historically, the staging of bladder cancer with various imaging modalities has been limited. CT scanning can detect only gross tumor extension beyond the bladder wall with an accuracy of 64% to 92%.²¹ In addition, its accuracy in detecting lymph node metastasis ranges from 70% to 90% with false-negative rates as high as 40%.²² Similarly, magnetic resonance imaging (MRI) has been disappointing with regard to staging, with accuracies ranging from 60% to 75%.²³ Furthermore, when used to assess disease spread to the pelvic lymph nodes, the false-negative rates are just as high as those reported with CT imaging. Both of these imaging modalities have been found to have a propensity for overstaging because their findings are based on anatomical changes that may not correlate with malignancy.^{21,24} Given the ability of PET to detect differential metabol-

ic activity, investigators began exploring the use of PET to stage bladder cancer.

As with prostate cancer, the use of PET in the context of bladder cancer is significantly limited because of the urinary excretion of FDG and subsequent poor differentiation of lesions in the bladder and adjacent lymph nodes. Nonetheless, PET has been demonstrated to identify both local and distant spread of bladder cancer with some success. Kosuda et al²⁵ employed PET to assess 12 patients with histologically proven bladder cancer who had undergone surgical procedures and/or radiotherapy for recurrent or residual tumor. The study demonstrated a true-positive rate of 66.7% and a false-negative rate of 33.3%. PET was able to identify 100% (17/17) of distant metastases (lung, bone, and remote lymph node) as well as 66.7% (2/3) of local pelvic lymph nodes. Heicappell and colleagues¹³ similarly demonstrated a detection rate of 66.7% for local lymph node metastasis. Locally recurrent or residual bladder tumors were not identified as effectively (60%) due to the accumulation of the excreted tracer in the bladder despite bladder irrigation and Foley drainage. However, PET was able to assist in the identification of extravesical extension in some patients, including one case with invasion into the sigmoid colon not demonstrated on CT. PET also successfully differentiated between recurrent tumor and radiation/chemotherapy-induced changes in the bladders of two patients.

Other studies have attempted to improve the sensitivity of PET by removing the tracer artifact in the bladder by using other tracers. For example, Ahlstrom et al²⁶ compared the use of FDG with ¹¹C-methionine (not excreted in the urine) and found the latter to be superior. However, tumor was still only identified with a sensitivity of 78% (18/23) using this method. The study also found that tracer uptake was proportional to tumor stage.

Although limited by the potential of tracer artifact in the pelvis, PET may have some use for staging in bladder cancer. Although not sensitive enough to be used in the detection of primary, low-stage bladder cancers, PET may have limited use, in conjunction with conventional studies, in staging locally extensive lesions. In addition, it may help identify lymph node and distant metastases and may help in differentiating recurrent disease from tissue changes following radiation.

Renal Cancer

PET has also been implemented in the diagnosis and monitoring of renal cell carcinoma (RCC). Bachor

et al²⁷ evaluated 29 patients with solid renal masses. FDG-PET had a sensitivity of 77% (20/26) in histologically confirmed cases of RCC, with 3 false-positive results. Ramdave et al²⁸ demonstrated better results with the use of PET in diagnosing RCC. In this study, 17 patients presenting with a primary renal mass were studied with CT and PET and then verified through histological examination or clinical follow-up. PET and CT were found to have equivalent accuracies of 94%. PET was true positive in 15 patients, true negative in 1, and false negative in 1, while CT was true positive in 16 and false-positive in 1. In addition, PET demonstrated an added benefit of identifying pulmonary metastases in 2 patients. Corresponding CT scans were not available.

PET has also been demonstrated to be invaluable in monitoring progression of treated RCC in the form of local recurrence or metastasis. Hoh et al²⁹ followed 21 patients with diagnosed RCC with PET scans every 3 to 6 months during their evaluation for interleukin-2-based therapy. PET was able to identify progression in 10 of 10 cases vs 7 of 10 cases by CT, and it accurately demonstrated absence of disease in 5 of 5 patients. Ramdave et al²⁸ similarly evaluated 8 patients with RCC for local recurrence or metastasis and found superior results with PET when compared to CT. PET was found to have 100% accuracy in demonstrating local recurrence and metastases as opposed to 88% for CT. PET was also able to better differentiate between a recurrent mass in the renal fossa bed and radiation necrosis when compared to CT.

