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PET/CT Limitations and Pitfalls in Urogenital Cancers

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Hybrid FDG PET/CT plays a vital role in oncologic imaging and has been widely adopted for the staging and restaging of a variety of malignancies. Its diagnostic value in urogenital malignancies is less well-known, not at least because of the variable FDG avidity of these tumor entities, the sites of these tumors, and technical challenges associated with sequential imaging of CT and PET. PET/CT interpretation thus can be especially challenging and is associated with many pitfalls, which can lead to both false-positive and false-negative diagnoses as well as incorrect assessment of metabolic change following therapy. Currently, FDG PET/CT is not the standard of care for the initial diagnosis or staging of early-stage or low-risk urogenital cancers; however, it can help evaluate distant metastatic disease, response to therapy, and disease recurrence in high-risk patients. Knowledge of imaging features of tumor metabolic avidity and pitfalls is essential for accurate interpretation.
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Introduction

Besides computed tomography (CT) and magnetic resonance imaging (MRI), hybrid positron emission tomography/CT (PET/CT) has improved imaging care for oncologic patients.2-deoxy-2-fluorodeoxyglucose (FDG) PET/CT has become widely used and made an enormous contribution to the diagnosis, staging, and treatment monitoring in patients with cancer.[1–3] As a glucose analog, FDG is taken up by cancer cells owing to the upregulation of glucose metabolism. Hybrid PET/CT combines functional with morphologic imaging and promises to provide greater diagnostic confidence and accuracy in cancer imaging than PET alone.[3–5] The clinical interest in obtaining FDG PET or PET/CT for patients with urogenital cancers was high during the 2008 U.S. National Oncologic PET Registry (NOPR), which was developed to collect data on the clinical utility of FDG PET for previously noncovered tumor entities in Medicare beneficiaries. Renal and urinary bladder malignancies accounted for 2877 and 3578 of 40,863 PET scans during the NOPR period, accounting for 16% of all PETs.[6] Other tumor entities with the highest number of PET and PET/CT scans performed included prostate cancer (13%), ovarian cancer (11%), and pancreatic cancer (8%), among others.

The clinical utility of FDG PET/CT depends on the type of malignancy and the clinical context, with current evidence-based literature embracing several indications for urologic cancers.[4,7,8] Although FDG PET/CT is not the standard of care for the diagnosis or initial staging of early-stage or low-risk urogenital cancers, it has added value to CT and MRI in evaluating advanced or high-risk disease, recurrent disease, response to surgical or chemotherapeutic treatments. Given the hybrid nature of PET/CT imaging, there are inherent technical challenges with it, which include respiratory motion artifacts and anatomic misalignment of the two datasets, as well as excreted urinary radioactivity present along the urinary tract. Other pitfalls include PET/CT misalignment due to intestinal peristalsis, PET halo artifacts around the bladder due to erroneous scatter correction, and mismatched volume and misregistration of the bladder due to bladder filling. PET/CT interpretation thus can be especially challenging and is associated with many pitfalls, which can lead to both false-positive and false-negative diagnoses as well as incorrect metabolic quantification following therapy. Knowledge of imaging features of nonspecific radioactivity, pitfalls, and tumor metabolic avidity is essential for an accurate interpretation. In this article, we review the clinical role of FDG PET/CT in renal cell cancer (RCC), bladder cancer, testicular cancer, and penile cancer based on the current National

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Comprehensive Cancer Network Clinical practice guidelines (NCCN guidelines, USA), along with case presentation to highlight some of the technical and interpretive challenges associated with PET/CT interpretation of urogenital cancers.

Imagining Protocol

As with all FDG PET/CT protocols, proper hydration prior to the exam is encouraged to enhance the excretion and dilute the radioactivity within the urinary tract. Patients must be asked to void the urinary bladder just before going onto the scanner to minimize the nonspecific urinary radioactivity, commonly seen in the renal collecting system, ureters, and bladder, which otherwise could limit lesion detection and characterization. Protocol considerations to minimize this physiologic urinary activity are especially relevant for urogenital malignancies. Delayed imaging following oral hydration or the use of IV furosemide to enhance the urinary excretion of FDG has been described in the literature but is rarely used in clinical practice.[9–11] Following the usual 60-minute FDG uptake, hybrid PET/CT requires sequential imaging, commonly with CT first for anatomical imaging and attenuation correction of PET data, followed by PET. The patient is instructed to lay still on the scanner during both scans so both CT and PET data are properly co-registered/aligned for imaging interpretation. In oncology, a torso PET/CT is typically performed from skull-base to mid-thigh, with CT being low-dose and non-enhanced (neCT) for attenuation correction and anatomic localization of PET data. As a special consideration for urogenital imaging, it is better to start the scan from the thigh up to the skull, not from skull to thigh, which helps avoid the nonspecific urinary activity within the bladder. This also allows for a better PET/CT co-registration of the bladder due to the two scans' negligible time delay.[12] Some institutions may opt for the placement of a urinary catheter to minimize the bladder radioactivity further.[13]

Various PET/CT workflows exist that address the specific CT needs as part of the PET/CT exam. The most common PET/CT protocol uses a low-dose CT without oral or IV contrast, in which the patient is asked to breathe normally during CT and PET scanning. A hybrid PET/CT scan can take 10-25 min to complete, dependent on the patients' habitus and scanner system.[14] A diagnostic contrast-enhanced CT protocol (ceCT) with iodinated oral and IV contrast media administration can improve diagnostic accuracy. In most instances, a portal-venous ceCT of the torso is acquired during normal breathing, which matches the PET field-of-view and mimics the diaphragmatic motion on PET; however, the anatomic structures around the diaphragm, in the lower chest and upper abdomen, commonly show some degree of misregistration/misalignment because the CT data is acquired at a random point of the respiratory cycle while the PET data is obtained during multiple respiratory cycles. An additional low-dose neCT of the chest in full inspiration allows for an optimal lung parenchyma evaluation. A multi-phase CT with arterial and portal-venous contrast enhancement focusing on a region of interest such as the kidneys is technically feasible but rarely indicated because most patients will already have undergone a diagnostic CT as part of their imaging workup prior to PET/CT.[14,15]

Technical Pitfalls

Attenuation and scatter correction

CT transmission data is used to correct for PET attenuation. The attenuation correction and scatter correction of PET data are well established, but technical challenges remain. A halo artifact is commonly seen around the bladder due to scatter correction errors in areas of intense radioactivity, such as the urinary bladder.[16] This artifact is also present but less evident at the level of the kidneys, particularly when there is hydronephrosis, which can mask PET findings and limit image interpretation. These artifacts can be reduced by using the latest time-of-flight (TOF) PET/CT technology, which can minimize errors in data normalization, attenuation, and scatter correction and help improve image quality for lesion detection.[16–18] Metal artifacts from orthopedic hardware in the hips can be extensive on CT, resulting in streak artifacts and limiting CT evaluation of the hips and pelvic structures. Further, CT-based attenuation correction is susceptible to errors in areas of metal implants, which can lead to falsely high or low FDG uptake.[19,20] Recent introduction of iterative CT algorithm to reduce metal artifact can improve not only the CT anatomy but also the PET image quality and quantification.[19,21]

A PET/CT with ceCT quality is often indicated in urogenital cancers to enhance lesion detection and characterization. When oral and/or IV contrast media are administered, high concentrations of intestinal or IV contrast media may cause artifacts in the reconstructed PET data because of inadequate CT attenuation correction. As a result, the PET image quality may be affected, and the standardized-uptake value (SUV) measurements can be falsely high.[22] However, these artifacts are usually very mild and considered acceptable, particularly when water-based contrast media is used.