A more recent study by Safaei and colleagues³⁰ also demonstrated the utility of PET in characterizing indeterminate lesions identified on conventional imaging in patients with a history of metastatic RCC. In this study, clinical PET was performed for re-staging in 36 patients with advanced RCC. Written reports of imaging studies (including CT, MRI, ultrasound, plain film, and bone scan), patient history, and extensive medical record reviews were used to define the clinical stage before PET (pre-PET stage). PET classified the clinical stage correctly in 32 (89%) of 36 patients and was incorrect in 4 (11%) (sensitivity and specificity: 87% and 100%). These investigators also studied the accuracy of PET in classifying lesions that were later biopsied. They found that PET correctly classified 21 (84%) of 25 of the biopsied lesions (sensitivity and specificity: 88% and 75%). Other studies and case reports have also demonstrated the utility of PET in detecting metastatic spread of RCC. While lymph node staging with CT has been found to have a sensitivity of 83% to 89%, imaging with PET has demonstrated an increased sensitivity of 100%^{31,32} In addition, because it is a whole body scan, PET offers the added utility of

demonstrating metastases in areas that would not otherwise be suspected. One case, for example, attested the use of PET in demonstrating an RCC metastasis to the intramedullary spinal cord.³³ Another study demonstrated the superiority of PET over bone scan in detecting active osseous metastasis of RCC.³⁴

PET, therefore, is a valuable tool in the diagnosis and management of RCC. While demonstrating at least equivalent accuracy in diagnosing primary RCC when compared with CT, the current gold standard, PET appears to be more accurate in monitoring for progression of disease, metastasis, or local recurrence in the renal fossa bed. At the very least, PET appears to be a useful adjunct to conventional imaging in the management of RCC.

Testicular Cancer

PET has also been extensively investigated in the context of staging testicular cancer. Currently, 20% to 30% of patients classified as having clinical stage I disease actually have involvement of the retroperitoneal lymph nodes when undergoing lymph node dissection.³⁵ In addition, up to 30% of patients with clinical stage I disease who are followed by surveillance eventually recur.³⁶ Finally, up to 25% of patients with clinical stage II disease have been found to be overstaged by conventional imaging modalities.³⁵ CT has been reported to have false-negative rates as high as 30% to 59% and false-positive rates as high as 25%.^{37,38} Ultrasound has proven even less helpful, with one study reporting a false-negative rate as high as 70%.³⁷

The limited accuracy with which testicular cancer is staged using conventional imaging modalities has led to the study of PET as an alternative staging tool. Albers et al³⁹ studied 37 patients with stage I or II seminomatous and nonseminomatous germ cell tumors of the testicle to compare the accuracy of CT vs PET. PET staging was correct in 34 of 37 patients compared to CT staging, which was correct in 29 of 37 patients. PET had a higher sensitivity (70% vs 40%) and a higher specificity (100% vs 78%) when compared to CT. Hain et al³⁵ demonstrated similar results when attempting to stage 31 patients with either seminomatous or nonseminomatous germ cell tumors. This study demonstrated 100% specificity and positive predictive value (PPV). The sensitivity and negative predictive values (NPVs) could not be conclusively determined because of inadequate follow-up in 6 patients. One limitation of PET in these studies was its inability to detect metastatic lesions less than 5 mm in diameter.³⁹ This is also a limitation of CT scanning, which is unable to accurately diagnose lymph node metastases until the nodal size

reaches 1 cm. In addition, PET was limited by its low sensitivity for detecting mature teratoma, which has a low glucose metabolic rate.³⁸

Another diagnostic challenge in the management of testicular cancer is the postchemotherapy evaluation of a residual mass in the retroperitoneum. The differentiation between residual tumor, fibrosis, and teratoma can play a significant role in guiding further therapy. Unfortunately, by providing purely anatomic images of the retroperitoneum, CT does not adequately differentiate among between these entities. Studies evaluating PET in this setting have demonstrated sensitivities ranging from 79% to 87% and specificities from 90% to 94%.^{40,41} In addition, PPVs of 80% to 96% and an NPV of 90% have been demonstrated.^{42,43} CT demonstrated an equivalent specificity of 94% but a significantly lower sensitivity of 73% in one study.⁴¹ Hain and associates⁴³ evaluated 55 patients following chemotherapy with elevated tumor markers, 47 of whom had a residual mass on CT. PET was demonstrated to have an equivalent PPV of 94% when compared to tumor markers but a higher NPV of 90%. These investigators also used PET in the assessment of patients with elevated tumor markers but no mass on CT, and they reported a PPV of 92% in this setting with the added benefit of identifying the location of the tumor. The NPV of PET in this population was only 50%, but this was significantly better than the NPV of CT, which by definition was 0%. PET has also been demonstrated to be possibly beneficial in monitoring the response of retroperitoneal disease to therapy, with a decrease in FDG uptake correlating with a positive response to treatment.⁴⁴

In the setting of pure seminoma, the management of postchemotherapy masses is particularly controversial. Most centers have uniformly agreed that lesions

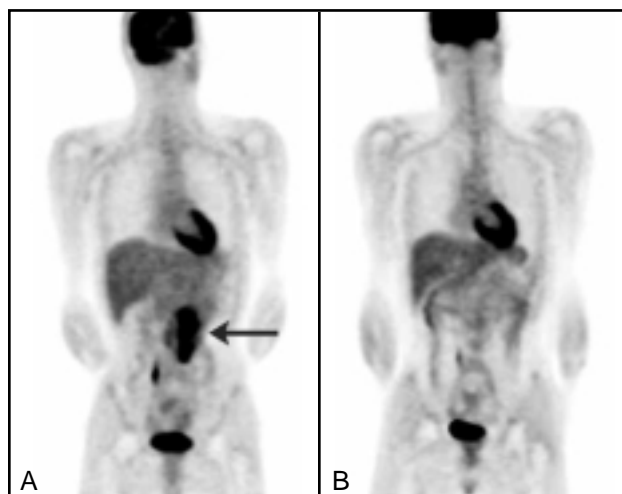


Fig 1. — (A) Prechemotherapy scan demonstrating a large hypermetabolic mass in the left retroperitoneum para-aortic region (pure seminoma). (B) Postchemotherapy scan demonstrating a complete metabolic response.

less than 3 cm in size need only observation because these lesions are most likely representative of fibrosis.⁴⁵ Some have also advocated surveillance for seminoma patients with residual postchemotherapy masses, regardless of size.⁴⁶ This conservative approach is based on the fact that retroperitoneal lymph node (RPLND) following chemotherapy for a seminoma involves significant morbidities. Until recently, studies have demonstrated that PET has not been successful in assessing postchemotherapy masses in patients with seminoma.⁴⁷ However, a recent multicenter study by De Santis et al⁴⁸ assessed PET in the evaluation of postchemotherapy retroperitoneal masses in patients with seminoma and demonstrated that PET accurately predicted 14 of 14 lesions greater than 3 cm in size and 22 of 23 lesions less than or equal to 3 cm in size. The study demonstrated a sensitivity, specificity, PPV, and NPV of 89%, 100%, 100%, and 97%, respectively. Fig 1 demonstrates an example of an FDG-PET scan performed before and after successful chemotherapy in a patient with pure seminoma.

Studies have demonstrated PET accuracy may be compromised if the scan is performed too soon (within 2 weeks) after chemotherapy, with reported false-negative findings due to early suppression of metabolic activity immediately after chemotherapy and false-positive findings due to increased macrophage activity in absorption of necrotic tissue, respectively.^{42,49,50} As a result, PET should not be employed until at least 2 weeks following chemotherapy.

Future Applications

PET has also become an important tool in experimental gene therapy for urologic oncology. The creation of micro-PET technology provides higher resolution, making it possible to image smaller animals in the context of experimental gene therapy.⁵¹ In a recent study, PET was used to successfully demonstrate the expression of a herpes simplex virus thymidine kinase (HSV1-tk) reporter gene in severe combined immunodeficient (SCID) mice with prostate tumor xenografts using fluorinated penciclovir as a radiotracer.⁵² By non-invasively quantifying *in vivo* gene expression, PET has the potential to correlate gene expression with therapeutic effect. In so doing, PET can serve as a vital tool in determining the therapeutic efficacy and safety of gene therapy protocols targeting urologic malignancies. Fig 2 depicts the use of PET technology to identify prostate cancer in a SCID mouse. The use of tissue-specific proteins that express a PET reporter gene in a restricted manner (such as PSA in the prostate and G250 antigen in the kidney) may improve the sensitivity and specificity limitations that currently exist. Final-