Respiratory artifact and PET/CT misregistration

Respiratory artifact and PET/CT misregistration are significant concerns for an accurate interpretation of urogenital cancers. Respiratory artifact occurs on both CT and PET because patients are breathing normally during the scans. Differences in respiratory/diaphragmatic motion between CT and PET can often induce co-registration errors in addition to respiratory motion artifacts. Thus, variable degrees of PET/CT misregistration is unavoidable (Fig. 1). Other causes of misalignment involve intestinal peristalsis and urinary excretion of radioactivity.[12,14,23] Blurry PET images and misregistered PET/CT data can negatively impact the PET image quality, particularly at the level of the kidneys, liver, and spleen. Various commercial respiratory motion correction methods are available, minimizing the respiratory artifact and improving the PET/CT misregistration.[24–29] Currently, most vendors use a respiratory gating method for PET

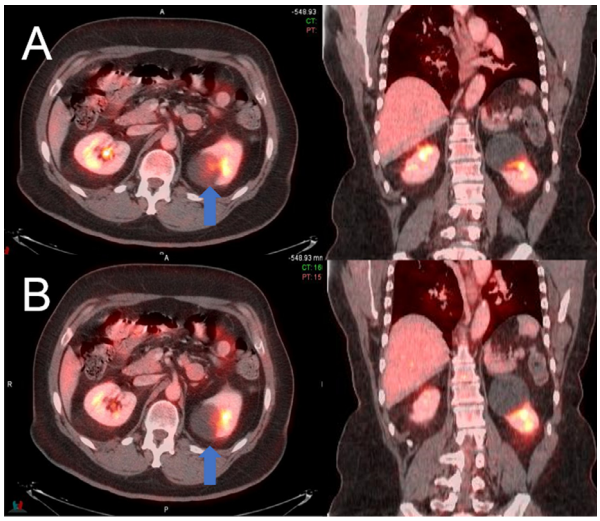

Figure 1 PET/ceCT of a 67-year-old woman with sequential CT and PET acquired during normal breathing. A, original fused images, axial and coronal, show a 3 × 5 cm benign left renal cyst with PET/CT misregistration due to respiratory motion (arrow). B shows manually adjusted PET/CT registration, axial and coronal; however, minimal misregistration remains due to the inherent differences in the respiratory motion between CT and PET (arrow). In clinical practice, a manual co-registration is feasible but will slow down the image review and interpretation process. Still, a manual co-registration is subjective and may not solve the misregistration well.

imaging, which divides the respiratory cycle into a specific number of bins and is simple to implement in clinical practice.[30] Though, respiratory motion correction is mainly used for the chest area at present, such as lung nodules and radiation treatment planning of lung cancer. Its use in evaluating intraabdominal lesions is limited to few reports and requires further validations.[28,29]

Tumor Entities

Renal Cell Carcinoma

Contrast-enhanced CT and MRI are the imaging modalities of choice for the initial diagnosis and staging of RCC.[31] They provide adequate diagnostic information on the local extent, nodal and vascular involvement, as well as distant metastasis. For initial staging, FDG PET was found to have a sensitivity and specificity of 60% and 100% compared with 92% and 100% for ceCT. The accuracy was slightly better for retroperitoneal nodal metastasis with a sensitivity and specificity of 75% and 100%, compared with 93% and 98% for ceCT.[32] In a meta-analysis published in 2012, FDG PET showed a pooled sensitivity and specificity of 62% and 88% for renal lesions and 79% and 90% for extrarenal lesions at staging.[33] With hybrid PET/CT, the sensitivity increased to 91% for extrarenal lesion, while the specificity was stable at 88%.[33] Some of the diagnostic challenges can be attributed to the variable FDG avidity of renal primaries and the presence of excreted urinary activity in the renal collecting system, which often obscures lesion detection. A higher FDG avidity of the primary is associated with higher tumor grading and increases the likelihood of nodal and metastatic disease. A maximum SUV of 3.0 has been shown to have 89% sensitivity and 87% specificity for differentiating low-grade from high-grade RCC.[34–37]

In a prospective study of 63 subjects with advanced RCC (T2-4 tumors), FDG PET/neCT showed a sensitivity of 90% and specificity of 83% for post-operative surveillance, which was equivalent to conventional imaging (chest CT, abdominal CT, and bone scan).[38] In another study by Alongi *et al.*, PET/neCT was found to have a sensitivity and specificity of 74% and 80%, and influenced the clinical management in 43% of patients with tumor recurrence. Moreover, a positive PET/CT scan was also associated with worse 5-year survival.[39] In a meta-analysis published in 2017, FDG PET/CT was found to have a sensitivity and specificity of 86% and 88% in detecting new metastatic or recurrent lesions.[40] False-negative scans are commonly attributed to small lesion size and limited spatial resolution of PET. As recurrent RCC may have low-level FDG uptake and may be masked by excreted urinary activity, PET/ceCT is preferred if clinically indicated to enhance lesion detection and characterization. False-positive findings are often a result of post-operative scar, post-radiation inflammation, or infection.[39,41] A summary of the most important meta-analyses related to FDG PET and PET/CT for RCC, urinary bladder cancer, testicular cancer, and penile cancer, is provided in Table 1.

Current NCCN guidelines do not recommend FDG PET/CT as a standard of care for the initial staging, or follow-up after therapy in RCC, and indicate that the clinical value of PET/CT in the management of RCC patients remains to be seen.[31] The current 2014 American College of Radiology (ACR) Appropriate Use Criteria suggest that PET/CT can be a valuable adjunct to conventional imaging for RCC post-treatment surveillance, particularly when CT or MRI is equivocal for local recurrence, and postoperative or post-radiation changes cannot be excluded.[42] At our institution, PET/CT has been requested for initial staging of high-risk RCC and post-treatment follow-up of advanced RCC. A case of RCC, clear cell type, whose primary shows only mild FDG avidity and lacks uptake in the tumor thrombi present in the portal vein as well as tumor extension within the proximal ureter is illustrated (Fig. 2). Because immunotherapy response may differ from traditional systemic therapies, PET/CT imaging can be helpful as it provides functional and morphologic evaluation of treatment response and has the potential to predict survival.[43–46] In a small study of 10 patients, the sum of lesion diameters at CT decreased to 80%, while the FDG uptake decreased to 75% after 2 months of therapy with sorafenib for metastatic RCC.[43] The advantage of hybrid PET/CT for evaluating treatment response in a patient with recurrent RCC treated with immunotherapy is shown (Fig. 3).

PET radiopharmaceuticals targeting prostate-specific membrane antigen (PSMA) show promise for imaging of RCC in addition to prostate cancer, due to the PSMA expression by tumor-associated neovasculature.[47] Most clear cell RCCs, the most aggressive subtype, are highly associated with PSMA expression. Less aggressive RCC subtypes can

Table 1 Summary of the Most Important Meta-Analyses Related to FDG PET and PET/CT for RCC, Urinary Bladder Cancer, Testicular Cancer, and Penile Cancer.

Ref. #	Year	Scan type (No of studies)	Tumor entity	Indication	No of studies (patients)	Sensitivity (95% CI), in %	Specificity (95% CI), in %
33	2012	PET/CT (2)	RCC	Staging, extra-renal lesions	2 (138)	91 (84-96)	88 (77-94)
		PET (12)		Staging, primary	4 (88)	62 (49-74)	88 (47-100)
				Staging, extra-renal lesions	8 (272)	79 (71-86)	90 (82-95)
40	2017	PET (8); PET/CT (7)	RCC	Restaging	15 (1168)	86 (88-93)	88 (84-91)
58	2015	PET (1); PET/CT (9)	Urinary bladder cancer	Staging	10 (433)	82 (75-88)	92 (87-95)
63	2020	PET/CT (7)	Urinary bladder cancer	Restaging	7 (603)	94 (91-96)	92 (88-95)
74	2014	PET (7); PET/CT (2)	Testicular seminoma	Restaging	9 (375)	78 (67-87)	86 (81-89)
75	2014	PET (15); PET/CT (1)	Testicular cancer (mostly seminomas)	Mostly restaging	16 (807)	75 (70-80)	87 (84-89)
88	2012	PET/CT (7)	Penile squamous cell cancer	Staging, inguinal - all nodes	7 (115)	81 (70-89)	92 (87-96)
				Nonpalpable nodes		57 (35-77)	86 (76-93)
				Palpable nodes		96 (82-100)	100 (84-100)

CI, confidence interval; Ref., reference.

Figure 2 A 67-year-old man was found to have left RCC, clear cell type, grade 3, with hemorrhage and necrosis at radical nephrectomy. An additional Klatskin tumor was thought to be cholangiocarcinoma but revealed metastatic RCC at endoscopic retrograde cholangiopancreatography (not shown). Subsequent staging PET/neCT shows a mildly FDG avid RCC mass located in the anterior aspect of the left kidney, measuring 6 × 8 cm with max. SUV 3.5 (A, B, C, axial images; arrow); reference liver SUV was 2.8. On a ceCT performed earlier (D, axial), there were tumor thrombi in the renal vein and tumor extension into the left mesentery, colonic wall and proximal ureter, which shows only mild uptake on PET (SUV 2.5, arrowhead). Mildly enlarged left paraaortic nodes demonstrate no abnormal FDG avidity and were benign at later histopathology. This case illustrates the pitfall of low FDG avidity in RCC and the advantage of ceCT in detecting tumor thrombi and local extension. He recently completed four cycles of ipilimumab and nivolumab.

also be PSMA positive in significant percentage of cases.[48,49] In a recent pilot study of 14 subjects, PSMA-targeted 18F-DCFPyL PET/CT appeared to have added value in the identification of patients with oligometastatic clear cell RCC.[50] Ongoing clinical trials are evaluating the diagnostic utility of PSMA PET agents.[51,52] Another novel PET approach involves the use of radiolabeled antibodies targeting the highly expressed carbonic anhydrase IX (CAIX) in clear cell RCC. Two recent pilot studies have demonstrated that anti-CAIX monoclonal antibody 89Zr-girentuximab PET/CT could have added value to CT and FDG PET in the clinical management of RCC patients.[53,54]

Urinary Tract Cancer

CT and MRI urography are standard of care for the initial evaluation of suspected urothelial malignancies given the greater sensitivity for lesion detection.[55,56] PET/CT is limited for early-stage urinary tract cancers because of the low-level FDG avidity and the excreted urinary activity, which can obscure the primary, particularly for the small ones. Compared to standard CT, FDG PET/neCT was found to have greater sensitivity (85% vs 77%) but lower specificity (25% vs 50%) in the detection of urinary bladder primary.[57] However, diagnostic potential was found to be better for staging of nodal and distant metastases, with a reported sensitivity of 82% and specificity of 92% in a meta-analysis by Zhang *et al.*[58]

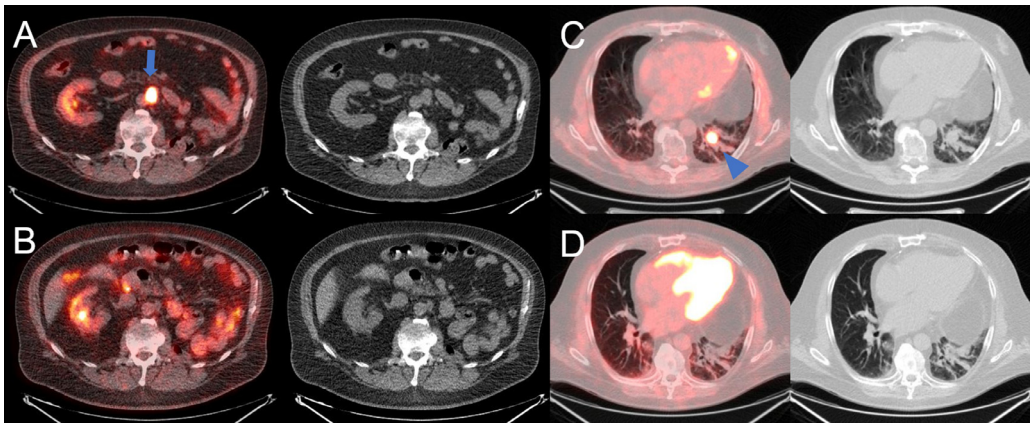

Figure 3 A 70-year-old man was diagnosed with grade 4 RCC with rhabdoid differentiation, underwent robotic left radical nephrectomy. Six months later while on immunotherapy with sunitinib, FDG PET/neCT was negative for residual or recurrent disease (not shown). However, at 12-month follow-up PET/neCT imaging, he developed a new FDG avid left lower lobe pulmonary nodule, 1.9 × 2.0 cm with max. SUV 8.1 (C, axial images; arrowhead) and a new FDG avid left paraaortic node, 2.0 × 2.4 cm with max. SUV 9.4 (A, axial images; arrow); reference liver SUV was 2.8. The retroperitoneal node was recurrent RCC at subsequent core needle biopsy. The therapy was switched from sunitinib to ipilimumab and nivolumab. PET/neCT four months later showed resolution of the paraaortic node (B, axial images) and pulmonary nodule (D, axial images), indicating complete treatment response.