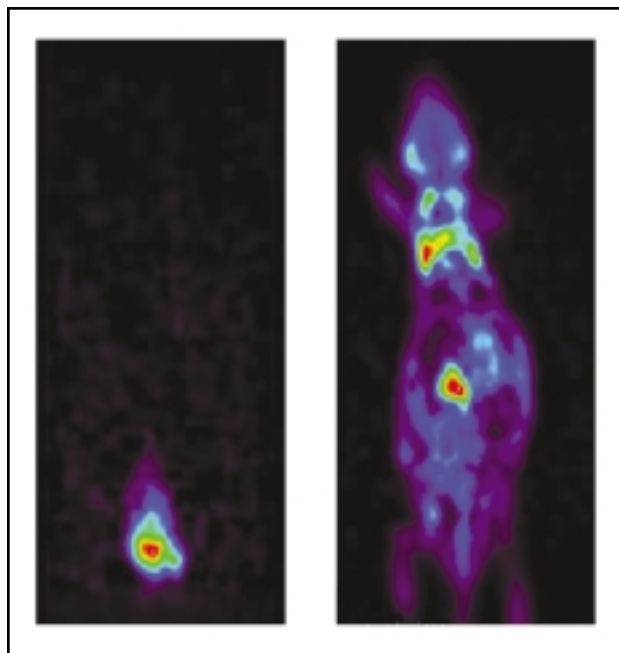


Fig 2. — Left panel: ventral tomographic cut through markedly enlarged orthotopically located prostate tumor in SCID mouse shows intense retention of PET probe within the tumor. Right panel: enlarged retroperitoneal adenopathy shows intense activity. Background activity can be seen in gastrointestinal tract, heart, and brain.

ly, the development of newer probes with longer half-lives that permit delayed images to be acquired after urinary excretion has been eliminated may also help overcome current limitations.

Conclusions

PET has demonstrated clinical utility in the field of urologic oncology (Table 2). The use of FDG-PET in the diagnosis of localized and metastatic prostate is primarily limited by the generally low tumor metabolic activity of prostate cancer and is secondarily limited by the high background activity of excreted tracer found in the bladder and ureters at the time of scanning. The similar signal yielded by benign prostatic hyperplasia and prostate cancer also makes the diagnosis primary prostate cancer with PET difficult. However, PET has demonstrated some benefit in identifying lymph node and distant organ including bone metastasis and may be successfully used for such indications.

PET is limited in the evaluation of bladder cancer. Again, because of the urinary excretion of FDG, the high background activity of tracer severely limits the ability to detect local bladder tumor involvement. However, PET can be employed to successfully demonstrate whether extravascular extension is present. In addition, PET may have some clinical utility in identifying pelvic lymph node and distant metastases.

Table 2. — Applications and Limitations of FDG-PET in Genitourinary Oncology

Cancer	Applications	Limitations
Prostate cancer	Lymph node staging Identification of distant metastasis Monitor response to therapy	Inherent low tumor glycolytic rate Inability to distinguish prostate cancer from benign prostatic hyperplasia Renally excreted tracer in the urinary bladder may hinder visualization of the primary tumor and pelvic lymph nodes
Bladder cancer	Lymph node staging Differentiation of tumor recurrence from postchemotherapy/radiation changes	Tracer activity in the urinary bladder limits detection of primary tumor and pelvic lymph nodes
Renal cell carcinoma	Characterization of an indeterminate renal mass Detection of local tumor recurrence lymph node metastases Monitor response to therapy	Renal excretion limits visualization of primary tumor Low sensitivity for detecting biologically and quiescent tumors
Testicular cancer	Initial staging of lymph nodes and distant metastasis Characterize postchemotherapy retroperitoneal masses Monitor response to chemotherapy	Cannot differentiate mature teratoma from fibrosis Lymph nodes ≤ 5 mm not reliably detected

PET has been used with considerable success in the diagnosis and management of RCC. While demonstrating similar accuracy to CT in diagnosing primary RCC, PET appears to be even more reliable in identifying local recurrence and distant metastasis as well as monitoring progression of disease and response to immunotherapy.

The diagnosis and management of testicular cancer can be significantly improved with PET. PET can be successfully used in conjunction with conventional imaging to more accurately diagnose retroperitoneal disease in patients with an initial diagnosis of primary testicular cancer. PET has an even more important role in the evaluation of a postchemotherapy residual mass. Because of its ability to differentiate between necrosis/fibrosis and residual or recurrent cancer, PET can be used to determine whether a postchemotherapy RPLND or additional chemotherapy is necessary. The use of PET for this application, however, must be undertaken with caution since PET cannot differentiate between teratoma and fibrosis. As a result, a negative postchemotherapy PET scan in a patient whose initial testicular tumor demonstrated a significant component of teratoma may not obviate an RPLND in such a patient.

Finally, the most exciting applications of PET appear to be in the context of gene therapy. PET has the capability of noninvasively demonstrating in vivo gene expression. As a result, this imaging modality

could be used in the future as a safe, noninvasive method of determining the efficacy of clinical gene therapy trials. With the advent of more optimal tracers as well as the combination of PET with conventional imaging modalities such as CT and MRI, PET may serve as an indispensable tool in the diagnosis and management of urologic malignancy.

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