When PET/neCT is performed, a correlation with a previous ceCT, if available, is highly recommended. The importance of correlating PET/neCT with ceCT when interpreting urogenital cancers is highlighted (Fig. 4). Other pitfalls may include nonspecific focal ureteral radioactivity due to focally dilated ureter, which can mimic disease, particularly on axial images. However, a correlation with coronal and sagittal images can help reduce this pitfall. Better yet, a PET/ceCT should be obtained instead of PET/neCT if clinically feasible to minimize false-positive interpretation and improve diagnostic accuracy. A PET halo artifact around the bladder due to erroneous scatter correction can be severe in some patients, limiting the assessment of the bladder wall and primary and pelvic lymph nodes. In other instances, the mismatched PET/CT volume and misregistration of the bladder anatomy can pose a severe pitfall to interpretation. Anatomic variations of the urinary bladder can also pose diagnostic challenges. Specifically, FDG retention within urinary bladder diverticula can resemble tumoral uptake. Herniation of the urinary bladder into the inguinal canal is uncommon but can mimic a metastatic inguinal lymph node following administration of FDG on PET. Image interpretation can also be challenging in patients who have had prior cystectomy and creation of an ileal conduit as the radiotracer excreted through the stoma can obscure disease evaluation or mimic peritoneal disease.[12]

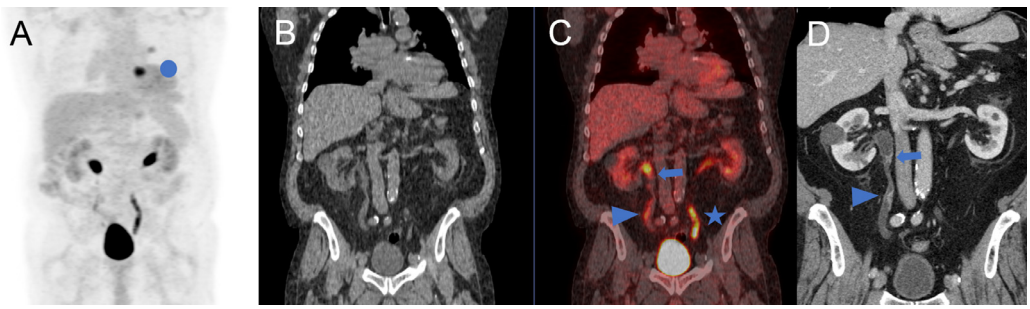

Figure 4 An 88-year-old man underwent PET/neCT for workup of a 3 cm left lower lobe pulmonary mass. A recent biopsy also found multifocal high-grade, invasive urothelial carcinoma along the left ureter. The left lower lobe mass is FDG avid and reveals invasive adenocarcinoma at subsequent core needle biopsy (A, maximum-intensity-projection image; circle). There is mild radioactivity along the right ureter with SUV 5.3 (B, C, coronal images; arrow and arrowhead); reference liver SUV was 3.3. This corresponds to multiple contrast-enhancing lesions measuring up to 0.7 × 1.4 cm in the right ureteropelvic junction and mid ureter, seen on a ceCT performed two weeks earlier (D, coronal images; arrow and arrowhead). PET/ceCT would have missed all these ureteral lesions, had the interpreting physician not known about the recent diagnosis of urothelial cancer and not reviewed the previous ceCT for correlation. No FDG avid retroperitoneal nodes are present. Note the prominent nonspecific urinary activity along the left ureter without tumor lesions or ureteral dilation.

The NCCN guidelines currently do not recommend FDG PET/CT for the initial staging of non-muscle invasive bladder cancer because the risk of metastatic disease is extremely low. However, PET/CT may be considered in patients with muscle-invasive disease (T2) or clinical stage III or greater.[59] PET/CT can be beneficial for these patients as it may influence clinical management. The added value of FDG PET/CT to resolve equivocal findings on diagnostic CT or MRI has also been acknowledged by the ACR.[60] Kibel *et al.* found that staging PET/neCT had a sensitivity of 70% and specificity of 94% for metastatic disease in muscle-invasive bladder cancer.[61] More importantly, additional occult metastatic disease was found in 7 of 42 patients with PET/CT compared with ceCT. In another study of 44 patients with muscle-invasive bladder cancer, the sensitivity for pelvic nodal metastasis was 57% for PET/neCT and 33% for ceCT.[57] A case of FDG avid multifocal bladder urothelial carcinoma with hilar nodal and pulmonary metastasis is illustrated (Fig. 5). It should be emphasized that PET/neCT should not be used to delineate the anatomy of the urinary tract as the neCT is low-dose and lacks the soft tissue contrast.

For tumor surveillance with or without prior cystectomy, FDG PET/CT may be considered, particularly in high-risk patients in whom metastasis is suspected. PET/CT findings can guide biopsy in select patients, alter patient management, and provide prognostic information compared with CT or MRI.[60] In a recent study of 41 patients with suspected recurrent bladder cancer, FDG PET/neCT showed a sensitivity of 87% and specificity of 94% for recurrent/metastatic bladder cancer, with identifiable lesions including abdominal and pelvic nodes, pulmonary and osseous metastases.[62] Moreover, PET/CT led to change in treatment decisions in 40% of patients and impacted the overall survival and progression-free survival. In a meta-analysis in 2020, PET/CT was found to have a 94% sensitivity and 92% specificity for restaging of urinary bladder cancer.[63] A case of recurrent urothelial bladder carcinoma with disease progression while on immunotherapy is shown (Fig. 6).

Testicular Cancer

Contrast-enhanced CT and MRI are primarily used for the initial staging of testicular malignancies.[64,65] Currently, the diagnostic value of PET/CT in the initial staging of testicular cancer is not well defined.[64] Most PET literature on initial staging of testicular cancer to date is based on FDG PET, not PET/CT, and indicates that PET may have slightly greater sensitivity than ceCT.[66–69] A limited number of retrospective PET/neCT studies also showed encouraging diagnostic performance for germ cell testicular cancers.[70,71] In a recent study, the diagnostic accuracy of PET/neCT for germ cell tumors was 81% for local regional metastasis and 93% for distant metastasis on a lesion-based analysis.[70] It appears however, FDG PET and PET/neCT have limited accuracy in nonseminomatous germ cell tumors and is suboptimal for differentiation between mature teratoma from necrosis or fibrosis.[72,73]

On the other hand, the role of PET/CT in surveilling seminomatous testicular cancer is well established. Treglia *et al.* reported a pooled sensitivity of 78% and specificity of 86% for restaging of seminomas in a meta-analysis published in 2014.[74] Similarly, a meta-analysis by Zhao *et al.* in 2014

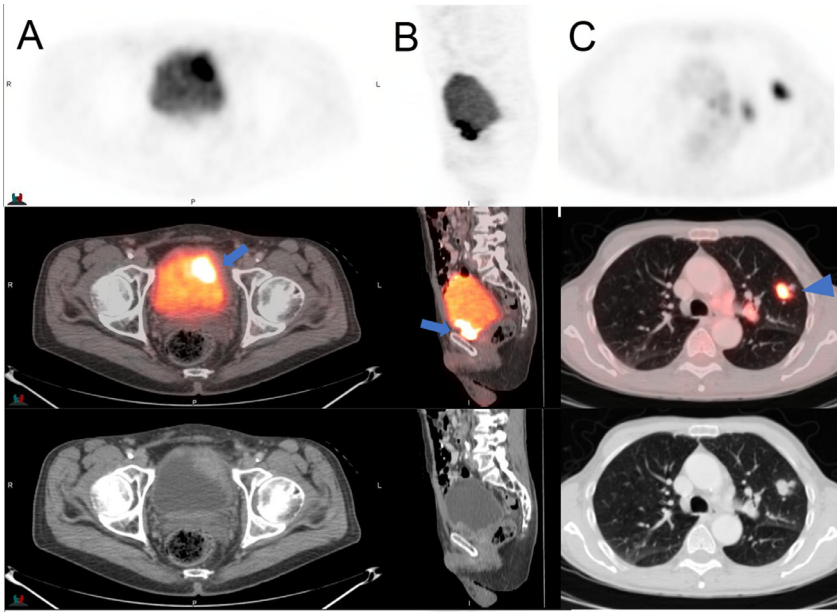

Figure 5 A 68-year-old-man with hematuria was found to have two foci of muscle-invasive urothelial carcinoma with mucinous features, high grade, invading the prostate on transurethral resection. Staging PET/ceCT reidentifies these contrast-enhancing lesions at the bladder neck (A, axial images; arrow) and base (B, sagittal images; arrow) measuring 4.1 × 4.6 cm with intense FDG uptake (max. SUV 9.6; reference liver SUV was 2.6). There are incidental findings of FDG avid left hilar node and left upper lobe pulmonary nodule (C, axial images; arrowhead), 1.2 × 2.3 cm with max. SUV 6.8. It revealed metastatic urothelial carcinoma at subsequent biopsy. The patient was treated with palliative chemotherapy with cisplatin and gemcitabine but died 5 months later.

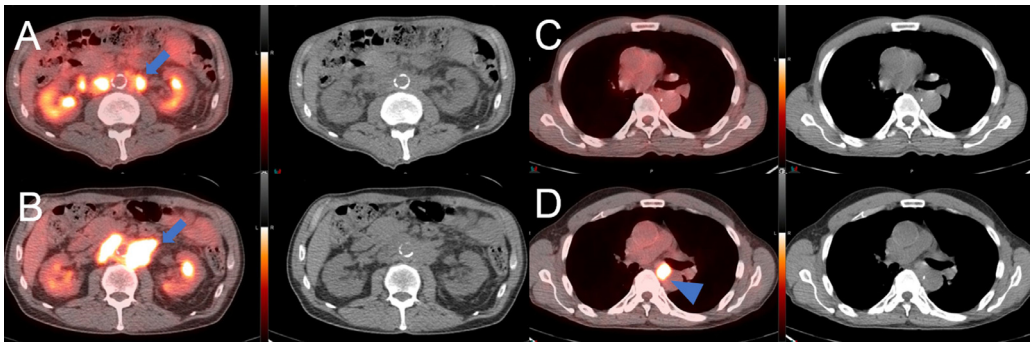

Figure 6 A 71-year-old man with history of poorly-differentiated urothelial carcinoma of the bladder had undergone cystoprostatectomy and pelvic nodal dissection with the creation of an ileal conduit. Five years later, while on immunotherapy with atezolizumab, PET/neCT shows several FDG avid paraaortic nodes, with the index lesion measuring 1.3 × 1.5 cm with max. SUV 6.3 (A, axial images; arrow), most consistent with disease recurrence. Follow-up PET/neCT performed 8 months later, while on therapy with carboplatin and gemcitabine, shows interval increase in size and FDG avidity of the paraaortic nodes (B, axial images; arrow) and a new FDG avid subcarinal node, 1.2 × 1.5 cm with max. SUV 6.3 (D, axial images; arrowhead) was not present on the prior exam (C, axial images). Findings are most consistent with disease progression. The patient died four months later.

reported a sensitivity of 75% and specificity of 87%, with most patients undergoing PET scanning for restaging of testicular seminomas.[75] The current NCCN guidelines indicate that PET/CT may be considered for stage II and III seminoma patients who are found to have a residual mass (>3 cm) on CT and normal serum alpha fetoprotein and beta hCG.[64] Imaging should be performed at 6 weeks or later after therapy, as earlier imaging may be false-positive in as much as 15% of patients due to post-treatment inflammation.[76] Lesions smaller than 3 cm are often associated with low cell proliferation and may lead to false-negative PET.[74] Nonetheless, PET/CT can detect metabolically active residual tumors while CT alone may not be able to differentiate between residual tumor and necrotic or fibrotic tissue.[74,77,78] A case of metastatic mixed germ cell tumor of the testis, which shows mild metabolic PET response to systemic chemotherapy but a slight increase in size on CT is presented (Fig. 7). PET/CT can also provide early detection of recurrent disease as tumor FDG avidity usually precedes CT morphology; thus, a negative PET/CT is reassuring.[74] Follow-up with diagnostic CT should follow for additional 5 years, as testicular germ cell tumors are often slow-growing with low FDG avidity, resulting in indeterminate imaging diagnosis.[74]

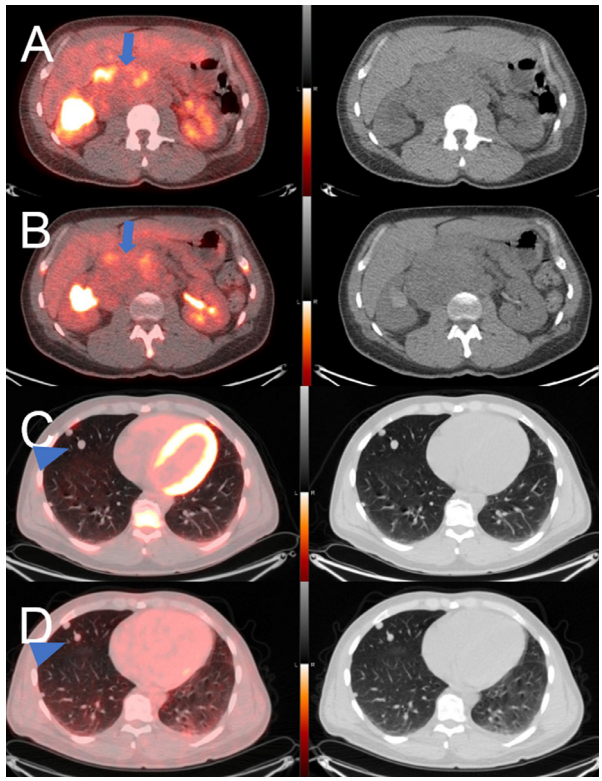

Figure 7 A 33-year-old man underwent orchidectomy for a mixed germ cell tumor with extensive tumor necrosis (60% seminoma, 30% teratoma, and 10% yolk sac tumor) and was known to have retroperitoneal and pulmonary metastases. Staging PET/neCT shows a heterogeneously FDG avid retroperitoneal mass measuring 12.2 × 6.4 cm with max. SUV 6.6 (A, axial images; arrow), reference liver SUV is 2.5; and bilateral pulmonary nodules measuring up to 1.2 cm with SUV 1.0 (C, axial images; arrowhead). Three months later, while on therapy with cisplatin, etoposide and ifosfamide, the size of the retroperitoneal mass is slightly increased, now measuring 13.3 × 7.8 cm (B, axial images; arrow), but the FDG uptake is decreased by 46%. The pulmonary nodules are not significantly changed in size or metabolic activity (D, axial images; arrowhead). The patient died nine months later.

Penile Cancer

Diagnostic CT chest, abdomen, and pelvis is typically performed to assess the size and extent of local tumor involvement and screen for nodal disease and distant metastasis; MRI may also be considered.[79,80] Imaging workup is vital as 13%-16% of patients without palpable inguinal lymph nodes may have occult metastases, and 20%-40% of patients with palpable lymph nodes may not have metastases.[79,80] The most common histology of penile cancer is squamous cell carcinoma, which is usually FDG avid.[81–84] However, PET/CT is not recommended for staging of low-risk patients because it is less sensitive to small nodal metastases that are below the PET spatial resolution.[85–87] A meta-analysis

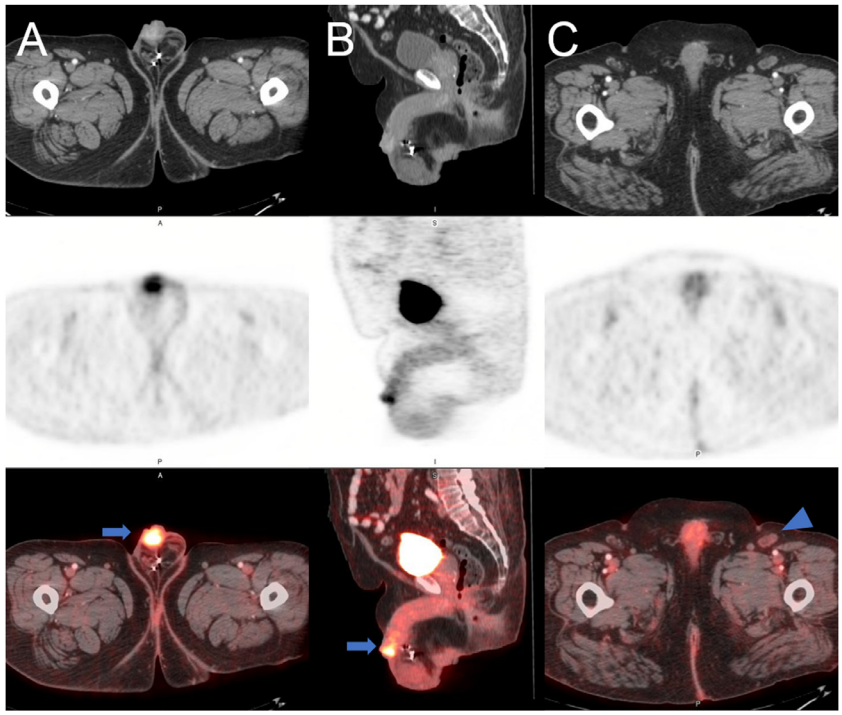

Figure 8 A 65-year-old man was diagnosed with an ulcerated, invasive, and moderate-poorly differentiated, predominantly non-keratinized squamous cell carcinoma of the glans penis. Staging PET/ceCT shows a 2.5 cm contrast-enhancing, FDG avid penile lesion, max. SUV 5.6 (A, axial; B, sagittal; arrow); reference liver SUV was 3.0. A slightly enlarged left inguinal lymph node measuring 1.2 × 2.1 cm shows no abnormal uptake (SUV 1.5), which favors a benign node; there is no PET/CT evidence of distant metastasis. The patient underwent partial penectomy and remains disease-free at his recent 5-year clinical follow-up.

showed that PET/CT had a pooled sensitivity of 81% and specificity of 92% for inguinal nodal staging of all lesion sizes. Specifically, the sensitivity was only 57% for non-palpable nodal metastases but increased to 96% when the nodes were palpable, Table 1.[88] Thus, FDG PET/CT is most valuable in those patients with clinically suspicious inguinal nodes or where initial CT or MRI shows equivocal findings for metastasis.[86,89–93] A case of moderate-poorly differentiated, non-keratinized squamous cell carcinoma of the penis with true-negative nodal and distant metastasis on clinical follow-up is shown (Fig. 8).

Conclusion

The diagnostic value of FDG PET/CT in urogenital malignancies is less well-known compared with other tumor entities not at least because of the variable FDG avidity of these tumor entities and interpretive challenges associated with the sites of these tumors and inherent limitations of hybrid imaging. Current evidence-based literature suggests that FDG PET/CT is not standard of care for initial diagnosis or local staging of early-stage or low-risk urogenital cancers; however, it can help evaluate distant metastatic disease, response to therapy, and disease recurrence. Further studies are warranted to assess its added value to standard-of-care CT and MRI fully.

References

1. Beyer T, Townsend DW, Brun T, et al: A combined PET/CT scanner for clinical oncology. J Nucl Med 41:1369-1379, 2000
2. Wechalekar K, Sharma B, Cook G: PET/CT in oncology—a major advance. Clin Radiol 60:1143-1155, 2005
3. Hillner BE, Tosteson AN, Song Y, et al: Growth in the use of PET for six cancer types after coverage by medicare: Additive or replacement? J Am Coll Radiol 9:33-41, 2012
4. Czernin J, Allen-Auerbach M, Schelbert HR: Improvements in cancer staging with PET/CT: Literature-based evidence as of September 2006. J Nucl Med 48(Suppl 1):78S-88S, 2007
5. Scarsbrook AF, Barrington SF: PET-CT in the UK: current status and future directions. Clin Radiol 71:673-690, 2016
6. Hillner BE, Siegel BA, Liu D, et al: Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: Initial results from the National Oncologic PET Registry. J Clin Oncol 26:2155-2161, 2008
7. Podoloff DA, Ball DW, Ben-Josef E, et al: NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw 7(Suppl 2):S1-26, 2009
8. The Royal College Of R, Royal College Of Physicians Of L, Royal College Of P: Evidence-based indications for the use of PET-CT in the United Kingdom 2016. Clin Radiol 71:e171-e188, 2016
9. d'Amico A, Gorczewska I, Gorczewski K, et al: Effect of furosemide administration before F-18 fluorodeoxyglucose positron emission tomography/computed tomography on urine radioactivity and detection of uterine cervical cancer. Nucl Med Rev Cent East Eur 17:83-86, 2014
10. Anjos DA, Etchebehere EC, Ramos CD, et al: 18F-FDG PET/CT delayed images after diuretic for restaging invasive bladder cancer. J Nucl Med 48:764-770, 2007

11. Nayak B, Dogra PN, Naswa N, et al: Diuretic 18F-FDG PET/CT imaging for detection and locoregional staging of urinary bladder cancer: prospective evaluation of a novel technique. Eur J Nucl Med Mol Imaging 40:386-393, 2013
12. Lakhani A, Khan SR, Bharwani N, et al: FDG PET/CT pitfalls in gynecologic and genitourinary oncologic imaging. Radiographics 37:577-594, 2017
13. Boellaard R, Delgado-Bolton R, Oyen WJ, et al: FDG PET/CT: EANM procedure guidelines for tumor imaging: version 2.0. Eur J Nucl Med Mol Imaging 42:328-354, 2015
14. Brechtel K, Klein M, Vogel M, et al: Optimized contrast-enhanced CT protocols for diagnostic whole-body 18F-FDG PET/CT: technical aspects of single-phase versus multiphase CT imaging. J Nucl Med 47:470-476, 2006
15. Pfannenberg AC, Aschoff P, Brechtel K, et al: Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. Br J Radiol 80:437-445, 2007
16. Minamimoto R, Levin C, Jamali M, et al: Improvements in PET Image Quality in Time of Flight (TOF) Simultaneous PET/MRI. Mol Imaging Biol 18:776-781, 2016
17. Mehranian A, Zaidi H: Impact of time-of-flight PET on quantification errors in MR imaging-based attenuation correction. J Nucl Med 56:635-641, 2015
18. Heusser T, Mann P, Rank CM, et al: Investigation of the halo-artifact in 68Ga-PSMA-11-PET/MRI. PLoS One 12:e0183329, 2017
19. Reinert CP, la Fougere C, Nikolaou K, et al: Value of CT iterative metal artifact reduction in PET/CT-clinical evaluation in 100 patients. Br J Radiol 92:20180756, 2019
20. Purohit BS, Ailianou A, Dulguerov N, et al: FDG-PET/CT pitfalls in oncological head and neck imaging. Insights Imaging 5:585-602, 2014
21. Abdoli M, Dierckx RA, Zaidi H: Metal artifact reduction strategies for improved attenuation correction in hybrid PET/CT imaging. Med Phys 39:3343-3360, 2012
22. Mawlawi O, Erasmus JJ, Munden RF, et al: Quantifying the effect of IV contrast media on integrated PET/CT: clinical evaluation. AJR Am J Roentgenol 186:308-319, 2006
23. Goerres GW, Burger C, Schwitter MR, et al: PET/CT of the abdomen: optimizing the patient breathing pattern. Eur Radiol 13:734-739, 2003
24. Nehmeh SA, Erdi YE, Pan T, et al: Four-dimensional (4D) PET/CT imaging of the thorax. Med Phys 31:3179-3186, 2004
25. Pan T, Mawlawi O, Nehmeh SA, et al: Attenuation correction of PET images with respiration-averaged CT images in PET/CT. J Nucl Med 46:1481-1487, 2005
26. Dawood M, Buther F, Stegger L, et al: Optimal number of respiratory gates in positron emission tomography: A cardiac patient study. Med Phys 36:1775-1784, 2009
27. Lamare F, Fayad H, Fernandez P, et al: Local respiratory motion correction for PET/CT imaging: Application to lung cancer. Med Phys 42:5903-5912, 2015
28. Walker MD, Morgan AJ, Bradley KM, et al: Evaluation of data-driven respiratory gating waveforms for clinical PET imaging. EJNMMI Res 9:1, 2019
29. Buther F, Jones J, Seifert R, et al: Clinical evaluation of a data-driven respiratory gating algorithm for whole-body PET with continuous bed motion. J Nucl Med 61:1520-1527, 2020
30. Pepin A, Daouk J, Bailly P, et al: Management of respiratory motion in PET/computed tomography: The state of the art. Nucl Med Commun 35:113-122, 2014
31. Kidney cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).Version 2.2021. February 3, 2021. Accessed 3/10/2021.
32. Kang DE, White RL Jr., Zuger JH: Clinical use of fluorodeoxyglucose F 18 positron emission tomography for detection of renal cell carcinoma. J Urol 171:1806-1809, 2004
33. Wang HY, Ding HJ, Chen JH, et al: Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma. Cancer Imaging 12:464-474, 2012
34. Nakajima R, Abe K, Kondo T, et al: Clinical role of early dynamic FDG-PET/CT for the evaluation of renal cell carcinoma. Eur Radiol 26:1852-1862, 2016
35. Takahashi M, Kume H, Koyama K, et al: Preoperative evaluation of renal cell carcinoma by using 18F-FDG PET/CT. Clin Nucl Med 40:936-940, 2015
36. Aide N, Cappele O, Bottet P, et al: Efficiency of [(18)F]FDG PET in characterizing renal cancer and detecting distant metastases: A comparison with CT. Eur J Nucl Med Mol Imaging 30:1236-1245, 2003
37. Lee H, Hwang KH, Kim SG, et al: Can Initial (18)F-FDG PET-CT imaging give information on metastasis in patients with primary renal cell carcinoma? Nucl Med Mol Imaging 48:144-152, 2014
38. Park JW, Jo MK, Lee HM: Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. BJU Int 103:615-619, 2009
39. Alongi P, Picchio M, Zattoni F, et al: Recurrent renal cell carcinoma: clinical and prognostic value of FDG PET/CT. Eur J Nucl Med Mol Imaging 43:464-473, 2016
40. Ma H, Shen G, Liu B, et al: Diagnostic performance of 18F-FDG PET or PET/CT in restaging renal cell carcinoma: a systematic review and meta-analysis. Nucl Med Commun 38:156-163, 2017
41. Fuccio C, Ceci F, Castellucci P, et al: Restaging clear cell renal carcinoma with 18F-FDG PET/CT. Clin Nucl Med 39:e320-e324, 2014
42. Casalino DD, Remer EM, Bishoff JT, et al: ACR appropriateness criteria post-treatment follow-up of renal cell carcinoma. J Am Coll Radiol 11:443-449, 2014
43. Lyrdal D, Boijsen M, Suurkula M, et al: Evaluation of sorafenib treatment in metastatic renal cell carcinoma with 2-fluoro-2-deoxyglucose positron emission tomography and computed tomography. Nucl Med Commun 30:519-524, 2009
44. Ueno D, Yao M, Tateishi U, et al: Early assessment by FDG-PET/CT of patients with advanced renal cell carcinoma treated with tyrosine kinase inhibitors is predictive of disease course. BMC Cancer 12:162, 2012
45. Kayani I, Avril N, Bomanji J, et al: Sequential FDG-PET/CT as a biomarker of response to Sunitinib in metastatic clear cell renal cancer. Clin Cancer Res 17:6021-6028, 2011
46. Farnebo J, Gryback P, Harmenberg U, et al: Volumetric FDG-PET predicts overall and progression- free survival after 14 days of targeted therapy in metastatic renal cell carcinoma. BMC Cancer 14:408, 2014
47. Ahn T, Roberts MJ, Abduljabar A, et al: A Review of Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) in Renal Cell Carcinoma (RCC). Mol Imaging Biol 21:799-807, 2019
48. Baccala A, Sercia L, Li J, et al: Expression of prostate-specific membrane antigen in tumor-associated neovasculature of renal neoplasms. Urology 70:385-390, 2007
49. Spatz S, Tolkach Y, Jung K, et al: Comprehensive evaluation of prostate specific membrane antigen expression in the vasculature of renal tumors: implications for imaging studies and prognostic role. J Urol 199:370-377, 2018
50. Meyer AR, Carducci MA, Denmeade SR, et al: Improved identification of patients with oligometastatic clear cell renal cell carcinoma with PSMA-targeted (18)F-DCFPyL PET/CT. Ann Nucl Med 33:617-623, 2019
51. Study of PSMA-targeted 18F-DCFPyL PET/CT in the evaluation of patients with renal cell carcinoma. Available at: https://clinicaltrialsgov/ct2/show/study/NCT02687139 (assessed 6/9/2021).
52. Preliminary evaluation of uptake of [68Ga]P16-093 in metastatic prostate and renal cancer. Available at: https://clinicaltrialsgov/ct2/show/NCT03073395 (assessed6/9/2021)
53. Hekman MCH, Rijpkema M, Aarntzen EH, et al: Positron Emission Tomography/Computed Tomography with (89)Zr-girentuximab Can Aid in Diagnostic Dilemmas of Clear Cell Renal Cell Carcinoma Suspicion. Eur Urol 74:257-260, 2018
54. Verhoeff SR, van Es SC, Boon E, et al: Lesion detection by [(89)Zr]Zr-DFO-girentuximab and [(18)F]FDG-PET/CT in patients with newly diagnosed metastatic renal cell carcinoma. Eur J Nucl Med Mol Imaging 46:1931-1939, 2019
55. Browne RF, Murphy SM, Grainger R, et al: CT cystography and virtual cystoscopy in the assessment of new and recurrent bladder neoplasms. Eur J Radiol 53:147-153, 2005
56. Beer A, Saar B, Zantl N, et al: MR cystography for bladder tumor detection. Eur Radiol 14:2311-2319, 2004
57. Lodde M, Lacombe L, Friede J, et al: Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. BJU Int 106:658-663, 2010

58. Zhang H, Xing W, Kang Q, et al: Diagnostic value of [18F] FDG-PET and PET/CT in urinary bladder cancer: a meta-analysis. Tumour Biol 36:3209-3214, 2015
59. Bladder Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).Version 6.2020 - July 16, 2020. Accessed 3/10/2021.
60. Expert Panel on Urologic I, Allen BC, Oto A, et al: ACR Appropriateness Criteria(R) Post-Treatment Surveillance of Bladder Cancer. J Am Coll Radiol 16(11S):S417-S427, 2019
61. Kibel AS, Dehdashti F, Katz MD, et al: Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 27:4314-4320, 2009
62. Alongi P, Caobelli F, Gentile R, et al: Recurrent bladder carcinoma: clinical and prognostic role of 18 F-FDG PET/CT. Eur J Nucl Med Mol Imaging 44:224-233, 2017
63. Xue M, Liu L, Du G, et al: Diagnostic Evaluation of 18F-FDG PET/CT imaging in recurrent or residual urinary bladder cancer: A meta-analysis. Urol J 17:562-567, 2020
64. Testicular cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).Version 1.2021. November 5, 2020. Accessed 3/10/2021.
65. Yacoub JH, Oto A, Allen BC, et al: ACR Appropriateness Criteria Staging of Testicular Malignancy. J Am Coll Radiol 13:1203-1209, 2016
66. de Wit M, Brenner W, Hartmann M, et al: [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumors: results of the German multicentre trial. Ann Oncol 19:1619-1623, 2008
67. Cremerius U, Wildberger JE, Borchers H, et al: Does positron emission tomography using 18-fluoro-2-deoxyglucose improve clinical staging of testicular cancer?—Results of a study in 50 patients. Urology 54:900-904, 1999
68. Hain SF, O'Doherty MJ, Timothy AR, et al: Fluorodeoxyglucose PET in the initial staging of germ cell tumors. Eur J Nucl Med 27:590-594, 2000
69. Lassen U, Daugaard G, Eigtved A, et al: Whole-body FDG-PET in patients with stage I non-seminomatous germ cell tumors. Eur J Nucl Med Mol Imaging 30:396-402, 2003
70. Soydal C, Araz M, Urun Y, et al: 18F-Flourodeoxy glucose PET-computed tomography in testicular carcinoma: diagnostic and prognostic value. Nucl Med Commun 40:1268-1274, 2019
71. Ambrosini V, Zucchini G, Nicolini S, et al: 18F-FDG PET/CT impact on testicular tumors clinical management. Eur J Nucl Med Mol Imaging 41:668-673, 2014
72. Oechsle K, Hartmann M, Brenner W, et al: [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol 26:5930-5935, 2008
73. Huddart RA, O'Doherty MJ, Padhani A, et al: 18fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22—the NCRI Testis Tumour Clinical Study Group. J Clin Oncol 25:3090-3095, 2007
74. Treglia G, Sadeghi R, Annunziata S, et al: Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in the postchemotherapy management of patients with seminoma: systematic review and meta-analysis. Biomed Res Int 2014:852681, 2014
75. Zhao JY, Ma XL, Li YY, et al: Diagnostic accuracy of 18F-FDG-PET in patients with testicular cancer: A meta-analysis. Asian Pac J Cancer Prev 15:3525-3531, 2014
76. Bachner M, Loriot Y, Gross-Goupil M, et al: 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: A retrospective validation of the SEM-PET trial. Ann Oncol 23:59-64, 2012
77. Becherer A, De Santis M, Karanikas G, et al: FDG PET is superior to CT in the prediction of viable tumor in post-chemotherapy seminoma residuals. Eur J Radiol 54:284-288, 2005
78. De Santis M, Becherer A, Bokemeyer C, et al: 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol 22:1034-1039, 2004
79. Ottenhof SR, Leone AR, Horenblas S, et al: Advancements in staging and imaging for penile cancer. Curr Opin Urol 27:612-620, 2017
80. de Vries HM, Brouwer OR, Heijmink S, et al: Recent developments in penile cancer imaging. Curr Opin Urol 29:150-155, 2019
81. Jeong HS, Baek CH, Son YI, et al: Use of integrated 18F-FDG PET/CT to improve the accuracy of initial cervical nodal evaluation in patients with head and neck squamous cell carcinoma. Head Neck 29:203-210, 2007
82. Schwartz DL, Rajendran J, Yueh B, et al: Staging of head and neck squamous cell cancer with extended-field FDG-PET. Arch Otolaryngol Head Neck Surg 129:1173-1178, 2003
83. Mahajan S, Barker CA, Singh B, et al: Clinical value of 18F-FDG-PET/CT in staging cutaneous squamous cell carcinoma. Nucl Med Commun 40:744-751, 2019
84. Nguyen NC, Abhishek K, Nyon S, et al: Are there radiographic, metabolic, and prognostic differences between cavitary and noncavitary non-small cell lung carcinoma? A retrospective fluorodeoxyglucose positron emission tomography/computed tomography study. Ann Thorac Med 11:49-54, 2016
85. Souillac I, Rigaud J, Ansquer C, et al: Prospective evaluation of (18)F-fluorodeoxyglucose positron emission tomography-computerized tomography to assess inguinal lymph node status in invasive squamous cell carcinoma of the penis. J Urol 187:493-497, 2012
86. Scher B, Seitz M, Reiser M, et al: 18F-FDG PET/CT for staging of penile cancer. J Nucl Med 46:1460-1465, 2005
87. Leijte JA, Graafland NM, Valdes Olmos RA, et al: Prospective evaluation of hybrid 18F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma. BJU Int 104:640-644, 2009
88. Sadeghi R, Gholami H, Zakavi SR, et al: Accuracy of 18F-FDG PET/CT for diagnosing inguinal lymph node involvement in penile squamous cell carcinoma: systematic review and meta-analysis of the literature. Clin Nucl Med 37:436-441, 2012
89. Salazar A, Junior EP, Salles PGO, et al: (18)F-FDG PET/CT as a prognostic factor in penile cancer. Eur J Nucl Med Mol Imaging 46:855-863, 2019
90. Ottenhof SR, Vegt E: The role of PET/CT imaging in penile cancer. Transl Androl Urol 6:833-838, 2017
91. Drager DL, Heuschkel M, Protzel C, et al: [18F]FDG PET/CT for assessing inguinal lymph nodes in patients with penile cancer - correlation with histopathology after inguinal lymphadenectomy. Nuklearmedizin 57:26-30, 2018
92. Graafland NM, Leijte JA, Valdes Olmos RA, et al: Scanning with 18F-FDG-PET/CT for detection of pelvic nodal involvement in inguinal node-positive penile carcinoma. Eur Urol 56:339-345, 2009
93. Penile cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).Version 1.2021. January 13, 2021. Accessed 3/10/2021.